A PHASE 1, OPEN-LABEL, SINGLE-DOSE, PARALLEL-GROUP STUDY TO EVALUATE THE PHARMACOKINETICS OF PF-07081532 IN ADULT PARTICIPANTS WITH TYPE 2 DIABETES MELLITUS WITH VARYING DEGREES OF RENAL IMPAIRMENT RELATIVE TO PARTICIPANTS WITHOUT RENAL IMPAIRMENT

Study Intervention Number:	PF-07081532
Study Intervention Name:	Not Applicable (N/A)
US IND Number:	147045
EudraCT/CTIS Number:	N/A
ClinicalTrials.gov ID:	Not Available
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C3991007
Phase:	1

Brief Title: A Study to Investigate the Effects of Renal Impairment on the Pharmacokinetics of PF-07081532

Document History

Document	Version Date
Original protocol	03 June 2022

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 1, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Pharmacokinetics of PF-07081532 in Adult Participants with Type 2 Diabetes Mellitus with Varying Degrees of Renal Impairment Relative to Participants without Renal Impairment.

Brief Title:

A Study to Investigate the Effects of Renal Impairment on the Pharmacokinetics of PF-07081532.

Regulatory Agency Identification Number(s):

US IND Number:	147045
EudraCT/CTIS Number:	Not Applicable (N/A)
ClinicalTrials.gov ID:	Not available
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C3991007
Phase:	1

Rationale:

The primary purpose of this study is to characterize the effect of varying degrees of renal impairment on the PK of a single oral dose of PF-07081532 in adult participants with T2DM compared to participants with T2DM with normal renal function.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To compare the PK of PF-07081532 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to age- and body weight-matched participants with T2DM, without renal impairment.	• Plasma: C_{max}, AUC_{inf}, AUC_{last}*, fu, $C_{max,u}$, $AUC_{inf,u}$ and $AUC_{last,u}$*, as data permit.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of a single oral dose of PF-07081532 when administered to adult participants with T2DM and varying degrees of renal impairment relative to age- and body weight-matched participants with T2DM, without renal impairment.	• Assessment of treatment emergent AEs, clinical laboratory abnormalities, vital signs, ECG parameters.

* AUC_{last} and $AUC_{last,u}$ will be treated as primary endpoints if data do not permit robust estimation of AUC_{inf} and $AUC_{inf,u}$, otherwise they will be treated as tertiary endpoints.

Overall Design:

This is an open-label, single-dose, parallel-group study to investigate the effect of varying degrees of renal function on the PK of PF-07081532 after a single, oral 20 mg dose administered in the fed state (standard, non-high fat breakfast). Safety and tolerability will be evaluated throughout the study.

Participants with T2DM with normal renal function, and with mild, moderate, and severe renal impairment, will be enrolled into 1 of 4 groups. This study will permit enrollment of 2-4 participants on dialysis, as part of the severe renal impairment group, to assist in recruitment of patients with more advanced renal impairment and to permit assessment of the PK of PF-07081532 in participants with the highest degree of renal impairment.

Number of Participants:

Approximately 32 participants with T2DM and varying degrees of renal function will be enrolled to receive study intervention. If recruitment of participants with eGFR <30 mL/min proves prohibitive, the number of participants to be enrolled in the group with severe impairment may be flexible (6-8 participants).

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

- Stable renal function (**for participants not on dialysis**) defined as ≤25% difference between 2 measurements of eGFR (calculated by the sponsor-identified laboratory using the **2021** CKD-EPI Scr-Scys combined equation as described in Section 4.1) obtained at Screening visits S1 and S2. The average of the 2 eGFR values obtained from S1 and S2 will be used for study enrollment and assignment to appropriate renal function group (see Table 1). ***Note:*** participants on dialysis will be placed in Group 4 regardless of eGFR from S1 and S2 (S2 is optional for dialysis participants, **only**).

- Meet eGFR criteria for inclusion in group with:

  - Normal renal function (≥90 mL/min); or

  - Mild (60-89 mL/min), moderate (30-59 mL/min), or severe (<30 mL/min) renal impairment.

- A prior diagnosis of T2DM with an HbA1c ≥6% and ≤10.5%, at Screening visit S1, confirmed by a single repeat, if deemed necessary.

- Male and female participants ≥18 years of age (or the minimum country-specific age of consent if >18), at the time of providing informed consent.

- BMI of 17.5 to 45.4 kg/m^2, inclusive; and a total body weight >50 kg (110 lb), at Screening visit S1.

- The group of participants with normal renal function should, at screening (S1), meet the demographic-matching criteria, including body weight within ±15 kg and age within ±10 years, of the average of the pooled renal impairment groups, as provided by the sponsor.

Key Exclusion Criteria

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

- Diagnosis of type 1 diabetes mellitus or secondary forms of diabetes, or history of diabetic ketoacidosis.

- Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, ileal resection). ***NOTE*:** Participants who have undergone cholecystectomy and/or appendectomy are eligible for this study as long as the surgery occurred more than 6 months prior to Screening visit S1.

- Any malignancy not considered cured (except basal cell carcinoma and squamous cell carcinoma of the skin); a participant is considered cured if there has been no evidence of cancer recurrence in the previous 5 years.

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

- History of acute pancreatitis within 6 months before Screening visit S1 or any history of chronic pancreatitis.

- Urinary incontinence.

- Participants with acute renal disease.

- Renal allograft recipients.

- Participants who have previously received a kidney, liver, or heart transplant.

- At Screening (S1), standard 12-lead ECG that demonstrates a clinically relevant abnormality that requires further diagnostic evaluation or intervention (eg, new, clinically relevant arrhythmia, conduction disturbance, findings suggestive of ischemia). A potential participant whose pre-dose ECG (on Day 1, 0 hour) demonstrates a clinically relevant abnormality that requires further diagnostic evaluation or intervention will be considered a screen failure.

- For females, pregnancy, as indicated by a positive serum pregnancy test at screening and/or positive urine pregnancy test in WOCBP at Day -1.

- Participants with ANY of the following abnormalities in clinical laboratory tests at Screening (S1), as assessed by the study-specific local laboratory and confirmed by a single repeat test, if deemed necessary:

  - 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.

  - Fasting C-peptide <0.8 ng/mL.

  - FPG >270 mg/dL (15 mmol/L).

- In addition, for participants with normal renal function:

  - Any of the following abonormalities in clinical laboratory tests at Screening, as assessed by the sponsor-approved laboratory and confirmed by a single repeat test, if deemed necessary:

- AST ≥1.5x ULN; or
- ALT ≥1.5x ULN.

- At Screening (S1), seated SBP ≥160 mmHg and/or DBP ≥100 mmHg after ≥5 minutes of seated rest. If BP is ≥160 mm Hg (systolic) or ≥100 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

- In addition, for participants with impaired renal function:
  - Any of the following abnormalities in clinical laboratory tests at Screening, as assessed by the sponsor-identified laboratory and confirmed by a single repeat test, if deemed necessary:
    - AST ≥2x ULN or
    - ALT ≥2x ULN
  - At Screening, Day -1 or Day 1, persistent severe, uncontrolled hypertension, as defined in the study protocol.

Study Arms and Duration:

Eligible participants with T2DM will be enrolled into 1 of 4 groups based on eGFR (calculated using the **2021** CKD-EPI Scr-Scys combined equation):

1. Normal renal function (≥90 mL/min).
2. Mild (60-89 mL/min) renal impairment.
3. Moderate (30-59 mL/min) renal impairment.
4. Severe (<30 mL/min) renal impairment.

A single oral 20 mg dose of PF-07081532 will be administered. For individual participants, the total study duration from Screening visit S1 to the Follow-up contact will be a minimum of approximately 6 weeks and a maximum of up to approximately 10 weeks. The study consists of an initial screening period of up to 28 days, a 7-day inpatient stay at the CRU which includes administration of a single oral dose of PF-07081532, and a follow up contact that will occur 28-35 days after PF-07081532 administration.

PF-07081532 will be supplied by Pfizer as 20 mg tablets in open-label bulk bottles along with individual dosing containers, as necessary, for unit dosing. Participants will take 1 PF-07081532 20-mg tablet orally with the morning meal.

Study Intervention(s)	
Intervention Name	PF-07081532
Arm Name **(group of participants receiving a specific treatment or no treatment)**	Group 1, Group 2, Group 3, Group 4
Unit Dose Strength(s)	20 mg
Route of Administration	Oral
Use	Experimental
IMP or NIMP/AxMP	IMP

Statistical Methods:

A sample size of approximately 32 participants (approximately 8 participants per group, with varying degrees of renal function in each of the 4 groups) has been selected to provide sufficient precision to detect a 1.5-fold difference in AUC_{inf} between each Test group (with renal impairment) and the Reference group (without renal impairment).

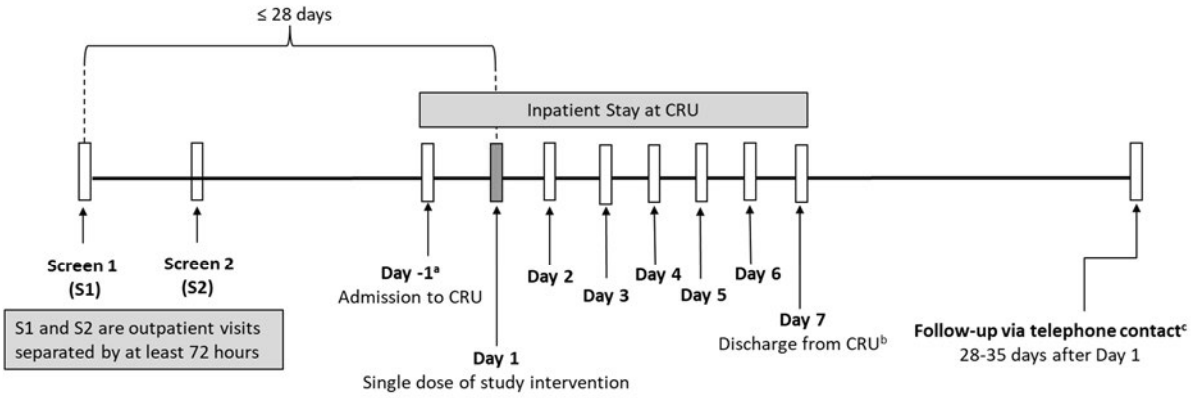
The effect of varying degrees of renal impairment on PK parameters will be assessed by constructing 90% CIs around the estimated difference between each of the Test (renal impaired) groups and the Reference (without renal impairment) group. ANOVA will be used to compare the natural log-transformed AUC_{inf}, AUC_{last}, C_{max}, f_u, $AUC_{inf,u}$, $AUC_{last,u}$ and $C_{max,u}$ of PF-07081532 for each of the renal impairment groups (Test) to the group without renal impairment (Reference), as data permit. The ANOVA model will include all groups. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. These will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and corresponding 90% CIs for the ratios.

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, following sponsor standards.

Ethical Considerations:

A single dose of PF-07081532 is not expected to provide any clinical benefit to study participants. This study is designed primarily to characterize the effect of varying degrees of renal impairment on the PK of PF-07081532. Results from this study will be used in conjunction with collective safety, tolerability, efficacy, and PK/PD (pharmacodynamic) data from other PF-07081532 studies to provide recommendations on dosing for participants with varying degrees of renal function.

1.2. Schema



a. Admission can occur at any time of day; once admitted, participant to be provided inpatient meal(s).
b. Following completion of procedures and morning meal, participant will be discharged from the CRU.
c. Follow-up telephone contact may occur as onsite visit for follow-up of abnormal laboratory tests and/or open AEs, at Investigator discretion, in the window of 28 to 35 days after Day 1.

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 (Section 8) 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.

Visit Identifier (for Abbreviations refer to Appendix 11)	Screening[a]			Study Period																		Follow-up	EOT
	S1	S2																					
Study Day	≤-28		-1	1											2		3	4	5	6	7	29-36[b]	
Hours Post Dose				0	0.5	1	2	4	6	8	10	12	14	15	24	36	48	72	96	120	144		
Informed consent & demography	X																						
COVID-19 assessment[c]	See footnote																						
Serious/Adverse event monitoring	X	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	X
Outpatient visit	X	X																					
Inpatient stay at Clinical Research Unit			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X		
Eligibility assessment	X	X	X	X																			
Medical history	X																						
Alcohol/tobacco & contraception use[d]	X	X	X																			X	X
Prior/concomitant treatments	X	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	X
Physical exam (height and weight at S1, only)[e]	X		X																		X		X
Alcohol breath test	X		X																				
Single, *supine* 12-lead ECG[f]	X			X[f]																	X		X
Single, *seated* vital sign assessment[f]	X		X	X[f]											X			X			X		X
Glucometer measurement[g]				X											X		X	X	X	X	X		
Standard meals/optional snacks[h]			X	X				X	X		X		X		X		X	X	X	X	X		
Study intervention administration[i]				X																			
Blood Sampling for:																							
Clinical safety laboratory tests[j]	X			X[j,k]														X			X		X
eGFR[l]	X	X		X[k]														X			X		X
Serum FSH (all females), HbA1c, C-peptide	X																						
Serum pregnancy test (all females)	X																						
Retained Research Sample Prep D1.5[m]				X[k]																			
CCI																							
Plasma PF-07081532 PK				X[k]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		X
PF-07081532 f_u in plasma				X[k]			X																
Urine Sampling for:																							
Urine PF-07081532 PK[n]				X	→	→	→	→	X	→	→	X	→	→	X								
Urine drug test[o]	X																						
Urinalysis (and microscopy, if needed)[j,p]	X			X[k]														X			X		X
Urine pregnancy test (WOCBP only)[q]			X																		X		X

a. Screening takes place over 2 outpatient visits (S1 and S2), separated by at least 72 hrs. S1 must be within the 28 days prior to D1 dose administration. S2 is to demonstrate stable renal function and is optional for patients on dialysis, only.

b. Follow-up visit to be performed as telephone contact and must occur in the window of 28 to 35 days (ie, Day 29-36) from administration of study intervention. A clinic visit may be performed in place of telephone contact, if deemed necessary by the investigator eg, for follow-up of abnormal laboratory tests and/or open AEs.

c. 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.

d. In confirmation of appropriate contraception use only.

e. Complete PE at Screening visit S1; at all other timepoints limited PE, at investigator discretion (see Section 8.3.1).

f. If done around the time of a blood draw, ECG and vital signs should be collected before the blood draw. ECG and vital signs on Day 1 at Time 0H must be done before collection of the pre-dose blood samples. If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (BP and pulse rate) should be collected before insertion of the catheter.

g. Glucometer measures will be taken before breakfast in participants with T2DM on all days while inpatient. Additional measurements may be made at the discretion of the investigator.

h. Meals/snacks will be provided on all days while inpatient as per Section 5.3.2. While inpatient, meal and snack times should match nominal time of approximately 0H, 4H, 6H (optional), 10H, 14H (optional) relative to dosing on Day 1. Meals/snacks on Day -1 must be timed such that there is at least an 8 hour fast prior to collection of the pre-dose PK sample on Day 1 (see Section 5.3.2).

i. Dosing will occur within approximately 10 minutes of completion of breakfast on Day 1.

j. Safety related laboratory tests may be collected on Day -1 at investigator discretion. ***If performed***, results must be reviewed prior to dosing and must reflect the participant to be in stable medical condition. Total bile acids, lipase, and amylase at Screening only.

k. Samples collected at Time 0 on Day 1 must be collected pre-dose.

l. eGFR determination will be performed by the laboratory using the 2021 CKD-EPI Scr-Scys combined equation, as described in Section 4.1 and Appendix 7.

m. 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.

n. Blank pre-dose urine sample to be collected within 24H prior to dosing. Urine should be collected at intervals of 0-6, 6-12 and 12-24 hours after dosing. See Section 8.5.3. If participant is on dialysis and has no urine output, no urine PK samples will be collected.

o. For a participant on dialysis who is anuric only, an alternative method (eg, saliva) for urine drug testing may be used.

p. For a participant on dialysis who is anuric only, urinalysis is not required to be collected.

q. Test result must be reviewed and deemed acceptable (ie, negative) to continue participation in the study. For a participant on dialysis who is anuric only, an alternative method (eg, blood) for pregnancy testing may be used.

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-1Rstimulates 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 currently being developed as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

2.1. Study Rationale

The primary purpose of this study is to characterize the effect of varying degrees of renal impairment on the PK of a single oral dose of PF-07081532 in participants with T2DM compared to participants with T2DM with normal renal function. Results from this study may be used in conjunction with collective safety, tolerability, efficacy, and PK/PD data from other PF-07081532 studies to provide recommendations on dosing for participants with varying degrees of renal function.

2.2. Background

2.2.1. Nonclinical Pharmacology

In vitro primary PD studies demonstrated that in cells expressing recombinant human and monkey GLP-1R, PF-07081532 promotes cAMP production. In contrast, no cAMP production was observed in cells expressing recombinant rat, mouse, and rabbit GLP-1R at tested concentrations (>10000 nM). PF-07081532 was shown to bind to the human GLP-1R using a competition binding assay. In vivo, PF-07081532 potentiated glucose-stimulated insulin secretion during an IVGTT in cynomolgus monkeys at plasma exposures that were consistent with its in vitro potency.

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

2.2.2. Nonclinical Pharmacokinetics and Metabolism

CCI [redacted]

Further details of the nonclinical PK and metabolism program are included in the IB.

2.2.3. Nonclinical Safety

PF-07081532 was administered PO to Wistar Han rats and cynomolgus monkeys in studies up to 6 and 9 months in duration, respectively. All in vitro and in vivo studies used the [redacted] form of PF-07081532 (78%–82.5% active moiety across all lots). The high dose ([redacted] mg/kg/day for rats and monkeys) in the pivotal toxicity studies were selected based on toleration and findings from earlier repeat-dose and exploratory studies. Based on the nonclinical studies conducted, the target organs and systems identified with PF-07081532 administration included the [redacted].

The NOAELs in the 6-month rat or 9-month monkey pivotal toxicity studies were [redacted] PF-07081532 was negative for mutagenicity in the bacterial reverse mutation assay in the presence and absence of metabolic activation. [redacted] demonstrated that PF-07081532 was not a genotoxic agent. Consistent with ICH S10 (2015),[5] PF-07081532 was assessed in the 3T3 neutral red uptake (NRU) phototoxicity test and did not demonstrate phototoxic potential.

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

2.2.4. Clinical Overview

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

One Phase 1 study, C3991003, is ongoing. This inpatient study is enrolling participants with T2DM inadequately controlled on metformin, and participants with obesity, to receive PF-07081532 or placebo QD for 42 days. The starting dose for the first cohort of this study is 20 mg PF-07081532, with subsequent dose levels to be determined 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 reported.

2.2.4.1. Clinical Safety

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

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 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.

2.2.4.2. Clinical Pharmacokinetics

The clinical PK of PF-07081532 have been evaluated to date in 2 completed studies (C3991001 and C3991002), the results of which are provided in the IB.

CCI [redacted]

CCI [redacted]

Following multiple dose administration of PF-07081532 in study C3991002, C_{max} was observed at 1 to 2 hours on Day 1, and 2 to 8 hours following last dose on Day 28 or 42. Across all dose groups, the mean $t_{½}$ ranged from 20.70 to 26.50 hours following last dose on Day 28 or 42. PF-07081532 exposure (C_{max} and AUC_{tau}) generally increased in an approximately dose proportional manner across the dose range studied (10 mg to 180 mg) and accumulation of less than 2.1-fold was observed with QD dosing. Urinary recovery of unchanged PF-07081532 was low, with less than 0.2% of the dose recovered in the 24-hour dosing interval following last dose on Day 28 or 42.

CCI [redacted]

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-07081532		
Gastrointestinal adverse reactions	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, exenatide, semaglutide and dulaglutide). In addition, GI AEs, the majority of which were mild in severity, have been observed in the clinical program with PF-07081532.	The single dose and dose level administered in this study minimize any potential risk. Participants are monitored during the clinical studies to prevent potential sequelae of any severe GI reactions, eg, dehydration.
Hypoglycemia	Clinical trials with injectable GLP-1R agonists have not demonstrated an increased risk for hypoglycemia. However, when administered in combination with anti-diabetic agents that are known to have an increased risk of hypoglycemia (such as insulin or sulfonylureas), an increased risk for hypoglycemia was observed.	The single dose and dose level administered in this study minimize any potential risk. Study includes inpatient monitoring of the participants following administration of a single dose of the IP. Finger stick blood glucose is monitored at least once daily during the in-patient stay with glucometers.
Increased heart rate	Based on the product labeling for the injectable GLP-1R agonist liraglutide for obesity, mean increases in resting heart rate ranged 2 to 3 bpm in clinical trials, with some participants experiencing greater increases in resting heart rate, up to 10-20 bpm. Following single dose administration of PF-07081532 in the completed FIH study, variable increases in heart rate were observed; the majority of individual values remained within normal	The single dose and dose level administered in this study minimize any potential risk. Study includes inpatient monitoring of the participants following administration of a single dose of the IP.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	ranges, and, throughout the study, no AEs or clinical symptoms related to vital sign parameters were reported.	
Other potential risks associated with long-term dosing of marketed GLP-1R agonists include thyroid C-cell tumors, pancreatitis, impairment in renal function, diabetic retinopathy complications, and acute gallbladder disease	These potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, dulaglutide, exenatide and semaglutide); additional information is provided in the IB.	The single dose and dose level administered in this study minimize any potential risk. Study includes inpatient monitoring of the participants following administration of a single dose of the IP. 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

A single dose of PF-07081532 is not expected to provide any clinical benefit to study participants. This study is designed primarily to characterize the effect of varying degrees of renal impairment on the PK of PF-07081532 to support further clinical development of PF-07081532 as a potential treatment of T2DM. Results from this study will be used in conjunction with collective safety, tolerability, efficacy, and PK/PD data from other PF-07081532 studies to develop dosing recommendations for the target patient population with varying degrees of renal function.

2.3.3. Overall Benefit/Risk Conclusion

In line with the clinical profile of marketed GLP-1R agonists, the most frequently reported AEs in the 2 completed studies with PF-07081532 administration have been in the Gastrointestinal Disorders SOC (Section 2.2.4). In addition, as has been reported for marketed GLP-1R agonists, modest increases in heart rate have been observed with PF-07081532 administration, with most heart rate values within the normal range. Based on available clinical data (Section 2.2.4 and current IB), a single 20 mg PF-07081532 dose is anticipated to be safe and well tolerated, including in participants with varying degrees of renal impairment, even if increased plasma concentrations were to be observed (Section 4.3).

Based on the profile of PF-07081532 observed in nonclinical and clinical studies to date, and taking into account the measures to minimize risk to study participants, the potential risk to the participants in this study is deemed to be minimal and is justified by the anticipated benefits that may be afforded to patients with varying degrees of renal impairment receiving PF-07081532 in the future.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To compare the PK of PF-07081532 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to age- and body weight-matched participants with T2DM, without renal impairment.	• Plasma: C_{max}, AUC_{inf}, AUC_{last}*, fu, $C_{max,u}$, $AUC_{inf,u}$, and $AUC_{last,u}$*, as data permit
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of a single oral dose of PF-07081532 when administered to adult participants with T2DM and varying degrees of renal impairment relative to age- and body weight-matched participants with T2DM, without renal impairment.	• Assessment of treatment emergent AEs, clinical laboratory abnormalities, vital signs, ECG parameters
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To compare additional plasma PK parameters of PF-07081532 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to age- and body weight-matched participants with T2DM, without renal impairment.	• Plasma: CL/F, CL_u/F, V_z/F, $V_{z,u}$/F, T_{max}, $t_{1/2}$, as data permit
• To compare urine PK parameters of PF-07081532 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to age- and body weight-matched participants with T2DM, without renal impairment.	• Urine: CL_r, Ae_{24}, Ae_{24}%
• CCI [redacted]	[redacted]

[redacted] AUC_{last} and $AUC_{last,u}$ will be treated as primary endpoints if data do not permit robust estimation of AUC_{inf} and $AUC_{inf,u}$, otherwise they will be treated as tertiary endpoints.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, single-dose, parallel-group study to investigate the effect of varying degrees of renal function on the PK of PF-07081532 after a single, oral 20 mg dose administered in the fed state (standard, non-high fat breakfast). Safety and tolerability will be evaluated throughout the study.

A total of approximately 32 participants with T2DM and varying degrees of renal function will be dosed in the study as shown in Table 1. If recruitment of participants with eGFR <30 mL/min proves prohibitive, the number of participants to be enrolled in the group with severe impairment may be flexible (6-8 participants). This study will permit enrollment of 2-4 participants on dialysis, as part of the severe renal impairment group, to assist in recruitment of patients with more advanced renal impairment and to permit assessment of the PK of PF-07081532 in participants with the highest degree of renal impairment. Since PF-07081532 has a high unbound non-renal clearance and a large unbound volume of distribution (given a f_u of 0.000376 in humans), dialysis is not expected to significantly impact the clearance of PF-07081532 and therefore the dialysis clearance of PF-07081532 will not be characterized in this study. Thus, Day 1 (per the SoA) will occur in dialysis patients on a day in which dialysis is not administered.

Table 1. Renal Function Categories based on eGFR

Group	Renal Impairment	No. of Participants	eGFR[a] (mL/min)
1	None (Normal Renal Function)	8	≥90
2	Mild	8	60-89
3	Moderate	8	30-59
4	Severe	8[b]	<30

a. See text below regarding determination of eGFR for study enrollment and group placement. ***Note***: participants on dialysis will be placed in Group 4 regardless of unnormalized eGFR value.

b. 2-4 participants on dialysis are permitted (not required). If recruitment proves to be prohibitive, study may dose 6-8 participants with severe renal impairment.

Screening will occur within 28 days of the first dose of study intervention on Day 1. All participants will provide informed consent and undergo Screening evaluations to determine their eligibility.

At each of the 2 Screening visits (S1 **and** S2), an estimate of eGFR will be determined for each participant as described in the steps below:

1. Calculate eGFR using the **2021** CKD-EPI Scr-Scys combined equation (see Appendix 7).

2. Multiply this eGFR value by each participant's ratio of BSA/1.73 to obtain the **BSA-unnormalized** eGFR value as shown below:

   - eGFR (mL/min) = eGFR (mL/min/1.73m^2) * [BSA (m^2) / 1.73]

   The BSA of an individual will be calculated using the following equation:[6]

   - BSA (m^2) = [Weight(kg)$^{0.425}$ × Height(cm)$^{0.725}$] × 0.007184

The **average of the 2 BSA-unormalized** eGFR values from Screening visits S1 and S2 will be used for study enrollment and group placement using the categories presented in Table 1. Participants who are not on dialysis must have stable renal function to enter the study, defined as ≤25% difference between 2 measurements of BSA-unnormalized eGFR obtained from the 2 Screening visits, S1 and S2 as listed in the SoA. Visit S2 is optional for participants on dialysis, who will be placed in Group 4 regardless of eGFR value.

Staged Enrollment of Study Groups

- Participants will be dosed in a staged manner such that those with moderate and severe renal impairment (Groups 3 and 4) will be enrolled first.

- Recruitment of participants with mild renal impairment (Group 2) will initiate when approximately 50% of the participants in Groups 3 and 4 have been dosed.

  Approval from the sponsor is ***required before*** proceeding with recruitment for Group 2.

- An average value for age and weight for Groups 2, 3, and 4 will be determined and participants in Group 1 will be recruited to match the average demographics (at a minimum, age and weight, and as much as practically possible gender) across the pooled Groups 2-4.

- Therefore, recruitment of participants without renal impairment (Group 1) may start when approximately 75% of total participants across Groups 2-4 (ie, approximately 17-18 participants) have been dosed.

  Approval from the sponsor is ***required before*** proceeding with recruitment for Group 1.

Refer to Section 1.2 for the Study Schema. For individual participants, the total study duration from Screening visit S1 to the Follow-up contact will be a minimum of approximately 6 weeks and a maximum of up to approximately 10 weeks. The study consists of an initial screening period of up to 28 days, a 7-day inpatient stay at the CRU which includes administration of a single oral dose of PF-07081532, and a follow-up contact (or site visit, per discretion of the PI) that will occur 28-35 days after PF-07081532 administration on Day 1.

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

4.2. Scientific Rationale for Study Design

The purpose of this study is to characterize the effect of varying degrees of renal impairment on the PK, safety and tolerability of PF-07081532. PF-07081532 is an oral GLP-1R agonist that is currently being investigated as a chronic therapy to improve glycemic control in adult participants with T2DM. CKD occurs in 20-40% of patients with diabetes and may be present at the time of diagnosis of T2DM.[7]

Although urinary recovery of PF-07081532 is low, with less than 0.2% of the dose recovered in the 24-hour dosing interval following multiple dose administration (Study C3991002), renal impairment has the potential to affect drug metabolism and transport in other organs (such as the liver), which may lead to clinically relevant changes in non-renal clearance.[8,9,10] CCI [redacted] Additionally, PF-07081532 is extensively bound to plasma proteins with a f_u of only 0.000376 in humans and as such plasma protein binding may be significantly affected in patients with CKD. Given all of the above, and since patients with T2DM may experience varying stages of CKD, a study design including participants with no, mild, moderate, and severe renal impairment (potentially including participants requiring dialysis) will be conducted. A single dose of PF-07081532 is proposed, as single dose plasma PK of PF-07081532 is generally predictive of exposure upon repeated dosing.

Consistent with the recommendation in the draft FDA Guidance on PK in patients with impaired renal function,[11] the population selected for this study will be participants with T2DM as this is representative of the typical patient population for the drug under development.

Following administration of single oral doses of PF-07081532 under either fasted or fed conditions in Study C3991001 (non-Japanese cohorts), the arithmetic mean terminal $t_{½}$ of PF-07081532 ranged approximately from 17 to 21 hours. Therefore, in this study serial PK samples will be collected up to 144 hours post-dose in order to allow adequate characterization of the elimination phase of the plasma concentration-time profile should an increased $t_{1/2}$ (up to 2-fold) in participants with varying degrees of renal impairment be observed.

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, a single dose of PF-07081532 will be administered with a standard, non-high fat breakfast to reflect the conditions for anticipated use of PF-07081532 in future trials and the target patient population.

Consistent with the recommendation in the draft FDA Guidance[11] plasma as well as urine samples will be collected and analyzed for PF-07081532. Since PF-07081532 is highly protein bound, to assess the in vivo protein binding of PF-07081532 with varying degrees of renal impairment, the f_u of PF-07081532 will be determined in each participant at approximately the expected T_{max}. CCI [redacted]

While GLP-1R agonists typically are not associated with hypoglycemia unless co-administered with anti-diabetic agents that can cause hypoglycemia (such as insulin or sulfonylureas), blood glucose concentrations will be monitored throughout the study via glucometer, and monitoring of symptomatic HAEs will be performed. As is typical for studies with renally impaired participants, vital signs will be obtained in the seated position.

To minimize the risks of COVID-19 related complications to participants and the study site personnel, 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.

CCI [redacted]. For more information regarding concomitant medications in this study, see Section 6.9.

4.2.1. Choice of Contraception/Barrier Requirements

Both women of childbearing potential, as well as those who are of non-childbearing potential, may be enrolled given the availability of EFD toxicity studies with PF-07081532. However, as marketed GLP-1R agonists are listed as contraindicated in pregnancy, measures will be taken to limit the risk of pregnancy in the female population enrolled (see SoA and Section 10.4).

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.[12]

4.2.2. Collection of Retained Research Samples

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

4.3. Justification for Dose

A single oral dose of 20 mg will be used in this study. This dose has been selected based on prior experience in clinical studies with PF-07081532 (Section 2.2.4) and also taking into account safety considerations for the participants with varying degrees of renal impairment in whom an increase in plasma PF-07081532 exposure may be observed.

In Study C3991001, a single dose of 30 mg was very well tolerated with an AE profile that did not differ from placebo. In the same study, single ascending doses up to 200 mg were tested and were considered safe and had a tolerability profile in line with expectations for the MOA, with the majority of AEs being mild in severity and in the GI SOC (with nausea and vomiting the most frequently observed). For participants that experienced vomiting (observed at the 100 and 200 mg dose levels, with increased incidence at 200 mg), this generally occurred after the attainment of C_{max} and with no apparent impact on PF-07081532 exposure. In addition, the dose proposed in the current study (20 mg) reflects adequate safety margins compared to nonclinical toxicity studies. After accounting for species differences in protein binding, this dose represents an exposure in participants with healthy renal function that is approximately CCI, lower than the exposure observed at the NOAEL in the pivotal 9-month toxicology study in monkeys (Section 2.2.3). Given the above it is anticipated that potential increases in plasma exposure in participants with varying degrees of renal impairment in the current study, if encountered, are not anticipated to pose an undue safety risk.

Although doses up to 260 mg QD may be evaluated in future clinical studies with PF-07081532, the proposed dose of 20 mg is viewed as appropriate for this study, given the potential of increased exposures in participants with renal impairment. Since no greater than dose-proportional increases in exposure of PF-07081532 have been observed over the range of clinical doses tested so far (up to single dose of 200 mg and up to 180 mg QD), the results from this study may be used to extrapolate and inform the effect of renal impairment on PK over doses exceeding 20 mg.

4.4. End of Study Definition

The end of the study is defined as the date of follow-up as 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 phases of the study, including the follow-up (telephone contact or onsite visit per investigator discretion) as shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. Use of a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, and race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

5.1.1. Participants in All Groups

Type of Participant and Disease Characteristics:

1. Stable renal function (**for participants not on dialysis**) defined as ≤25% difference between 2 measurements of BSA-unnormalized eGFR (calculated by the sponsor-approved laboratory using the 2021 CKD-EPI Scr-Scys combined equation as described in Section 4.1) obtained at Screening visits S1 and S2. The average of the 2 eGFR values obtained from S1 and S2 will be used for study enrollment and assignment to appropriate renal functiongroup (see Table 1. ***Note:*** participants on dialysis will be placed in Group 4 regardless of eGFR value (S2 is optional for dialysis participants, **only**).

2. A prior diagnosis of T2DM with an HbA1c ≥6% and ≤10.5%, at Screening visit S1, confirmed by a single repeat, if deemed necessary.

Age and Sex:

3. Male and female participants ≥18 years of age (or the minimum country-specific age of consent if >18), at the time of providing informed consent.

    - Women may be of child-bearing potential, however, cannot be pregnant, breastfeeding, or planning to become pregnant while participating in the study. Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Weight

4. BMI of 17.5 to 45.4 kg/m^2, inclusive; and a total body weight >50 kg (110 lb), at Screening visit S1.

Other Inclusion Criteria:

5. Stable concomitant medications for the management of medical conditions relevant to an individual participant's medical history. Participants receiving fluctuating concomitant medications/treatments may be considered, ***on a case-by-case basis*** with approval from sponsor, if the underlying disease is stable.

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

7. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations (as described in Section 5.3), and other study procedures.

5.1.2. ***Additional*** Inclusion Criteria for Participants with Normal Renal Fuction (Group 1)

1. Normal renal function (mean eGFR ≥90 mL/min) based on an **average** of measures from Screening visits S1 and S2 (eGFR should be calculated using the **2021** CKD-EPI Scr-Scys combined equation, as described in Section 4.1).

2. Demographically comparable to participants with impaired renal function at Screening visit S1:

   a. A body weight within ±15 kg of the mean body weight of the pooled renal impairment groups (Groups 2, 3 and 4), as provided by sponsor;

   b. An age within ±10 years of the mean age of the pooled renal impairment groups (Groups 2, 3 and 4), as provided by sponsor;

   c. **Attempts will be made** to ensure that the male to female distribution in Group 1 is comparable to that in the pooled renal impairment groups (Groups 2, 3 and 4).

5.1.3. ***Additional*** Inclusion Criteria for Participants with Impaired Renal Function (Groups 2-4)

1. Meet the eGFR criteria listed for Groups 2, 3, or 4 (for participants not on dialysis) in Table 1 based on an average of measures from Screening visits S1 and S2 (eGFR should be calculated using the **2021** CKD-EPI Scr-Scys combined equation, as described in Section 4.1).

2. For Group 4 participants on dialysis **only**, participants must have required hemodialysis for at least 6 weeks prior to Screening visit S1 and need dialysis sessions 3 times per week. ***Note:*** participants on dialysis will be placed in Group 4 regardless of eGFR from S1 and S2 (S2 is optional for dialysis participants, **only**).

5.2. Exclusion Criteria

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

5.2.1. Participants in All Groups

Medical Conditions:

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

- ***NOTE*:** Participants who have undergone cholecystectomy and/or appendectomy are eligible for this study as long as the surgery occurred more than 6 months prior to Screening visit S1.

2. Any malignancy not considered cured (except basal cell carcinoma and squamous cell carcinoma of the skin); a participant is considered cured if there has been no evidence of cancer recurrence in the previous 5 years.

3. Diagnosis of type 1 diabetes mellitus or secondary forms of diabetes, or history of diabetic ketoacidosis.

4. History of myocardial infarction, unstable angina, arterial revascularization, stroke, New York Heart Association Functional Class II-IV heart failure, or transient ischemic attack within 3 months of Screening visit S1.

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

6. History of acute pancreatitis within 6 months before Screening visit S1 or any history of chronic pancreatitis.

7. Urinary incontinence.

8. Participants with acute renal disease.

9. Renal allograft recipients.

10. Participants who have previously received a kidney, liver, or heart transplant.

11. Other medical or psychiatric condition including recent (within the past year) 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.

    NOTE: Participants who have chronic conditions other than T2DM (for example, hypercholesterolemia or hypertension) but are controlled by either diet or stable doses of 2 or fewer medications may be included (for example, a participant with hypercholesterolemia on appropriate treatment is eligible). See Section 6.9 for further information on concomitant medications.

Prior/Concomitant Therapy:

12. Use of prohibited prior/concomitant therapies as outlined in Section 6.9, Appendix 9 and Appendix 10.

Prior/Concurrent Clinical Study Experience:

13. Previous administration with an IP (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Investigational products [redacted] are prohibited within 14 days plus 5 half-lives prior to the dose of study intervention.

14. 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:

15. At Screening (S1), standard 12-lead ECG that demonstrates a clinically relevant abnormality that requires further diagnostic evaluation or intervention (eg, new, clinically relevant arrhythmia, conduction disturbance, findings suggestive of ischemia). A potential participant whose pre-dose ECG (on Day 1, 0 hour) demonstrates a clinically relevant abnormality that requires further diagnostic evaluation or intervention will be considered a screen failure.

16. A positive drug test at Screening (S1). However, participants in **Groups 2-4,** only, who have been medically prescribed medications, eg. opiates, opioids, cannabinoids, benzodiazepines, methylphenidate (or similar), and report the use of these drugs to the investigator at the screening visit may be allowed to participate, after approval from the sponsor, and if in line with protocol specifications regarding prohibited medications (see Section 6.9, Appendices 9 and 10).

    NOTE: Repeat drug testing to assess study eligibility is **not** permitted in this study.

17. At screening ***or*** Day -1, a positive breath alcohol test, as assessed using kits approved by sponsor; for the screening test, a single repeat (which may be on a separate day) before Day -1 is permitted to assess eligibility, if needed.

18. For females, pregnancy, as indicated by a positive serum pregnancy test at screening and/or positive urine pregnancy test in WOCBP at Day -1.

19. Participants with ANY of the following abnormalities in clinical laboratory tests at Screening (S1), as assessed by the study-specific local laboratory and confirmed by a single repeat test, if deemed necessary:

    - 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.

    - Fasting C-peptide <0.8 ng/mL.

- FPG >270 mg/dL (15 mmol/L).

20. ***If performed*** at investigator discretion, safety related laboratory tests collected on Day -1, upon review prior to dosing reflect the participant not to be in stable medical condition.

Other Exclusion Criteria:

21. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing and until the Follow-up contact.

22. History of sensitivity to heparin or heparin-induced thrombocytopenia, only if heparin is used to flush IV catheters used during serial blood collections.

23. History of regular alcohol consumption exceeding 7 drinks/week for female participants or 14 drinks/week for male participants (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months before Screening visit S1.

24. 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.

5.2.2. ***Additional*** Exclusion Criteria for Participants with Normal Renal Function (Group 1)

Participants presenting with any of the following will ***not*** be included in the study:

1. Any of the following abnormalities in clinical laboratory tests at Screening, as assessed by the sponsor-approved laboratory and confirmed by a single repeat test, if deemed necessary:

   - AST level ≥1.5 × ULN **or**

   - ALT level ≥1.5 × ULN.

2. At Screening (S1), seated SBP ≥160 mmHg and/or DBP ≥100 mmHg after ≥5 minutes of seated rest. If BP is ≥160 mm Hg (systolic) or ≥100 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.

5.2.3. ***Additional*** Exclusion Criteria for Participants with Impaired Renal Function (Groups 2, 3, and 4)

Participants presenting with any of the following will ***not*** be included in the study:

1. At Screening, Day -1 or Day 1, persistent severe, uncontrolled hypertension as outlined below:

   - **Groups 2, 3 and 4 at Screening (S1) or Day -1:** ***seated*** SBP ≥180 mmHg or DBP ≥105 mmHg after ≥5 minutes of seated rest, with a single repeat permitted at each of these 2 visits to assess eligibility, if needed; if done, the repeat assessment overrides initial results.

     NOTE*:* For participants with SBP ≥160 and ≤179 mmHg ***or*** DBP ≥100 and ≤104 mmHg at Screening, the period between Screening and Day -1 may be used to refine the doses of the agents used for management of BP with the aim of having stable BP by Day -1.

   - **Groups 2 and 3 *only*, at Day 1**: ***seated*** SBP ≥160 mmHg or DBP ≥100 mmHg after ≥5 minutes of seated rest, with a single repeat permitted to assess eligibility, if needed; if done, the repeat assessment overrides initial results.

   - **Group 4 *only*, at Day 1**: ***seated*** SBP ≥160 mmHg or DBP ≥105 mmHg after ≥5 minutes of seated rest, with a single repeat permitted to assess eligibility, if needed; if done, the repeat assessment overrides initial results.

2. Any of the following abnormalities in clinical laboratory tests at Screening, as assessed by the sponsor-identified laboratory and confirmed by a single repeat test, if deemed necessary:

   - AST ≥2 × ULN **or**

   - ALT level ≥2 × ULN.

3. For participants in **Group 4 on dialysis only**: Hemodynamic instability during or at the conclusion of dialysis during the 2 weeks prior to dosing on Day 1, as marked by symptomatic hypotension.

5.3. Lifestyle Considerations

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

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

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

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to all fasting clinical laboratory evaluations and at least 8 hours prior to the collection of the pre-dose PK sample on Day 1.

- Water may be consumed as desired (ad libitum).

- On **Day 1**, following an overnight fast of at least 8 hours, participants should begin a standard, non-high fat breakfast approximately 30 minutes prior to PF-07081532 administration. The breakfast will be consumed over approximately a 20-minute period with PF-07081532 administered within approximately 10 minutes after completion of the meal. Participants will be encouraged to complete the entire breakfast. There will be no water restrictions prior to dosing.

- Otherwise, while inpatient, all meals will be standardized as follows:

    - Standard morning meal, lunch, an optional afternoon snack, an evening meal, and an optional evening snack will be provided at a similar clock time to the clock time when these meals are provided relative to dosing on Day 1 while inpatient (ie, approximately 0H, 4H, 6H [optional snack], 10H, and 14H [optional snack]).

    - The total daily nutritional composition should be approximately 55% carbohydrate, 30% fat and 15% protein. The nutritional macronutrient composition consumed by each participant should be maintained, as much as practically possible.

- The daily caloric intake per participant should not exceed approximately 3,200 kcal.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to Day 1 and until collection of the final PK blood sample.

- When a meal or snack 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.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will abstain from alcohol for ≥24 hours prior to admission for inpatient stay on Day -1 (and for red wine, abstain for at least 7 days prior to Day 1), and continue abstaining from alcohol until collection of the final PK blood sample.

    - Participants will undergo breath alcohol tests at timepoints indicated in the SoA, and at the discretion of the investigator.

- Consumption of caffeinated drinks and tobacco (or nicotine containing products) is permitted during participation in the study; however, there may be a need for brief interruption while at the site, depending on local site policy. In addition:

    - Participants must abstain from caffeine-containing products for a minimum of 2 hours prior to all vital signs and ECG measurements conducted throughout study participation (from Screening S1 to the final Follow-up contact).

    - Smoking may not be permitted when it would interfere with the timing of scheduled study procedures. In addition, participants must abstain from use of tobacco- or nicotine-containing products: for a minimum of 2 hours prior to all vital sign and ECG measurements; for a minimum of 2 hours prior to and following administration of study intervention.

5.3.4. Activity

- Participants will ***not*** be permitted to engage in physically strenuous exercise (for example: heavy lifting, weight training, calisthenics, and aerobics) within 48 hours before each blood sample collection for clinical laboratory tests while participating in the study; physical activity at an individual participant's normal pace is permitted.

- In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for study procedures eg, 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.

In this study, participants may be rescreened only after contact with a sponsor Clinical representative. This may be permitted when, for example, a participant who qualified for this study but did not enroll within the protocol prescribed screening period of 28 days due to logistical constraints or administrative reasons. In addition, **for participants in Groups 2-4 only**, rescreening may be appropriate following mild intercurrent illness after the condition has resolved. Otherwise, individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened.

In case of re-screening, all screening procedures must be repeated and the participant assigned a new 8-digit SSID number. Participants must be deemed to meet all the eligibility criteria under the new 8-digit SSID *before* progressing to Day 1. Reconsent is required.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct. For the purposes of this protocol, study intervention refers to PF-07081532.

6.1. Study Intervention(s) Administered

Study Intervention(s)	
Intervention Name	PF-07081532
Arm Name (group of participants receiving a specific treatment or no treatment)	Group 1, Group 2, Group 3, Group 4
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength(s)	20 mg
Dosage Level(s)	20 mg, single dose
Route of Administration	Oral
Use	Experimental
IMP or NIMP/AxMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to the IPM.
Packaging and Labeling	Study intervention will be provided as open-label supply in bulk bottles along with individual dose containers, as necessary, for unit dosing.
Current/Former Name(s) or Alias(es)	PF-07081532 20 mg tablets

Study Arm(s)				
Arm Title	Group 1	Group 2	Group 3	Group 4
Arm Type	Experimental	Experimental	Experimental	Experimental
Arm Description	Participants without renal impairment will receive a single 20 mg dose of PF-07081532, administered orally	Participants with mild renal impairment will receive a single 20 mg dose of PF-07081532, administered orally	Participants with moderate renal impairment will receive a single 20 mg dose of PF-07081532, administered orally	Participants with severe renal impairment will receive a single 20 mg dose of PF-07081532, administered orally
Associated Intervention Labels	PF-07081532	PF-07081532	PF-07081532	PF-07081532

PF-07081532 will be supplied by Pfizer as 20 mg tablets in open-label bulk bottles along with individual dosing containers, as necessary, for unit dosing. Participants will take 1 tablet orally, with the morning meal as described in Section 5.3.2.

6.1.1. Administration

Following an overnight fast of at least 8 hours, participants will receive breakfast as outlined in Section 5.3.2 (Meals and Dietary Restrictions). The participants will then receive study intervention at approximately 08:00 hours (plus or minus 2 hours) on Day 1. Investigator site personnel will administer study intervention with ambient temperature water to a total volume of ***approximately 240 mL***. Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

6.2. Preparation, Handling, Storage, and Accountability

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

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

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported toPfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to the labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM.

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

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

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

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. 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 as described in the IPM.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant, in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

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

6.3. Assignment to Study Intervention

This is an open-label study. Following completion of informed consent at Screening visit S1, each participant will be assigned a single 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 of when informed consent is obtained. Each participant who is dosed with the study intervention will be assigned a separate, distinct number (as provided to the site by the Sponsor) to enable execution of Sponsors'standard processes for analysis of PK 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 study intervention was ingested.

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

6.6. Dose Modification

Dose modification of PF-07081532 is not allowed.

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

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

6.8. Treatment of Overdose

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

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 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

All concomitant treatments (both prescription and over-the-counter) 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 study intervention dosing on Day 1 will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

Participants on certain medications are excluded from the study (see Appendix 9 for list of prohibited medications due to potential DDI and Appendix 10 for a list of other prohibited medications). Sites are encouraged to contact the sponsor should there be questions as to whether a medication is permitted or prohibited.

Females using hormonal contraceptives or taking hormone replacement therapy are eligible to participate in this study. See Appendix 4 for hormonal contraceptives that are permitted in this study.

Participants with T2DM and either normal renal function or renal impairment are permitted to be on stable doses of background medications for the management of their concomitant medical condition(s), as long as this is in line with protocol specifications regarding prohibited medications as described in this Section and in Appendix 9 and Appendix 10. On a **case-by-case basis**, with approval from the sponsor, participants receiving fluctuating concomitant medication/treatment may be considered if the underlying disease is under control. ***Whenever possible***, attempts must be made to ***not*** add new medications or alter the doses and regimens of the concomitant medications after enrollment and for the duration of participation in this study, except in circumstances where a change is deemed medically necessary. Any changes must be captured in the CRF.

In addition, participants with T2DM using insulin are permitted to have sliding scale insulin or dose adjustment in insulin while confined to the CRU to attempt to maintain fasting and post-prandial glucose readings at similar levels that are achieved at home and based on the calories consumed while confined in the CRU.

Participants may receive permitted background medications according to their stable medication routine at their usual dosing times. This is with the exception of phosphate binders, antacids, and bile acid binding resins (eg, cholestyramine, colestipol), which must not be administered within the 8 hours before study intervention dosing on Day 1 or within the 4 hours after study intervention dosing. **On Day 1**, the investigator will determine the appropriate time to administer medications that are to be taken on an empty stomach. Otherwise, permitted concomitant medications that may be administered under fed conditions can be taken with breakfast on the morning of Day 1. On all other study days, participants are to receive their background medications at their usual times.

6.9.1. Rescue Medicine

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is N/A.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

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

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

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

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants may be rescreened after contact with a sponsor Clinical representative as described in Section 5.4.

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

If done around the time of a blood draw, ECGs and vital sign assessments (pulse rate, BP, and temperature) 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 150 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, neck, skin, heart and lung examinations, lymph nodes, and GI, musculoskeletal, and neurological systems.

A limited 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 regulations.

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

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

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Pulse Rate

BP and pulse rate will be measured as defined in the SoA.

- ***Single, seated*** BP and pulse rate will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mmHg, following a seated rest of **≥5 minutes**;
- Same arm (preferably the dominant arm) will be used for BP/pulse rate assessment throughout the study;
- BP/pulse rate assessment should not be taken from the arm with an IV catheter, if placed;
- Participants should be instructed not to speak during BP/pulse rate 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

Supine standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for **at least 5 minutes** in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. 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 2-4 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.

8.3.4.1. Fasting Fingerstick Blood Glucose (via Glucometer)

Investigators will monitor fasting FSBG using a glucometer. While the participant is confined to the CRU, FSBG measurements should be taken each morning before breakfast.

FSBG readings will be maintained at the CRU in source documents, and only the glucose results from the laboratory will be reported in the study database. The sites may share the FSBG readings with the sponsor, if necessary for the purpose of safety monitoring, but these data will be stored in the CRU source documents unless related to an AE as described in Section 8.3.4.2.

If an FSBG result is <70 mg/dL

- A **second FSBG** should be obtained to confirm the glucose value – this is **in addition to a venous sample** that will be sent to the clinical laboratory for confirmation.
- If the value from this second FSBG is also <70 mg/dL, the **second value** will be recorded as an HAE (see Section 8.3.4.2) and must be captured on the AE CRF, with specific details captured on the HAE CRF.
- FSBG will continue to be monitored until the glucose value returns to ≥70 mg/dL. Samples may be taken more frequently if deemed necessary by the investigator.

FSBG readings from a glucometer are permitted at any time if the investigator or participant notes symptoms of hypoglycemia. Any episode of hypoglycemia must be captured on the AE CRF with specific details captured on the HAE Form CRF.

8.3.4.2. Definition and Severity of Hypoglycemic Adverse Event

The investigator must assess any glucose values, if measured, as well as any signs or symptoms reported by the study participant.

HAE is defined as one of the following:[13]

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

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

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

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

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

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

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

3. Either:

    - If blood glucose was measured and was ≤54 mg/dL (2.7 mmol/L) using glucometer (or laboratory); **or**
    - If blood glucose was not measured, the clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or IV glucose.

Events that do not meet all the criteria above for severe HAE are characterized as mild or moderate in severity.

8.3.5. 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.

8.3.6. Pregnancy Testing

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

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

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
- A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.

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

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

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

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

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

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

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

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

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

8.5. Pharmacokinetics

8.5.1. Plasma for Analysis of PF-07081532

Blood samples of approximately 3 mL, to provide a minimum volume of 1 mL plasma, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of PF-07081532 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples will be used to evaluate the PK of PF-07081532. Samples collected for analyses of plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

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

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

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

8.5.2. Plasma for Determination of PF-07081532 Unbound Fraction

During the study, blood samples of approximately 10 mL to provide sufficient plasma (approximately 4 mL) for unbound fraction determination, will be collected into appropriately labeled tubes containing K_2EDTA, as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples collected for analyses of PF-07081532 plasma protein binding 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 plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

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

The samples for determination of PF-07081532 plasma protein binding 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.

8.5.3. Urine for Analysis of PF-07081532

Urine will be collected at times specified in the SoA (NOTE that ***no*** urine will be collected for anuric dialysis participants).

- ***Prior to dosing*** on Day 1, each participant must complete a forced void with an aliquot (approximately 10 mL) from this urine (urine blank), labeled and stored frozen for measurement of drug concentrations, per detailed instructions offered in a laboratory manual prior to the start of the study.

- ***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, as specified in the SoA.

    - At the end of each collection interval, participants must complete a forced void with this complete void included as part of the interval collection. Each collection interval should have its own collection container.

- At the end of each urine collection interval, all urine collected in the associated collection container will be mixed thoroughly and total volume plus weight of the urine collected during the interval will be recorded. Subsequently, a urine aliquot (approximately 2 mL) will be withdrawn for measurement of PF-07081532 concentrations.

Details regarding the processing, storage and shipping of the samples will be provided in the laboratory manual. Samples collected for urine analyses of PF-07081532 may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study. The urine samples must be processed as indicated to maintain sample integrity. Any deviations from the urine sample processing steps given in the protocol or lab manual, including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation. Samples for urine PK analysis of PF-07081532 will be analyzed using validated analytical methods in compliance with Pfizer SOPs.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

A 2 mL blood sample optimized for DNA isolation Prep D1.5 will be collected according to the SoA, as local regulations and IRBs/ECs allow.

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

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

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8.7.2. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

8.7.3. Specified Protein Research

Specified protein research is not included in this study.

8.7.4. Specified Metabolomic Research

Specified metabolomic research is not included 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.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

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

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to 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.

Participant Analysis Set	Description
Safety analysis set	All participants assigned to study intervention and who take at least 1 dose of study intervention.
PK Concentration Set	The PK concentration population is defined as all participants who received at least 1 dose of PF-07081532 and in whom at least 1 plasma concentration value is reported.
PK Parameter Set	The PK parameter analysis population is defined as all participants who received at least 1 dose of PF-07081532 and have at least 1 of the PK parameters of interest calculated.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. General Considerations

Endpoints will be reported and analyzed according to the renal impairment group to which participants actually belong, based on their average eGFR value (see Table 1).

9.3.1.1. Analyses for PK Endpoints

Natural log-transformed PK parameters will be analyzed using an ANOVA model including renal impairment group as fixed effect. Estimates of the adjusted means and of the adjusted mean differences (Test-Reference) with their corresponding 90% CIs will be obtained before being exponentiated to provide estimates of the adjusted geometric means and of the ratio of adjusted geometric means (Test/Reference).

9.3.2. Primary Endpoint(s) Analysis

9.3.2.1. Definition of Endpoint(s)

The plasma PK parameters for PF-07081532 following single dose administration will be derived from the concentration-time profiles as detailed in Table 2. Actual PK sampling times will be used in the derivation of plasma PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of plasma PK parameters. The fraction of PF-07081532 unbound in plasma (f_u) will be determined by the analytical lab and reported for each participant.

The urine PK parameters listed in Table 3 will be calculated for PF-07081532.

Table 2. Plasma PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}).	Linear/Log trapezoidal method.
AUC_{inf}*	Area under the plasma concentration-time profile from time zero extrapolated to infinite time.	$AUC_{last} + (C_{last}*/k_{el})$, where C_{last}* is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	Maximum plasma concentration.	Observed directly from data.
T_{max}	Time for C_{max}.	Observed directly from data as time of first occurrence.
$t_{1/2}$*	Terminal half-life.	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear Concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F*	Apparent clearance.	$Dose/AUC_{inf}$.
V_z/F*	Apparent volume of distribution.	$Dose/(AUC_{inf} \cdot k_{el})$.
fu	Fraction of unbound drug in plasma.	Cu/C (where Cu represents unbound concentration and C represents total concentration).
$AUC_{last,u}$	Unbound AUC_{last}.	$fu \cdot AUC_{last}$.
$AUC_{inf,u}$*	Unbound AUC_{inf}.	$fu \cdot AUC_{inf}$.
$C_{max,u}$	Unbound C_{max}.	$fu \cdot C_{max}$.
CL_u/F*	Unbound CL/F.	$Dose/AUC_{inf,u}$.
$V_{z,u}$/F*	Unbound V_z/F.	$Dose/(AUC_{inf,u} \cdot k_{el})$.

* as data permit.

Table 3. Urine PK Parameters

Parameter	Definition	Method of Determination
Ae_{24}	Total amount of unchanged drug excreted in urine over 24 hours.	Sum of amount excreted for each collection period.
Ae_{24}%	Total amount of unchanged drug excreted in urine over 24 hours, expressed as percent of dose.	$100 \cdot (Ae_{24}/Dose)$
CL_r	Renal clearance.	Ae_{24}/AUC_{24}.

9.3.2.2. Main Analytical Approach

The effect of varying degrees of renal impairment on PK parameters will be assessed by constructing 90% CIs around the estimated difference between each of the Test (renal impaired) groups and the Reference (without renal impairment) group. A one-way ANOVA will be used to compare the natural log transformed PF-07081532 AUC_{inf}, C_{max}, AUC_{last}, f_u, and associated unbound parameters ($AUC_{inf,u}$, $C_{max,u}$, $AUC_{last,u}$), as data permit, for each of the renal impairment groups (Test) to the group without renal impairment (Reference). Estimates of the adjusted mean differences (Test - Reference), and corresponding 90% CIs, will be obtained from the model. These will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

Individual PF-07081532 concentrations will be listed and summarized descriptively by nominal PK sampling time and renal impairment group. Individual participant and summary profiles of the concentration-time data (using actual and nominal times, respectively) will be plotted by renal impairment group for both total plasma PF-07081532 and unbound PF-07081532.

Box and whisker plots for individual PK parameters (AUC_{inf}, AUC_{last}, C_{max}, f_u, $AUC_{inf,u}$, $AUC_{last,u}$ and $C_{max,u}$) will be constructed by renal impairment group and overlaid with geometric means. PK parameters of PF-07081532 will be listed and summarized descriptively by renal impairment group

For summary statistics and median or mean plots by sampling time, the nominal PK sampling time will be used. For individual partivipant plots by time, the actual PK sampling time will be used.

9.3.2.3. Supplementary Analyses

Linear regression may be used to characterize the potential relationship between appropriate PK parameters (eg, CL/F, CL_u/F and CL_r) for PF-07081532 and renal function (eGFR). eGFR values obtained on Day 1 will be included in the regression analysis. Estimates of the statistical slope and intercept, together with their precision (90% CIs), and the coefficient of determination will be obtained from the model.

The effect of covariates such as weight, gender, and age may be explored, and details will be provided in the SAP.

Plots of PK parameters (eg, CL/F, CL_u/F and CL_r) for PF-07081532 versus renal function (eGFR as obtained on Day 1) will be constructed. A regression line and 90% confidence region for the PK parameters and eGFR will be included if appropriate. Vertical lines for the renal function group cut-off values will also be presented on the plots. Different symbols will be used to identify participants from different renal function groups.

Exploratory analyses, similar to those listed above (using the eGFR values determined with the 2021 CKD-EPI Scr-Scys combined equation) may be conducted using eGFR values determined with the 2021 CKD-EPI Scr only, the Cockcroft-Gault or the MDRD formulas as described in the SAP.

9.3.3. Secondary Endpoint Analysis - 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 following sponsor standards.

Medical history and physical examination 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 examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported. Alcohol test results will be considered source data and will not be required to be reported. COVID-19 specific assessment data will remain as source and will not be reported.

9.3.3.1. Electrocardiogram Analyses

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

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

Safety QTcF Assessment

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

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9.3.5. Other Analyses

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

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. 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 32 participants (approximately 8 participants per group, with varying degrees of renal function in each of the 4 groups) has been selected to provide sufficient precision to detect at least a 1.5-fold difference in AUC_{inf} between each Test group (with renal impairment) and the Reference group (without renal impairment). Table 4 presents the 90% CIs (with 80% coverage probability) for various possible effects on AUC_{inf}. The same table would be applicable for possible effects on C_{max}.

Table 4. Expected Widths of the 90% CIs (with 80% Coverage Probability) for Different Possible Estimated Effects

Estimated Effect (Test/Reference)	AUC_{inf}	
	Probable 90% CI	Probable CI Width
75%	52% to 109%	58%
100%	69% to 146%	77%
150%	103% to 218%	115%
200%	137% to 291%	154%
400%	275% to 582%	307%

These estimates are based on an assumed conservative standard deviation of 0.4 for $\log_e AUC_{inf}$ (also applicable to $\log_e C_{max}$) based on data from previous internal studies with PF-07081532 administered either as a single dose in the fed/fasted state in healthy participants (C3991001) or as multiple doses in the fed state in participants with T2DM (C3991002).

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

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

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 5. Protocol -Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis[i]	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) ***Plasma*** Glucose (fasting) Calcium Sodium Potassium Chloride Magnesium Phosphate Total CO_2 (Bicarbonate) AST ALT Alkaline phosphatase GGT Total bilirubin Direct bilirubin[a,b] Indirect bilirubin[a,b] Creatine kinase[a,c] Uric acid Albumin Total protein eGFR[h]	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[d]	**At times specified in SoA:** • Urine pregnancy test (WOCBP ***only***)[f] **At Screening only:** • Serum FSH (***all*** females) • Serum pregnancy test (β-hCG) (***all*** females) • Total bile acids • Amylase • Lipase • HbA1c • C-peptide • Urine drug test[g] **At screening and Day -1:** • Breath alcohol test[e] **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) • CystatinC (Scys) • eGFR[h] • Spot (dipstick) UACR

a. At screening and Day 1, **only**. unless conditions for testing are met after Day 1 per notes "b" and "c" below.

b. After Day 1, direct and indirect bilirubin assessed when total bilirubin is > ULN, **only**.

c. After Day 1, creatine kinase assessed when ALT is > ULN, **only**.

d. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.

e. Testing to be done on-site using kits approved by sponsor.

f. Performed on-site using kits approved by sponsor. For a participant on dialysis who is anuric only, an alternative method (eg, serum) for urine testing may be used.

g. Minimum testing requirements include cocaine, THC, opiates and opioids, benzodiazepines and amphetamines. For a participant on dialysis who is anuric only, an alternative method (eg, saliva) for urine testing may be used.

h. eGFR should be calculated using the **2021** CKD-EPI Scr-Scys combined equations; see Appendix 7.

i. For a participant on dialysis who is anuric only, urinalysis is not required to be collected.

j. For list of abbreviations, refer to Appendix 11.

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

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

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition

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

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

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

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

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

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor**.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT. • If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available. • After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

A female participant is eligible to participate if she (a) is not pregnant or breastfeeding; (b) agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for 28 days after last dose of study intervention; and (c) at least 1 of the following conditions applies:

- Is not a WOCBP (see definition in Section 10.4.3).

  OR

- Is a WOCBP who agrees to use a highly effective contraceptive method (failure rate of <1% per year) with low user dependency during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

  OR

- Is a WOCBP and agrees to use a highly effective (failure rate of <1% per year) user-dependent method of contraception during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition to her use of the highly effective method above, she agrees to concurrently use an effective barrier method. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for reviewing the woman's medical history, menstrual history, and recent sexual activity in order to decrease the risk of enrolling a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner.
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral + barrier*.
    - Intravaginal + barrier*.
    - Transdermal + barrier*.
7. Progestogen only hormone contraception associated with inhibition of ovulation:
    - Oral + barrier*.
    - Injectable + barrier*.
8. Sexual Abstinence.
9. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-07081532 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

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

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

- The samples will be retained as indicated:

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

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, 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. Additionally, baseline and postbaseline serum Scys makes it feasible to distinguish AKI from other causes of Scr increase. In this study, eGFR will be determined using the 2021 CKD-EPI Scr-Scys combined equation (see Table below) and both Scr and Scys will be measured as part of the protocol-required safety laboratory assessments at all times specified in the SoA.

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[14]

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

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

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

• QTcF prolongation >500 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex>120 ms).
• New-onset right bundle branch block (QRS complex>120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

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

ECG Findings That Qualify as SAEs

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

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

10.9. Appendix 9: Prohibited Concomitant Medications 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 participation of any participant with prohibited medication use during the study.

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

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

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

CCI

CCI

[redacted]

CCI

10.10. Appendix 10: Other Prohibited Prior/Concomitant Medications

The following medications are prohibited until the follow-up visit, unless stated otherwise. If a participant receives a prohibited medication, the investigator should contact the sponsor clinician or sponsor medical monitor to determine if the participant should be included in the study/continued in the study.

Drug Classes and/or Drugs	Timeframe of Restriction
Other GLP-1R agonists	90 days prior to Screening visit (S1) until final follow-up contact
DPP-4 inhibitors, pramlintide, repaglinide	Screening visit (S1) until final follow-up contact
Systemic glucocorticoids such as prednisone, dexamethasone, triamcinolone, budesonide, betamethasone. ***Note:*** As an exception, steroid-containing inhalers, nasal sprays and topical formulations are permitted.	Screening visit (S1) until final follow-up contact
Immunosuppressants such as cyclosporine and tacrolimus	Screening visit (S1) until final follow-up contact
Cannabinoids (eg, medically prescribed THC)	Screening visit (S1) until final follow-up contact

10.11. Appendix 11: Abbreviations

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

Abbreviation	Term
Abs	absolute
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
ANOVA	Analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
AV	atrioventricular
AxMP	auxiliary medicinal product
BBS	Biospecimen Banking System
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease epidemiology
CL	clearance
CL/F	apparent clearance
CL_u/F	unbound CL/F
C_{max}	maximum plasma concentration
$C_{max,u}$	unbound C_{max}
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CCI	[redacted]
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CTIS	Clinical Trial Information System

Abbreviation	Term
CCI	[redacted]
DBP	diastolic blood pressure
DCT	data collection tool
DDI	drug-drug interaction
DHT	digital health technology
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
EFD	embryo fetal development
eGFR	estimated glomerular filtration rate
EOT	end of treatment
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clincal Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FIH	first-in-human
FPG	fasting plasma glucose
FSBG	fingerstick blood glucose
FSH	follicle-stimulating hormone
f_u	fraction unbound in plasma/unbound fraction
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
H	hour
HbA1c	hemoglobin A1c
HAE	hypoglycemic adverse event(s)
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure

Abbreviation	Term
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IV	Intravenous(ly)
IVGTT	intravenous glucose tolerance test
K_2EDTA	ethylene diamine tetraacetic acid
KDIGO	Kidney Disease Improving Global Outcomes
LBBB	left bundle branch block
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
MEN2	multiple endocrine neoplasia type 2
MOA	mechanism of action
MQI	medically qualified individual
MTC	medullary thyroid cancer
N/A	not applicable
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
NRU	neutral red uptake
CCI	[redacted]
PD	pharmacodynamic(s)
PE	physical examination
PI	principal investigator
PK	pharmacokinetic(s)
PO	oral
CCI	[redacted]
PR	pulse rate
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	once daily

Abbreviation	Term
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
S1	Screening visit 1
S2	Screening visit 2
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
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 identification
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	type 2 Diabetes Mellitus
$t_{½}$	terminal half-life
T bili	total bilirubin
THC	tetrahydrocannabinol
T_{max}	time for C_{max}
UACR	urine albumin/creatinine ratio
CCI [redacted]	[redacted]
ULN	upper limit of normal
US	United States
V_Z/F	apparent volume of distribution
$V_{z,u}/F$	unbound V_z/F
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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