A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF MULTIPLE ORAL DOSES OF PF-07081532 IN ADULT PARTICIPANTS WITH TYPE 2 DIABETES MELLITUS

Study Intervention Number:	PF-07081532
Study Intervention Name:	N/A
US IND Number:	CCI
EudraCT Number:	N/A
ClinicalTrials.gov ID:	N/A
Protocol Number:	C3991003
Phase:	1

Brief Title: A Phase 1 Study of Multiple Oral Doses of PF-07081532 in Adult Participants With Type 2 Diabetes Mellitus

Document History

Document	Version Date
Original protocol	21 October 2021

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: A Phase 1 Study of Multiple Oral Doses of PF-07081532 in Adult Participants With Type 2 Diabetes Mellitus

Rationale

The purpose of this study is to evaluate the safety, tolerability, and PK of multiple doses of PF-07081532 in participants with T2DM, inadequately controlled on metformin. The study may also enroll non-diabetic participants with obesity.

The study will also assess the effect on PD biomarkers, including MDG.

Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of multiple doses of PF-07081532, administered orally, in adult participants with inadequately controlled T2DM on metformin and if enrolled, in non-diabetic participants with obesity.	• Assessment of AEs, safety laboratory tests, vital signs and 12-lead ECGs.
Secondary:	**Secondary:**
• To characterize plasma PK of PF-07081532 following multiple doses administered orally, in adult participants with inadequately controlled T2DM on metformin and if enrolled, in non-diabetic participants with obesity.	• PF-07081532 plasma PK parameters AUC_{24}, C_{max}, T_{max} on Day 1 and Day 42 and $t_{½}$ on Day 42, as data permit.
Exploratory:	**Tertiary:**
• To characterize the PD effect on glucose, insulin, glucagon, and C-peptide excursions after a MMTT following multiple doses of PF-07081532, administered orally, in adult participants with inadequately controlled T2DM on metformin.	• CFB in response to MMTT at all postdose timepoints as specified in the SoA for $AUC_{(0-4)}$ for glucose, insulin, glucagon, and C-peptide.

Objectives	Endpoints

• To explore the PD effect on MDG*, HbA1c*, plasma glucose, plasma insulin, and HOMA-IR following multiple doses of PF-07081532, administered orally, in adult participants with T2DM inadequately controlled on metformin and, if enrolled, in non-diabetic participants with obesity.	• CFB at all post-dose timepoints as specified in the SoA for:
	  • Fasting plasma glucose;
	  • Fasting plasma insulin;
	  • HOMA-IR;
	  • HbA1c*;
	  • MDG*.

• To assess the PD effect on body weight changes following multiple doses of PF-07081532, administered orally, in adult participants with T2DM inadequately controlled on metformin and if enrolled, in non-diabetic participants with obesity.	• CFB in body weight at all post-dose timepoints as specified in the SoA.
• To further characterize plasma PK of PF-07081532 following multiple doses administered orally, in adult participants with inadequately controlled T2DM on metformin and if enrolled, in non-diabetic participants with obesity.	• Additional PF-07081532 plasma PK parameters following multiple dose administration including, as data permit: AUC_{24}(dn), AUC_{inf}, AUC_{last}, C_{av}, CL/F, C_{max}(dn), C_{min}, R_{ac}, $R_{ac,Cmax}$, PTR, V_z/F

Estimands are not applicable.
*not analyzed in non-diabetic population with obesity, if enrolled.

Overall Design

Brief Summary

This is a Phase 1, randomized, double-blind, sponsor-open, placebo-controlled study to assess the safety, tolerability, and PK of multiple oral doses of PF-07081532 in adult participants with type 2 diabetes mellitus and in non-diabetic participants with obesity, if enrolled.

Number of Participants

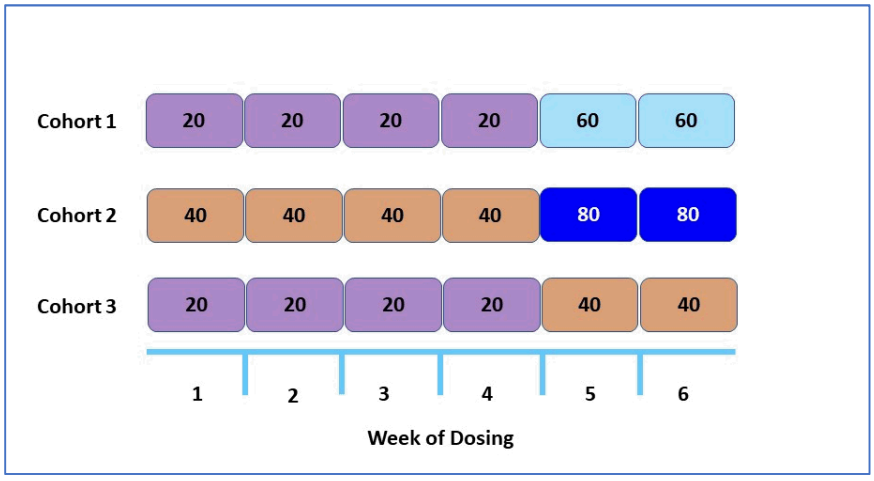
Within each cohort, approximately 12 participants will be randomized to receive either PF-07081532 or placebo (9 PF-07081532: 3 placebo) for a treatment duration of 42 days (approximately 6 weeks).

Intervention Groups and Duration

The duration of the study from the Screening visit to the last follow-up visit will be approximately 16 weeks, of which 52 days will be inpatient at the CRU, followed by a follow up period of 4-5 weeks, post last dose. Screening may take up to 28 days prior to randomization. The treatment period with double-blind study intervention will be once daily, for 42 days.

The study will begin with 3 planned cohorts and may be conducted concurrently, partially overlapping or sequentially. Based on emerging data,up to 3 additional cohorts may be added to evaluate additional doses, dosing schemes, or additional patient population ie, non-diabetic participants with obesity.

A sample dosing scheme with dose designations (in mg/day) for planned cohorts is below. The actual doses, treatment sequence and dose increments will be provided to the investigator, prior to the start of each cohort.



Data Monitoring Committee or Other Independent Oversight Committee: No

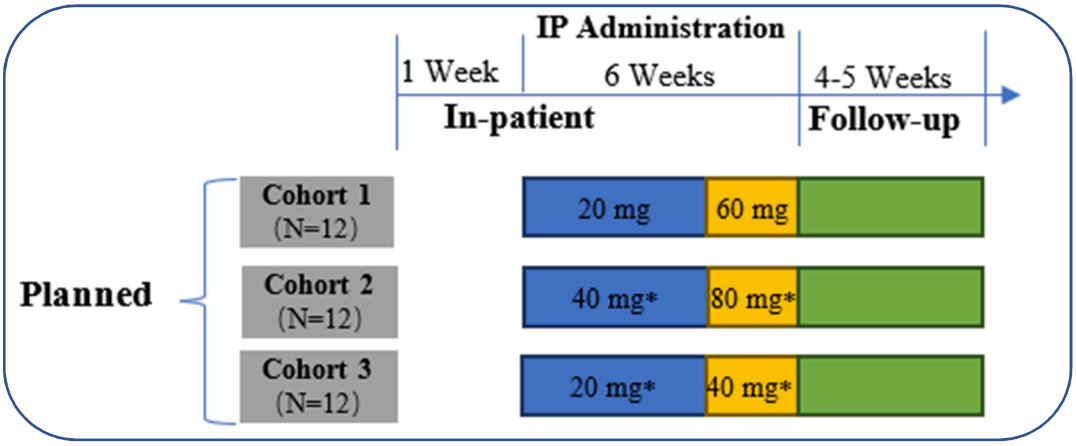
Statistical Methods

Primary endpoint: clinical safety laboratory tests, thorough assessments of vital signs and 12-lead ECGs, physical examinations, and AE monitoring will be performed to provide essential data to evaluate the safety and tolerability of PF-07081532.

Secondary endpoints: PK parameters for PF-07081532 including AUC_{24}, C_{max}, T_{max} on Day 1 and Day 42 and $t_{½}$, following multiple dose administration on Day 42 will be derived from

the concentration-time profiles using non-compartmental methods as data permit, and will be summarized descriptively.

1.2. Schema



Dose levels represent PF-07081532 or matching placebo.
∗ Proposed doses; Dosing in Cohort 1 will be conducted as shown; actual doses, dose increments and dosage duration for subsequent cohorts may be adjusted based on emerging data.
Additional cohorts may be added to explore additional doses and dosing schemes
The cohorts in this study may be run concurrently, partially overlapping or sequentially.

1.3. Schedule of Activities

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

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

Table 1. Overall Visit Schedule and List of Procedures (use with Table 2 for full details)

Protocol Activity	Screen	Study Day (all activities at 0H [prior to dosing] unless otherwise specified)																				Follow-Up		Early Termination
Abbreviations used in this table may be found in Appendix 10.		-7	-1	1	2	3-7	8	9-13	14	15-21	22	23-27	28	29	30-35	36	37-41	42	43	44	45	49-56	70-77[a]	
Outpatient visit (after ≥8-H fast)	x																					x		
Informed consent	x																							
Adverse event monitoring	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x	x	x	x
Demography and height	x																							
Inpatient stay at CRU		x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x			
Medical history	x	x																						
Review drug, alcohol, tobacco use	x	x																				x		
Review prior/concomitant treatments	x	x																				x	x	x
Review contraception use/requirement	x																				x	x	x	x
Physical examination[b]	x	x									x								x					x
Body weight	x	x		x			x		x		x			x		x			x			x		x
COVID-19 questionnaire[c]	x	x																						
COVID-19 testing[d]	x	x																						
COVID-19 check temperature[e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Supine 12-lead ECG[f]	x		See Table 2	See Table 2	x[g]		x		x		x		See Table 2	x		x		See Table 2	x[g]	x	x	x		x
Supine vital signs (blood pressure and pulse)[h]	x				x[g]		x		x		x			x		x			x[g]	x	x	x		x
Fasting fingerstick blood glucose measurement[i]		x			x	x	x	x	x	x	x	x		x	x	x	x		x	x	x			
Standardized meals/snacks[j]		x			x	x	x	x	x	x	x	x		x	x	x	x		x	x	x			
Liquid meal (for MMTT)[k]																								
IP Administration																								
Blinded IP administration[l]					x	x	x	x	x	x	x	x		x	x	x	x							
Blood Sampling for:																								
- Safety laboratory tests[m]	x						x		x							x					x	x		x
- FSH,[n] HIV, HBsAg, HBcAb, HCVAb, HBsAb	x																							
- Free T4, calcitonin, amylase, lipase, HbA1c, TSH, lipids	x																					x		
- Glucose, insulin, C-peptide,[m] glucagon																								
- PF-07081532 PK					x[g]		x		x		x			x		x			x[o]	x[o]	x[o]			x
- 4-β-hydroxycholesterol/cholesterol																								
CCI																								
Urine Sampling for:																								
- Urine drug test	x	x																						
- Urinalysis (and microscopy, as appropriate)	x						x		x							x					x	x		x

a. This follow-up contact may be conducted as a phone call.
b. Full physical exam at times indicated; limited exam for previous findings, new/open AEs, or investigator discretion.
c. Enquire about exposure to positive participant, residence or travel in area of high incidence and check for COVID-19 related signs and symptoms.
d. The testing for COVID-19 pathogen by PCR will be performed at Screening and Admission. At Admission, testing will be done prior to confinement. Additional testing may be conducted at the discretion of the investigator.
e. To be done at least daily during residence.
f. Single 12-lead ECG at Screening, follow-up and Early Termination (if applicable). Measure in triplicate at all other times indicated.
g. Measurement/sample at 0H corresponds to the 24H timepoint as detailed in Table 2 (ie, listed in both tables, but only one sample/measurement should be collected).
h. Single vital signs at Screening, follow-up and Early Termination (if applicable). Measure in triplicate at all other times indicated.
i. Fingerstick glucose via glucometer on admission to CRU and prior to breakfast on all inpatient days; may be more frequent at the discretion of the investigator.
j. Meals to be provided on all days while inpatient at approximately 0H, 4H, and 10H relative to dosing; snacks may be provided. Refer to Section 5.3.
k. This procedure is to be conducted in participants enrolling with T2DM only.
l. Dose administration to occur with breakfast or liquid meal daily on Days 1 to 42, inclusive, see Section 5.3 and Section 6.
m. See Appendix 2 for safety lab tests to be collected at each timepoint, see Section 5.3 for fasting requirements. Note: C-peptide is collected as part of safety labs at Screening.
n. FSH in females to confirm postmenopausal status only.
o. PK samples on Day 43, 44, and 45 are to be collected 24H, 36H, 48H, and 72H after the final PF-07081532 dose on Day 42.

Table 2. Detailed Schedule (selected study days)

	Study Day	Hours Relative to Dosing at 0H[a]													
		0	0.25	0.5	1	1.5	2	3	4	6	8	10	12	16	24[b]
Triplicate, supine 12-lead ECG	Days -1, 1, and 42	x			x		x		x		x		x		x
Triplicate, supine vital sign (blood pressure and pulse)	Days -1, 1, and 42	x			x		x		x		x		x		x
Fasting fingerstick blood glucose measurement[b,c]	All inpatient days	x													
Liquid meal (for MMTT)[d]	Days -1, 28[e] and 42	x													
Standardized meal/snack[f]	all inpatient days	x[g]							x			x		x	
Blinded investigational product administration	Daily: Day 1 to Day 42	x[h]													
Blood sampling for:															
- Safety laboratory tests[i]	Days -1, 28, and 42	x[j]													
- HbA1c[k], TSH	Days -1, 28, and 42	x[j]													
- Plasma glucose[l]	Days -1, 28[e] and 42	x[j]	x	x	x	x	x	x	x	x	x	x	x	x	x
- Plasma insulin[l]	Days -1 and 42	x[j, m]	x	x	x	x	x	x	x						
- Plasma C-peptide[k], glucagon[k])	Days -1 and 42	x[j]	x	x	x	x	x	x	x						
- Free T4, calcitonin, amylase, lipase, lipids	Days -1, 28, and 42	x[j]													
- PF-07081532 PK	Days 1 and 42	x		x	x		x		x	x	x	x	x	x	x
- 4-β-hydroxycholesterol/cholesterol	Days 1 and 42	x													
- Retained research samples for Prep D1.5	Day -1 only[n]	x													
- Retained research samples for Prep B1.5 and Prep B2.5	Day -1 and Day 42	x													
Urine sampling for:															
- Urinalysis and microscopy, as appropriate	Days -1, 28, and 42	x													

a. On Day -1, time of 0H procedures to match approximate planned clock time of collection on Day 1. All other days, 0H procedures to be completed pre-dose.
b. The 24H sample is to be collected prior to dosing on the following morning, as indicated in Table 1.
c. Fingerstick glucose via glucometer on admission to CRU and prior to breakfast on all inpatient days; may be more frequent at the discretion of the investigator.
d. Liquid meal given at 0H (or on Day -1 at the anticipated clock time of Day 1 dose) to be consumed over 10 mins. The 0.25 H sample is 5 minutes after completion of the liquid meal. This procedure is to be conducted in participants enrolling with T2DM only.
e. Indicated procedures will be conducted on Days -1, 28, and 42 for Cohort 1; decision for Day 28 procedures in subsequent cohorts will be provided in writing prior to initiation of dosing for each cohort.
f. Standardized meals/snacks to be provided on all days while inpatient; identical meals/snacks on days when MMTT is being conducted. Refer to Section 5.3.
g. Standard breakfast NOT provided on days when MMTT is being conducted; refer to Section 5.3.
h. Dosing to occur with breakfast or liquid meal daily from Day 1 to day 42, inclusive.
i. See Appendix 2: Clinical Laboratory Tests for safety lab tests to be collected at each timepoint.
j. See Section 5.3 for fasting requirements.
k. Participants enrolling with T2DM only.
l. Fasting (0H) sample is to be collected in all participants. Post-dose timepoints in participants enrolling with T2DM only.
m. Fasting (time 0H ***only***) insulin to be measured in triplicate on Day -1 and Day 42, all other measurements single, see Section 8.9.2.
n. 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.

2. INTRODUCTION

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

PF-07081532 is a potent and selective, orally administered, small molecule GLP-1R agonist that is being developed as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

2.1. Study Rationale

The purpose of the study is to evaluate the safety, tolerability and PK of multiple doses and different dosing schemes of PF-07081532 in participants with T2DM, inadequately controlled on metformin and, if enrolled, in non-diabetic participants with obesity.

The study will also assess the effect of PF-07081532 on PD biomarkers, including MDG in participants with T2DM.

2.2. Background

Diabetes is estimated to affect approximately 425 million adults (8.8% of people aged 20-79 years) world-wide. [5,6] . The increase in the global prevalence of T2DM is largely attributed to rising rates of excess body weight and obesity.[7]

T2DM is characterized by insulin resistance, a disorder in which cells do not respond effectively to insulin, resulting in higher blood glucose levels. Elevated blood glucose levels and increasing severity of insulin resistance result in the need for more insulin over time, eventually resulting in progressive pancreatic β-cell failure.[8] Patients with poorly controlled T2DM have an increased risk of developing complications associated with both microvascular and macrovascular disease, including nephropathy, neuropathy, retinopathy, cardiovascular disease and stroke, and are at 2 to 4 times increased risk of mortality than adults who do not have diabetes.[9] While existing pharmacological options for the treatment of diabetes may provide satisfactory glycemic control for some patients, there remain many patients who do not achieve target HbA1c levels, suggesting a need for additional therapeutic options.

Based on the clinical history of injectable GLP-1R agonists, an oral GLP-1R agonist is expected to improve glucose control and reduce HbA1c levels in patients with T2DM, while decreasing food intake and body weight and avoiding the subcutaneous injection required by a majority of currently available peptidic GLP-1R agonists.

2.2.1. Nonclinical Overview

2.2.1.1. Nonclinical Pharmacology

In vitro primary pharmacodynamic studies demonstrated that in cells expressing recombinant human and monkey GLP-1R, PF-07081532 promotes cAMP production. CCI

CCI [redacted]. 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.

2.2.1.2. Nonclinical Pharmacokinetics and Metabolism

CCI [redacted]

CCI [redacted]

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

2.2.1.3. Nonclinical Safety

PF-07081532 was evaluated in genetic toxicity studies and oral, repeat-dose rat and cynomolgus monkey toxicity studies as well as cardiovascular and neuropulmonary safety pharmacology studies. CCI [redacted]

In the 8-week oral gavage toxicity study conducted in cynomolgus monkey at 20, 60, and 100 mg/kg/day, no adverse effects were detected and the NOAEL was defined as the high dose of 100 mg/kg/day. CCI [redacted]

A 6-week oral gavage toxicity study was conducted in Wistar Han rats with PF-07081532 and the intermediate dose of 100 mg/kg/day was considered to be the NOAEL CCI [redacted]. Details of both studies can be found in the IB.

Safety pharmacology studies conducted to assess potential pharmacodynamic effects on central nervous and respiratory systems did not identify any effects at doses up to 300 mg/kg in rats. CCI [redacted]

PF-07081532 was not mutagenic or clastogenic both in vitro and in vivo (rat micronucleus study) and was negative for phototoxic potential.

2.2.2. Clinical Overview

The safety of PF-07081532 has been assessed in 1 completed clinical Study C3991001, and is being assessed in 1 ongoing clinical Study C3991002.

Table 3. Completed and Ongoing Clinical Studies

Study Identifier	Study Design and Type of Control	Dosing Regimen, Formulation Dose	Number of Participants Randomized	Population	Treatment Duration	Study Status
C3991001	Phase 1, double-blind, randomized, placebo controlled, single ascending dose study. Two interleaving cohorts of healthy adult participants with crossover, placebo substitution design. One cohort of healthy adult Japanese participants with crossover placebo substitution design.	PF-07081532 or placebo. Orally administered solution Dose Range: 10 mg to 200 mg	PF-07081532: 22 Placebo: 12	Healthy Adult Participants	Single dose	Completed
C3991002	Phase 1, randomized, double-blind (investigator- and participant-blind), sponsor-open, placebo-controlled, multiple oral dose-escalating study.	Orally administered tablet	Part A: 10 (8 PF-07081532: 2 placebo) planned participants/cohort		Multiple doses	Ongoing: dosing completed, data analysis and reporting ongoing
		Target dose range: PF-07081532 10 mg to 180 mg or placebo		Adult Participants with T2DM	28 days' dosing	
		Target dose PF-07081532 180 mg or placebo	Part B: 15 (12 PF-07081532: 3 placebo) planned participants/cohort	Adult Participants with Obesity	42 days' dosing	
		Target dose PF-07081532 180 mg or placebo	Part C: 10 (8 PF-07081532: 2 placebo) planned participants/cohort	Adult Participants with T2DM	42 days' dosing	

2.2.2.1. Clinical Safety

Clinical data for the completed study, C3991001, are provided in the current version of the IB.

A blinded summary of currently available data from study C3991002 is provided below. These data should be considered preliminary and subject to update on final reporting of the study's results. PF-07081532 or matching placebo have been administered to a total of 51 participants with T2DM and 15 participants with obesity. A dose titration approach was used, where doses within a cohort were titrated up to a target dose over the dosing period. The duration of titration varied across cohorts. The target doses ranged from 10 mg (no titration phase) to 180 mg PF-07081532 or matching placebo. Each cohort was expected to receive study drug at the target dose level for a minimum stable dosing period of 7 days.

Four cohorts of participants with T2DM have been randomized to receive doses of PF-07081532 (target doses of 10 mg to 120 mg) or matching placebo once daily for 28 days. One cohort of 10 participants with T2DM has been randomized to receive PF-07081532 titrated to a target dose of 180 mg, or matching placebo, once daily for 42 days. One cohort of 15 participants with obesity has been randomized to receive PF-07081532 titrated to a target dose of 180 mg or matching placebo once daily for 42 days. One participant who completed dosing (blinded target dose 30 mg/placebo) experienced an SAE of acute gallstone pancreatitis during the follow-up period. The investigator reported that there was a reasonable possibility that the event was related to blinded study drug. The totality of available data, including medical history, has been reviewed by the Sponsor. The overall evidence, in the opinion of Sponsor, points to gallstone, rather than drug-induced pancreatitis, as the likely cause of this event. There was no change to the benefit/risk profile of PF-07081532, nor was any change to the conduct of the ongoing clinical study judged to be required.

A majority of TEAEs reported have been mild in severity. The most frequently reported TEAEs have been in the GI system as consistent with reports for marketed GLP-1R agonists. While there have been isolated values for laboratory tests, vital signs and ECG intervals outside of the reference ranges, no clear adverse trends were apparent in these parameters. As has been reported for marketed GLP-1R agonists,[10,11] a trend toward modest increases in heart rate has been observed, with most heart rate values within the normal range.

CCI [redacted]

CCI [redacted]

2.3. Benefit/Risk Assessment

This study is designed primarily to generate safety, tolerability, and PK data from adult participants with T2DM and, potentially, participants with obesity and without T2DM. The purpose of the study is to provide the basis for further clinical development of PF-07081532 as a potential new, pharmacological agent for the treatment of T2DM.

Based on the clinical history of injectable GLP-1R agonists, an oral GLP-1R agonist is expected to improve glucose control, reduce HbA1c levels, diminish food intake, and decrease body weight in patients with T2DM, while avoiding the requirement for subcutaneous injections that accompany a majority of currently available peptidic GLP-1R agonists.

As of the issuance of this protocol, no specific human risks associated with PF-07081532 administration have been identified. The doses being evaluated in this study are anticipated to be in the range of doses previously tested. Data gathered during nonclinical and clinical studies with PF-07081532 to date are summarized in the current IB and in Section 2.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention – PF-07081532		
Potential risks associated with marketed GLP-1R agonists including thyroid C-Cell tumors, pancreatitis, changes in heart rate and blood pressure	The potential risks are based on product labeling for marketed GLP-1R agonists (liraglutide, dulaglutide, and exenatide); additional information is provided in the current IB.	• Study includes inpatient monitoring of the participants following administration of multiple, oral doses of the investigational product. • Potential participants with a personal or family history of medullary thyroid carcinoma or MEN2 are not eligible for study entry. Potential participants with acute pancreatitis or a history of chronic pancreatitis are not eligible for study entry. • Clinical safety laboratory tests, including thyroid function, serum amylase and lipase, thorough assessments of vital signs and ECGs, physical examinations and adverse event monitoring will be undertaken throughout the dosing period.
Gastrointestinal adverse events	The potential risks are based on product labeling for marketed GLP-1R agonists (liraglutide, exenatide and	Participants are monitored during the study to prevent potential sequelae of any severe gastrointestinal reactions,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	dulaglutide). In addition, gastrointestinal AEs, the majority of which were mild in severity, have been observed in the clinical program with PF-07081532 to date.	eg, dehydration. Concomitant medication for nausea is permitted in the study
Other Factors Potentially Impacting Study Results		
Risk of COVID-19 exposure	N/A	All participants will be tested for COVID-19 and confirmed negative, prior to admission to the site; once admitted, all participants will be monitored daily for COVID-related symptoms, including fever

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

Considering all available clinical and nonclinical data, the benefit-risk profile of PF-07081532 supports continued clinical development.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of multiple doses of PF-07081532, administered orally, in adult participants with inadequately controlled T2DM on metformin and, if enrolled, in non-diabetic participants with obesity.	• Assessment of AEs, safety laboratory tests, vital signs and 12-lead ECGs.
Secondary:	**Secondary:**
• To characterize plasma PK of PF-07081532 following multiple doses administered orally, in adult participants with inadequately controlled T2DM on metformin and, if enrolled, in non-diabetic participants with obesity.	• PF-07081532 plasma PK parameters AUC_{24}, C_{max}, T_{max} on Day 1 and Day 42 and $t_{½}$ on Day 42, as data permit.
Exploratory:	**Exploratory:**
• To characterize the PD effect on glucose, insulin, glucagon, and C-peptide excursions after a MMTT following multiple doses of PF-07081532, administered orally, in adult participants with inadequately controlled T2DM on metformin.	• CFB in response to MMTT at all postdose timepoints as specified in the SoA for $AUC_{(0-4)}$ for glucose, insulin, glucagon, and C-peptide.

• To explore the PD effect on MDG*, HbA1c*, plasma glucose, plasma insulin, and HOMA-IR following multiple doses of PF-07081532, administered orally, in adult participants with T2DM inadequately controlled on metformin and, if enrolled, in non-diabetic participants with obesity.	• CFB at all post-dose timepoints as specified in the SoA for:
	  • Fasting plasma glucose;
	  • Fasting plasma insulin;
	  • HOMA-IR;
	  • HbA1c*;
	  • MDG*.

Objectives	Endpoints
• To assess the PD effect on body weight changes following multiple doses of PF-07081532, administered orally, in adult participants with T2DM inadequately controlled on metformin and, if enrolled, in non-diabetic participants with obesity.	• CFB in body weight at all post-dose timepoints as specified in the SoA.
• To further characterize plasma PK of PF-07081532 following multiple doses administered orally, in adult participants with inadequately controlled T2DM on metformin and, if enrolled, in non-diabetic participants with obesity.	• Additional PF-07081532 plasma PK parameters following multiple dose administration including, as data permit: AUC_{24}(dn), AUC_{inf}, AUC_{last}, C_{av}, CL/F, C_{max}(dn), C_{min}, R_{ac}, $R_{ac,Cmax}$, PTR, V_z/F.

Estimands are not applicable.
*not analyzed in non-diabetic population with obesity, if enrolled.

4. STUDY DESIGN

4.1. Overall Design

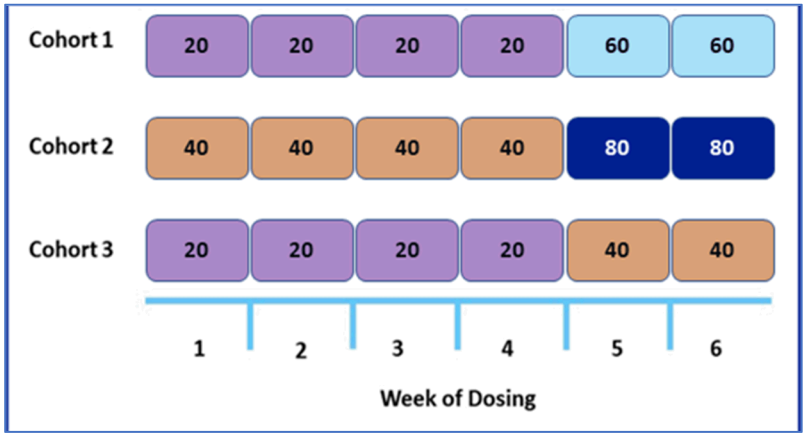
This is a randomized, double-blind (investigator- and participant- blind), sponsor-open, placebo-controlled, multiple oral dose-escalating study of PF-07081532.

In this study, adult participants with T2DM inadequately controlled on metformin will be enrolled and will receive PF-07081532 or placebo daily, for 42 days.

- Enrollment in 3 cohorts is planned with approximately 12 participants (9 PF-07081532: 3 placebo) per cohort.

A sample dosing scheme is provided below. Dosing in Cohort 1 will be conducted as shown. Increments in doses and duration of dosing at each step for subsequent cohorts, as well as the number of cohorts conducted, may be adjusted based on emerging data. The dosing scheme for each cohort will be provided in writing prior to its initiation.

Figure 1. Sample Dosing Scheme



If a participant does not tolerate dose increment to the next dose level, as determined by the investigator and with notification to the sponsor, the participant may be reverted to the previously tolerated dose level. Following this dose modification, 2 separate attempts at increasing the dose to the next dose level are permitted, per investigator discretion. If, per investigator assessment, unacceptable intolerance (eg, severe vomiting) occurs shortly following dose administration, the dose will not be re-administered on the same day, and the participant may resume dosing at the current dose level at the next scheduled dosing time. Participants whose dose level is tolerability-limited may continue in the study for the intended duration of their assigned cohort at their own individual MTD, as judged to be appropriate by the PI and sponsor.

The planned cohorts in the study (Cohorts 1-3) may be conducted concurrently, partially overlapping or sequentially. The sponsor may decide not to conduct all planned cohorts, if it is judged that study objectives have been met. Up to 3 additional cohorts may be enrolled if judged necessary to meet the study objectives. One or more of the study cohorts may be conducted in non-diabetic participants with obesity, see Section 4.2.1 and Section 5.

Determination of eligibility will occur within 28 days of randomization based on criteria including medical history, vital sign, ECG and laboratory parameters, as detailed in Section 5. Participants deemed eligible will be admitted to the CRU 7 days prior to start of dosing (Day -7) and will remain on-site until at least Day 45, post first dose.

The treatment period with double-blind study intervention will be 42 days, with study drug administered once daily. The participants within a given cohort will be blinded to the study treatment (PF-07081532 versus placebo). Participants who discontinue prior to completion of the study may be replaced, at the discretion of the PI and sponsor.

Upon discharge from the CRU, participants will return to the CRU 7 to 14 days after the last administration of IP for an on-site follow-up visit. A further follow-up contact with participants will be conducted at least 28 days and up to 35 days after the last administration of IP; this contact may be done via a phone call.

The total duration of the study from the Screening visit to the last follow-up visit will be approximately 16 weeks of which 52 days will be inpatient at the CRU, followed by a follow-up period of 4-5 weeks, post last dose.

The study will be conducted in the USA.

4.2. Scientific Rationale for Study Design

The primary objective of the study is to evaluate the safety and tolerability of multiple doses of PF-07081532 administered with different doses and dosing schemes over 42 days in participants with T2DM, inadequately controlled on metformin. Due to the gastrointestinal-related tolerability issues associated with GLP-1 receptor agonism[12] that have been shown to tolerate with repeated dosing, this study will evaluate safety and tolerability of different starting doses and titration increments in order to optimize the titration schemes for studies of longer duration.

4.2.1. Population(s)

Participants enrolled in this study will be adults with inadequately controlled T2DM (as indicated by HbA1c at screening) on metformin monotherapy, which is considered first-line therapy for glycemic control according to current treatment guidelines.[13] At screening, this study requires that participants with T2DM have been taking a minimum stable metformin dose of at least 500 mg/day for at least 2 months prior to the screening visit. The dose of metformin, where possible, is expected to remain the same until completion of study participation (ie, follow-up visit). Available in vitro data suggest that PF-07081532 is not expected to impact the PK of metformin via inhibition of OCT2, and the risk of a clinical interaction is deemed negligible. One or more cohorts of non-diabetic participants with obesity may be enrolled in this study. The safety, tolerability, PK and PD data collected in this study may be used to select doses and dosing scheme algorithms for future studies of PF-07081532.

The population planned for this study will be male and female adult participants. Female participants will be WONCBP, since at the present time embryofetal development toxicity studies with PF-07081532 have not been conducted. In male participants appropriate measures are expected to be followed to limit potential transfer of PF-07081532 in semen to partners (see Appendix 4).

4.2.2. Concomitant Medications

CCI [redacted] For more information regarding concomitant medications in this study, see Section 6.8.

4.2.3. Study Blinding

To permit an unbiased assessment of safety, the participants' treatment assignments (PF-07081532 versus placebo, but not cohort designation) will be blind to both site staff (except those involved in preparation of doses) as well as the study participants. However, to permit real-time review of the safety and PK data, a limited number of sponsor study team members will be unblinded (see Section 9.4).

4.2.4. Endpoints

Clinical safety laboratory tests, thorough assessments of vital signs and 12-lead ECGs, physical examinations, and AE monitoring will provide essential data to evaluate the safety and tolerability of PF-07081532. To supplement standard clinical safety laboratory tests, calcitonin, amylase, lipase, TSH, T4 and lipid panel will be assessed based on the study population and guided by data available on marketed GLP-1R agonists.[12] In addition, TBA will be assessed, based on non-adverse findings in the nonclinical studies with PF-07081532 (see Section 2.2.2 and the IB).

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 a glucometer at least once daily (pre-breakfast), and careful monitoring of symptomatic hypoglycemic AEs will be performed.

In an effort to reduce variability and better quantify any potential changes in heart rate and BP during the study, all measurements of ECG and vital signs (pulse and BP) will be collected in triplicate (except as noted in the SoA) and the mean values will be used for analysis at each time point.

The effect of PF-07081532 on glucose response in participants with T2DM will be evaluated by determining the change from baseline in MDG. Since MDG is the time-averaged response over a day, it is expected that this glycemic parameter will be predictive of longer term glycemic control. The effect of PF-07081532 on body weight, FPG and other glycemic markers including insulin, C-peptide, HbA1c, and glucagon will also be assessed. FPG and FPI levels will be assessed and used to calculate HOMA-IR. In order to reduce variability in FPI for HOMA-IR calculation,[14]triplicate measurements will be collected as indicated in the SoA and Section 8.9.2. In an effort to reduce variability, minimize any potential effect of placebo or CRU confinement and better quantify any potential changes to these parameters, the participants will be admitted to the CRU on Day -7 in order to monitor compliance with background metformin and recommended diet.

Baseline (Day -1) assessments with time-matched procedures will permit within participant comparisons, as appropriate. In addition, placebo-adjusted (between participant) comparisons of dose-response will also be conducted.

4.2.5. Collection of Retained Research Samples

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

4.3. Justification for Dose

Doses for the study will be determined considering all relevant information obtained from nonclinical safety studies along with safety, tolerability, and PK data observed in completed study C3991001, ongoing Study C3991002 and emerging data from prior cohorts of this study, as applicable. The dose levels to be assessed in this study are anticipated to be within the dose range evaluated in C3991002 (10 mg to 180 mg QD), where no safety concerns with PF-07081532 have been identified. The total duration of dosing for PF-07081532 or placebo in this study will be 42 days, as supported by completed nonclinical toxicity studies (see Section 2.2.1.3).

Cohort 1 will receive PF-07081532 20 mg, or placebo, QD for 28 days followed by 60 mg or placebo, QD for the remaining 14 days. This was selected to assess whether a starting dose of 20 mg QD offers a profile that will allow its use as the initial titration step in future longer duration studies. The dosing schemes in subsequent cohorts may be adjusted based on emerging data in order to generate valuable information (eg, on different starting doses or dose increment steps) that will enable optimization of the dosing schemes for use in future studies. The doses and dose increments will be selected for this study in order to obtain data on these initial steps and not to necessarily reach the target doses where efficacy of PF-07081532 could be evaluated in future studies of longer duration.

4.4. End of Study Definition

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

A participant is considered to have completed the study if he/she has completed all periods of the study, including the last visit or the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male and female participants must be between the ages of 18 and 70 years, inclusive, at the time of signing the ICD.

2. Females must be of non childbearing potential.

   - Refer to Appendix 4 for reproductive criteria for males (Section 10.4.1) and females (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

3. Patients with T2DM who are treated with metformin.

   Note: Participants must be taking metformin monotherapy as their only anti-hyperglycemic treatment. Metformin dose must be at least 500 mg per day and must be stable, defined as no change in the treatment and participant-reported compliance with treatment, for at least 2 months prior to the screening visit.

4. HbA1c ≥7.0% and ≤10.5% at screening (confirmed by a single repeat, if necessary).

   Note: For non-diabetic participants with obesity (if enrolled), HbA1c <6.5% at screening.

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

Weight and BMI:

6. Total body weight >50 kg (110 lbs) and BMI ≥24.5 to ≤45.5 kg/m^2.

   Note: For non-diabetic participants with obesity (if enrolled) BMI >30.5 to ≤45.5 kg/m^2.

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, hepatic, psychiatric, neurological, dermatological, or

allergic disease (including drug allergies but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

- Participants who have chronic conditions other than T2DM and obesity (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 6.8 for further information on concomitant medications.

- For non-diabetic participants with obesity (if enrolled), a medical history of T2DM.

2. Diagnosis of type 1 diabetes mellitus or secondary forms of diabetes.

3. Evidence or history of clinically significant cardiovascular disease. In particular, history of myocardial infarction, unstable angina, arterial revascularization, stroke, New York Heart Association Functional Class II-IV heart failure, or transient ischemic attack within 6 months of screening.

4. 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.

5. Acute pancreatitis or history of chronic pancreatitis.

6. Acute gallbladder disease.

7. Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, or any area of intestinal resection, active inflammatory bowel disease or pancreatic insufficiency).

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

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

Prior/Concomitant Therapy:

10. Participants who have received any vaccine within the 1 week prior to admission to the CRU.

11. Use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.8 and Appendix 8.

Prior/Concurrent Clinical Study Experience:

12. Previous administration with an investigational drug 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).

13. Known prior participation (ie, randomized and received at least 1 dose of investigational product) in a trial involving PF-07081532. Note that a given individual may only participate in one cohort of this study.

Diagnostic Assessments:

14. A positive urine drug screen at screening or admission.

    Note: Participants who have been medically prescribed benzodiazepines and report the use of these drugs to the investigator at the screening visit may be allowed to participate if approved by the sponsor.

15. Positive testing at screening for HIV, HBsAg, HBcAb, HBsAb or HCVAb. Positive COVID-19 test at screening or admission.

    Note: A positive HBsAb due to hepatitis B vaccination is permissible.

16. Screening supine BP ≥160 mm Hg (systolic) or ≥100 mm Hg (diastolic) following at least 5 minutes of supine 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.

17. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF interval >450 msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias).

    If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants.

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

    - AST or ALT level ≥1.5 times ULN;

- Total bilirubin level ≥1.5 times the 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;
- TSH > ULN;
- Fasting C-peptide <0.8 ng/mL;
- Serum calcitonin > ULN;
- Amylase > ULN;
- Lipase > ULN;
- eGFR <60 mL/min/1.73m^2 as calculated by MDRD equation;
- FPG >270 mg/dL at **screening or admission**.

Other Exclusions:

19. History of alcohol abuse or binge drinking and/or any illicit drug use or dependence within 6 months of Screening.

    Note: Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces ([240 mL] beer, 1 ounce [30 mL] of 40% spirit or 3 ounces [90 mL] of wine).

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

21. History of sensitivity to heparin or heparin induced thrombocytopenia, if heparin is used to flush IV catheters.

22. Known intolerance to any GLP-1R agonist.

23. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol, including restrictions on caffeine, alcohol and tobacco use.

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

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 8 hours prior to the blood sample collection at the outpatient **Screening** and on-site **follow-up** visits.

- Participants are required to fast for 4 hours (except water) prior to **admission** to CRU.

- Participants must abstain from all food and drink (except water) at least 8 hours prior to the first blood sample on inpatient study days [eg, for FSBG, safety laboratory, PK, or PD assessment].

- Noncaffeinated drinks (except as indicated below) may be consumed with meals and the evening snack.

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

- The initial caloric intake/menu assigned to each participant will be based on the Harris Benedict formula (sedentary lifestyle; to be provided to the site prior to study start) using the participant's body weight measured at screening.

- **Breakfast** will be provided at approximately 0800 hours on each inpatient day:

    - A standard breakfast will be provided for consumption after dosing on all days except those when liquid meal (for MMTT) is administered;

    - On days where liquid meal is administered, in lieu of breakfast, the meal will be provided as 16 ounces of Ensure Plus® and will be administered as listed in the SoA. The entire Ensure Plus® meal is to be consumed within 10 minutes (See Section 8.9.1).

- **Lunch** will be provided approximately 4 hours after dosing (approximately 1200 hours) and at approximately the same time on each inpatient day. On days withliquid meal for breakfast, lunch will be provided after the 4-hour post-dose blood collection samples for the MMTT have been completed.

- **Dinner** will be provided approximately 10 hours after dosing (approximately 1800 hours) and at approximately the same time on each inpatient day.

- An **evening snack** may be permitted at approximately 2200 hours on non-MMTT days. On days when the MMTT is performed, an evening snack will be provided.

    - On days with MMTT as listed in the SoA (including the evening prior to MMTT) participants will be encouraged to consume all provided food, including the liquid

meal and all standard meals and snacks provided on these days. Meals on these days will be standardized such that participants receive the same menus for all meals on these days (including the evening prior).

- If participants do not consume their entire meal on Day -1, they will be instructed to consume the same amount of food (±10%) on the other days with MMTT that they ate on Day -1.

- The start time of all meals (including liquid Ensure Plus™ meal) on these days will be noted in the CRU source documents and should be available to the sponsor on request. Participants will be encouraged to eat all standard meals within 30 minutes on days with liquid meal administration.

- Participants will receive the same snack each evening prior to the MMTT the following day. On these days, participants will be encouraged to consume the entire evening snack.

- Participants will not be required to consume all provided food during standard meals on other study days.

- When a meal or snack is scheduled at the same time as an ECG, the meal will be provided after the ECGs are completed.

- Details on the meals provided to participants including the menu items, portion sizes, and approximate calories with nutritional macronutrient (% carbohydrate, fat and protein) breakdown of the meal will be maintained in source documentation at the CRUs. This information will not be collected in the case report form; however, it may be submitted to the sponsor on request. The approximate percentage of food consumed (based on visual inspection by the site staff) should likewise be recorded in CRU source documents.

5.3.2. Caffeine, Alcohol, and Tobacco

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

- Caffeine-containing products, up to the equivalent of two 8-ounce cups of coffee per day, will be permitted.

  - **However,** participants must abstain from caffeine-containing products for a minimum of 2 hours prior to <u>all</u> vital signs and ECG measurements conducted throughout study participation (from screening to the final follow-up visit).

  - On days when MMTT is conducted, participants may ingest caffeine-containing products (up to the equivalent of two 8-ounce cups of <u>unsweetened</u> black coffee

per day). This may be permitted provided that there are no additional calories consumed and there is no anticipated impact to the MMTT data, that is no sugar, sweetener, flavorings, milk, cream etc.

- Participants may use tobacco- or nicotine-containing products as permitted by the CRU (eg, during smoking breaks, or in specified locations).

  However, smoking may not be permitted when it would interfere with the timing of scheduled study procedures or during frequent sampling procedures (eg, MMTT). 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 investigational product.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.
- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

5.3.4. Contraception

The investigator or his or her designee, in consultation with the male participant, will confirm that the participant has selected an appropriate method of contraception for the individual male participant and his partner(s) from the permitted list of contraception methods (seeAppendix 4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the male participant of the need to use effective contraception consistently and correctly and document the conversation and the male 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). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant's female partner.

Female participants will not require use of contraception as they cannot be women of childbearing potential.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the eligibility criteria for participation in this study (screen failure) may not be rescreened. As an exception, a participant who otherwise qualified for this study but did not enroll due to positive COVID-19 test, due to recent vaccination (see Section 5.2), or due to exhibiting COVID-19-related symptoms or potential exposure, may be rescreened after an appropriate interval, if judged appropriate by the investigator. In such cases, all screening procedures must be repeated and the participant assigned a new 8-digit SSID.

A participant who qualified for this study but did not enroll for administrative reasons (eg, delays in IP shipping, cohort filled) may be re-screened. In such cases, all screening procedures must be repeated (if the time between screening and dosing exceeds 28 days) and the participant assigned a new 8-digit SSID.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

For the purposes of this protocol, study intervention refers to PF-07081532 or matching placebo.

6.1. Study Intervention(s) Administered

PF-07081532 and matching placebo will be supplied by Pfizer as tablets. The tablets will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

6.1.1. Administration

On Day 1, participants will receive IP at approximately 0800 hours (plus or minus 2 hours). Dosing of IP is planned to occur in the fed state, ie, with breakfast. Details on meals and dietary requirements and activity restrictions are given in Lifestyle Considerations section of the protocol. Investigator site personnel will administer investigational product with approximately 240 mL ambient temperature water. Participants will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing.

- Blinding will be maintained by keeping the number of tablets the same for PF-07081532 and placebo within a given cohort.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate temperature conditions 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 or administer study intervention. 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 for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, 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 definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

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

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

6. See the IP manual for storage conditions of the study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) 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 IP manual. 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 IP manual.

6.2.1. Preparation and Dispensing

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in a blinded fashion to the participants.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

All participants will be assigned to randomized study intervention using a randomization scheme, maintained by Pfizer (or designated CRO vendor). Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. Unblinded personnel will access randomization scheme to prepare or dispense the appropriate study treatment.

The randomization scheme/list will be provided directly and securely to the site pharmacist(s). The unblinded pharmacist(s) will be responsible for the preparation and dispensing of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense or visual presentation following randomization and no blinded site staff are able to view the administration.

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

6.3.2. Breaking the Blind

The method for breaking the blind in this study will be manual. A sealed envelope that contains the study intervention assignment(s) for each participant will be provided to the investigator. The sealed envelope will be retained by the investigator (or representative) in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF/DCT.

Once the study is complete, all envelopes (sealed and opened) must be inventoried and retained until authorization for destruction has been provided.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Dose Modification

Refer to Section 4.3 for details of dosing scheme, and circumstances under which modifications may be acceptable.

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

No intervention will be provided to study participants at the end of their study participation.

6.7. Treatment of Overdose

For this study, any dose of PF-07081532 greater than 2.5 g is projected to result in exposures greater than 404255 ng/mL for C_{max} (ie, 152 ng/mL unbound) or 5664894 ng·h/mL for AUC_{24} (ie, 2130 ng·h/mL unbound) within a 24-hour time period and will be considered an overdose. The exposures above are based on the unbound exposures at the NOAEL in the NHP toxicity study (see Section 2.2.1.3) after accounting for protein binding in humans.

There is no specific treatment for an overdose.

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

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-07081532 (whichever is longer).
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 medical monitor (determined on a case-by-case basis).

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

6.8. Concomitant Therapy

6.8.1. Permitted Medications

Participants may be on certain concomitant medications that have been prescribed to treat concurrent diseases such as hyperlipidemia and hypertension. Attempts must be made not to alter the doses and regimens of the background/concomitant medications after randomization and for the duration of participation in this study. Any changes must be captured in the CRF. Where applicable, participants are expected to bring their supply of permitted prescription medications prior to confinement to the unit.

Medications, prescription or non-prescription, or herbal supplements not specifically listed in the protocol may be permitted, but only after review and approval by the sponsor

6.8.1.1. Metformin

All participants enrolling with T2DM are required to be taking metformin monotherapy at a minimum dose of 500 mg/day. On all study days while in the CRU, participants will be given their morning dose of metformin at the same time as PF-07081532/placebo.

Sponsor will not provide metformin during the study and participants are expected to bring their current supply of metformin prior to confinement to the unit.

For participants taking metformin more frequently than once a day, the investigator will determine the appropriate times during the day to administer those doses. For metformin (required) and other permitted concomitant medications, the timing of administration should be the same between inpatient days, and care should be taken to minimize changes to the participants stable medication routine. The dose of metformin, where possible, is expected to remain the same until completion of study participation ie, last follow-up visit.

6.8.1.2. Antihypertensive and Lipid-Modifying Agents

The use of background antihypertensive and/or lipid-modifying agent(s) is permitted, unless prohibited as per Prohibited Medications section of the protocol. Doses of such agents must be stable for at least 4 weeks prior to screening and are expected to remain the same until completion of study participation (ie, follow-up visit).

6.8.1.3. Medications for Management of Nausea and Vomiting

Nausea and vomiting have been reported with administration of GLP-1R agonists. Participants experiencing such symptoms may be managed conservatively with bed rest and/or fluid management at the discretion of the investigator. If the nausea and vomiting are not amenable to conservative management, anti-emetics (eg, prochlorperazine, promethazine, ondansetron) may be administered at the investigator's discretion with notification to the sponsor and entry in the CRF.

6.8.2. Prohibited Medications

Use of medications, other than metformin, for glycemic control is not permitted in this study.

6.8.2.1. Medications Not Permitted During the Study due to Potential Drug-Drug Interaction and Other Prohibited, Prior and Concomitant Medications

See Appendix 8 for list of prohibited concomitant medications due to potential drug-drug interaction and Appendix 9 for a list of other, prohibited prior and concomitant medications.

Sites are encouraged to contact the sponsor should there be questions as to whether a medication is permitted or prohibited.

6.8.3. 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 (see Section 6.8.1.3).

For medical management of hypoglycemia, the investigator may administer oral carbohydrate, glucagon, or IV glucose according to his or her medical judgment. At a minimum however, treatment or administration of a scheduled meal should be given if glucose falls <60 mg/dL for at least 15 minutes, irrespective of whether the participant exhibits symptoms. Investigators may choose to administer treatment sooner if participants have bothersome symptoms of hypoglycemia along with glucose values of ≤70 mg/dL.

No rescue therapy will be provided for hyperglycemia. If a participant has sustained elevated fasting plasma glucose concentrations that are >270 mg/dL on 3 consecutive measurements over 3 days, that participant will be discontinued, and the investigator will recommend further appropriate glycemic treatment according to the local healthcare standards and national guidelines.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following: ECG changes, adverse events, laboratory abnormalities, potential cases of acute kidney injury or taking of prohibited medications, as described below.

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

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

7.1.1. ECG Changes

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

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

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

7.1.2. Adverse Events

Treatment will be discontinued and the participant withdrawn from the study for:

- Treatment-related SAEs;
- Other serious or severe AEs, at the discretion of the investigator or sponsor.

7.1.3. Laboratory Abnormalities

All of the following laboratory abnormalities require discontinuation if they are confirmed:

- Hyperglycemia: see Section 6.8.3 and Section 8.2.4.2;
- Creatine kinase >10 × ULN;

  Note: Urine myoglobin and SCr will be performed as reflex testing for any participant with creatine kinase >10 × ULN.

- AST or ALT that meets ANY of the following:
  - >3 × ULN with at least one total bilirubin value >2 × ULN;
  - >3 × ULN accompanied by signs or symptoms consistent with hepatic injury (eg, new onset elevated PT/INR);
  - Two sequential AST or ALT elevations >5 × ULN, regardless of total bilirubin or accompanying signs or symptoms.

  NOTE: See also Appendix 6 for potential cases of drug-induced liver injury.

7.1.4. Potential Cases of Acute Kidney Injury

Abnormal values in SCr concurrent with presence or absence of increase in BUN that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 μmol/L) in SCr level relative to the participant's own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 μmol/L] in SCr relative to the participant's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 μmol/L), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 healthy participants at a given dose level are noted to have 2 *consecutive* SCr results of ≥0.3 mg/dL (or ≥26.5 μmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.1.5. Prohibited Medications

Participants who are treated with any prohibited medication during the course of the study may require discontinuation. Participants who are administered or take a prohibited medication should be discussed with the sponsor for possible withdrawal from the study.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Participants may be withdrawn at the discretion of the investigator. Reasons for discontinuation from the study may 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.

If a participant withdraws from the study, he/she 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 should be performed and no additional data should 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 him or her 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 he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

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

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

8. STUDY ASSESSMENTS AND 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.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

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

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

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

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

Procedures conducted as part of the participant's routine clinical management (eg, laboratory data) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol specified criteria and were performed within the time frame defined in the SoA.

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 may 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 he or she has 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.

All efforts will be made to conduct procedures at the exact nominal time relative to dosing. Procedures up to and including 10 hours after dose administration that are conducted within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) relative to dosing will not be captured as a protocol deviation, as long as the exact time of the procedure is noted on the source document and data collection tool (eg, CRF/DCT). Procedures scheduled more than 10 hours after dose administration that are conducted ≤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 procedure is noted on the source document and data collection tool (eg, CRF/DCT).

When multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible:

- ECGs: obtain prior to vital sign measurements and as close as possible to the scheduled time, but prior to blood specimen collection (see Section 8.2.3);
- Vital Signs (BP and pulse rate): obtain as close as possible to the scheduled time, but prior to blood specimen collection (see Section 8.2.2);
- Weight: obtain as close as possible to the scheduled time, but prior to eating and drinking and prior to dose administration, where applicable (see Section 8.9.3);
- Fasting blood samples: after assessment of 12-lead ECG and vital signs but prior to dosing;
- PK blood specimens: obtain at the scheduled time (for 0H samples, collect before dosing and as close as possible to dosing time, where applicable);
- Dosing: must occur at the scheduled nominal time and following predose blood sample collection;
- Breakfast: provided for consumption following dosing, where applicable (see Section 5.3.1).

Safety/laboratory/analyte results obtained following 1st dose of the study intervention (Day 1) that could unblind the study (ie, glucose, insulin, glucagon, C-peptide, HbA1c, and PK), will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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 is approximately, ***up to*** 425 mL. If participants with obesity are enrolled, approximately, ***up to*** 245 mL blood will be collected. 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.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

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

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

Height will also be measured and recorded per the SoA.

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 8.3.1 to 8.3.3.

8.2.2. Vital Signs

Supine BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements. When triplicate measurements are obtained, they should be collected approximately 2 minutes apart; the average of the triplicate measurements at each nominal time point on Day -1 will serve as each participant's time-controlled baseline value.

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.

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals 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. When a meal or snack is scheduled at the same time as an ECG, the ECG measurement must be performed prior to the meal/snack.

Triplicate 12-lead ECGs will be obtained approximately 3 minutes (±1 minute) apart; the average of the triplicate ECG measurements collected at each nominal time point on Day -1 will serve as each participant's time-controlled baseline value. Any clinically significant changes from the baseline/Day 1 ECG may potentially be AEs (Appendix 7) and should be evaluated further, as clinically warranted. To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any postdose QTcF interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QT value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then a single ECG measurement 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 msec from the baseline **and** is >450 msec; or b) an absolute QT value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals 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 7.

8.2.4. 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 relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which 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 significantly abnormal during participation in the study or within 3 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 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 drug-induced liver injury.

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 (exception may be made for medically prescribed benzodiazepines, see Section 5.2).

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

8.2.4.1. Fasting Fingerstick Blood Glucose (via Glucometer)

Investigators will monitor FSBG using a glucometer at the times specified in the SoA. 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 8.2.4.2.

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 a hypoglycemic AE (see Section 8.2.4.2).
- 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.

8.2.4.2. Hypoglycemia Reporting

Hypoglycemia will be assessed and reported in several categories: severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, and probable hypoglycemia.

Severe hypoglycemia: In order to be considered severe hypoglycemia *all* of the following 3 criteria must be met:

1. The participant had 1 of the following:
   - Blood glucose <50 mg/dL; or
   - If blood glucose was not measured, the clinical manifestations were reversed by carbohydrate administration.
2. The participant required the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
3. The participant exhibited at least 1 of the following neurological symptoms:
   - Memory loss;
   - Uncontrollable behavior;
   - Irrational behavior;
   - Unusual difficulty in awakening;
   - Suspected seizure;
   - Seizure;

- Loss of consciousness.

Documented symptomatic hypoglycemia: An event during which typical symptoms of hypoglycemia are accompanied by a measured glucose concentration <70 mg/dL.

Asymptomatic hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia but with a measured glucose concentration <70 mg/dL.

Probable symptomatic hypoglycemia: An event, during which typical symptoms of hypoglycemia are not accompanied by a real time glucose determination, but were presumably caused by a plasma glucose concentration <70 mg/dL. The clinical picture must include prompt resolution with oral carbohydrates, subcutaneous glucagon, or intravenous glucose.

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

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

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

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

During the active collection period as described in Section 8.3.1, each participant/parent/legal guardian/legally authorized representative 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.

8.3.1. 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 the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention.

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

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

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

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

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers 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.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 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 it being available.

8.3.1.2. 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 8.3.1, 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.

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

8.3.2. 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.

8.3.3. 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 given in Appendix 3.

8.3.4. 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.

8.3.5. 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 exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

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

8.3.5.1. 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 exposes a female partner prior to or around the time of conception.

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion.

    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion then exposes his female partner prior to or around the time of conception.

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until at least 5 terminal half-lives 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;
- 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.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding 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 exposure during breastfeeding 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 exposure during breastfeeding 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 exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. 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.

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. 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.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	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.

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

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.

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

8.4. Pharmacokinetics

8.4.1. Plasma for Analysis of PF-07081532

Blood samples of approximately 3 mL, to provide approximately 1 mL of plasma, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of PF-07081532 at times 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. Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol deviation.

Samples will be used to evaluate the PK of PF-07081532. Samples collected for measurement of plasma concentrations of PF-07081532 will be analyzed using a validated analytical method in compliance with applicable SOPs.

Samples collected for analyses of PF-07081532 plasma concentrations 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. Any remaining volume may be retained and stored for the duration of the study. Upon completion of the study, these retained samples may be used for exploratory purposes. Any such data generated 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.

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 decide as to whether sample integrity has been compromised.

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

8.4.2. Plasma for Analysis of 4-β-hydroxycholesterol/cholesterol

Blood samples of approximately 4 mL, to provide plasma volume of approximately 2 mL, will be collected into appropriately labeled tubes containing lithium heparin at times specified in the SoA. As part of the understanding of the properties of the investigational product, these samples may be used for analysis of 4-β-hydroxycholesterol/cholesterol as a marker of CYP3A activity, for metabolite identification, evaluation of bioanalytical methods and/or other internal exploratory purposes. Data generated from these samples may not be included in the CSR. Instructions for the collection and handling of biological samples will be provided in the laboratory manual.

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CCI [redacted]

CCI [redacted]

8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.9. Pharmacodynamics

Samples will be analyzed using a validated analytical method in compliance with Pfizer/vendor SOPs.

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

As part of understanding the PD effects of PF-07081532, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes. Any remaining volume may be retained and stored for the duration of the study. Upon completion of the study, these retained samples may be used for exploratory purposes. Any such data generated 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.

8.9.1. Liquid Meal (for MMTT)

A liquid meal consisting of approximately 700 kcal (**16 fluid ounces**) of Ensure Plus® (Vanilla) will be administered to the participants as listed in the SoA. The liquid meal will be **consumed within approximately 10 minutes** on all MMTT days.

8.9.2. Plasma Glucose, Plasma Insulin, C-Peptide, Glucagon and HbA1c

At each timepoint specified in the SoA, a sufficient amount of blood will be collected for analysis of plasma glucose, plasma insulin, C-peptide, glucagon, and HbA1c for MMTT.

The timing of blood samples for assessment of $AUC_{(0-4)}$ as part of the MMTT will be based on the start time of the liquid meal such that the sample for the 15-minute time point is collected approximately 5 minutes after completion of the liquid meal.

Where triplicate FPI is to be measured, the 3 samples should be collected approximately 5 minutes apart. FPI and FPG values will be used to calculate HOMA-IR (see Section 9.3.4).

8.9.3. Body Weight

Body weight measurements will be obtained at the time points outlined in the SoA. If possible, the same scale should be used for a particular participant for all body weight measurements obtained at the CRU. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface.

Body weight will be measured at outpatient visits to the study site as listed in the SoA under the following conditions:

- After void of urine;
- After removal of shoes, bulky layers of clothing, and jackets so that only light clothing remains;
- While remaining still during measurement.

During admission to the CRU, body weight will be measured at the time points listed in the SoA. Measurement will be taken under the following conditions:

- In the morning, prior to eating and drinking and prior to dose administration, where applicable;
- After the participant has been asked to void;
- While wearing only a hospital gown and no shoes;
- While remaining still during measurement.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a 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 (Table 4) are defined:

Table 4. Populations to be Analyzed

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.
Full Analysis Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.
Safety Analysis Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK Concentration Set	The PK concentration population is defined as all randomized 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 population is defined as all randomized participants that received at least 1 dose of PF-07081532 and have at least 1 of the PK parameters of interest calculated.
PD population Set	The PD population set is defined as all randomized participants that received at least 1 dose of PF-07081532 and have at least 1 of the PD 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

9.3.2. Primary Endpoint

All participants who received at least 1 dose of study intervention will be included in the safety analyses and listings. AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of

participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

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

Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data (unless noted below), 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. In addition, selected screening laboratory data: free T4, HbA1c, TSH, calcitonin, amylase, lipase, TBA and C-peptide will be reported.

9.3.2.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by treatment and time.

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

Safety QTc Assessment			
Degree of Prolongation	**Mild (msec)**	**Moderate (msec)**	**Severe (msec)**
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

At the nominal time points, the mean of the triplicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the study report in order to place the >500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec.

In addition, an attempt may be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. The results of such analyses will not be included in the CSR.

9.3.3. Secondary Endpoints

The populations for PK concentration and PK parameter analyses are defined in Table 4.

PK parameters for PF-07081532 following multiple dose administration will be derived from the concentration-time profiles using non-compartmental methods as data permit. The PK parameters to be assessed in this study, their definition, and method of determination are outlined in Table 5. In all cases, actual PK sampling times will be used in the derivation of PK parameters. PK samples from placebo samples will not be routinely analyzed.

The plasma PK parameters will be summarized descriptively by treatment and day. Each cohort will be considered as a separate treatment. If data permit, dose-normalized area under the plasma concentration time profile from time 0 to 24 hours [AUC_{24} (dn)] and dose-normalized C_{max} [C_{max} (dn)] may be plotted against treatment for each day (potentially on a logarithmic scale depending on the extent of the dose range), and will include individual participant values and the geometric means for each treatment. These plots will be used to help understand the relationship between the PK parameters and dose.

Plasma concentrations of PF-07081532 will be listed and descriptively summarized by treatment, day and nominal PK sampling time. Individual participant and median profiles of the plasma concentration-time data will be plotted by treatment and day using actual and nominal times, respectively. Median profiles will be presented on both linear-linear and log-linear scales. Each cohort will be considered as a separate treatment.

Table 5 Definition of Plasma PK Parameters for PF-07081532

Parameter	Day 1 (D1) or Day 42 (D42)	Definition	Method of Determination
C_{max}	D1 and D42	Maximum plasma concentration observed from time zero to 24 hours	Observed directly from data
T_{max}	D1 and D42	Time for C_{max}	Observed directly from data as time of first occurrence
AUC_{24}	D1 and D42	Area under the plasma concentration-time profile from time zero to time 24 hours	Linear/Log trapezoidal method
$t_{½}$[a]	D42	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.
C_{max}(dn)	D1 and D42	Dose normalized C_{max}	C_{max}/Dose
AUC_{24}(dn)	D1 and D42	Dose normalized AUC_{24}	AUC_{24}/Dose
C_{min}	D42	Minimum plasma concentration during the dosing interval	Observed directly from data
C_{av}	D42	Average concentration over 24 hours	AUC_{24}/24
CL/F[a]	D42	Apparent clearance	Dose/AUC_{24}
Vz/F[a]	D42	Apparent volume of distribution	Dose/(AUC_{24} * k_{el})

Table 5 Definition of Plasma PK Parameters for PF-07081532

Parameter	Day 1 (D1) or Day 42 (D42)	Definition	Method of Determination
PTR	D42	Peak-to-trough ratio	C_{max}/C_{min}
R_{ac}	D42	Observed accumulation ratio for AUC_{24}	Steady State AUC_{24}(dn)/Day 1 AUC_{24}(dn)
$R_{ac,Cmax}$	D42	Observed accumulation ratio for C_{max}	Steady State C_{max}(dn)/Day 1 C_{max}(dn)
AUC_{last}	D42	Area under the plasma concentration-time profile from time zero to time of last quantifiable concentration	Linear/Log trapezoidal method
AUC_{inf}[a]	D42	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 and 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.

a. If data permit
This table includes all PK parameters; AUC_{24}, C_{max}, T_{max}, $t_{½}$ are secondary endpoints, all others are exploratory.

9.3.4. Other Analyse(s)

The MDG will be computed by AUC_{24}/24 hour.

The $AUC_{(0-4)}$ for glucose, insulin, glucagon and C-peptide will also be calculated.

HOMA-IR will be mathematically calculated using FPG and FPI values.

All exploratory PD endpoints related to glucose, insulin, C-peptide, glucagon, HbA1c, and HOMA-IR will be summarized descriptively by treatment, time point and day. Additional analyses or summaries of these endpoints will be detailed in the SAP. Analysis of exploratory endpoints may not be included in the CSR.

For body weight, absolute values, CFB, and percent CFB will be summarized descriptively by treatment and day where the set of summary statistics will include n, mean, median, SD, minimum, and the maximum.

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Analysis of 4-β-hydroxycholesterol/cholesterol levels in plasma samples, if performed, will not be reported in the CSR.

9.4. Interim Analyses

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

9.5. Sample Size Determination

A sufficient number of participants will be screened to achieve an estimated total of approximately 12 evaluable participants per cohort (9 PF-07081532:3 placebo).

The number of participants was selected empirically to provide a sufficient number of participants to assess and characterize the safety and tolerability of various doses and dosing schemes of PF-07081352.

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 (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

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

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

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

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative 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 or their legally authorized representative 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 study participant or his or her legally authorized representative 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 or his or her legally authorized representative must be informed that his/her 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 or his or her legally authorized representative.

The participant or his or her legally authorized representative must be informed that his/her 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 or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her 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 or his or her legally authorized representative must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICD.

10.1.3. Data Protection

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

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

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

10.1.3.1. Data Monitoring Committee

This study will not use a DMC.

10.1.4. 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, and/or www.pfizer.com, and other public registries 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

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data sharing

Pfizer provides researchers secure access to patient-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. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

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.

10.1.5. 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 retain 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.

10.1.6. 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 investigator site file, 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.

Study monitors will perform ongoing source data verification 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.

10.1.7. 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. 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.

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.

10.1.8. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications, such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor 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- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.9. Sponsor’s Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study team on demand (SToD).

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an Emergency Contact Card (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 investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she 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 and/or reflex testing may be obtained at any time during the study at the discretion of the investigator to assess any perceived safety issues.

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry/Other	Urinalysis	At specified times
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/Urea Serum Creatinine[a] **Plasma** Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST ALT Total bilirubin Direct bilirubin Indirect bilirubin Alkaline phosphatase Uric acid Albumin Total Bile Acids	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[b]	<u>At screening only:</u> • FSH[c] • HBsAg • HCVAb • HBcAb • HBsAb • HIV • C-peptide[d] <u>At times specified</u> in the SoA: • Urine drug screening[e] • Free T4 • TSH • Calcitonin • Amylase • Lipase • Lipid profile (ie, total cholesterol, triglycerides, direct HDL, direct LDL)

a. GFR will be calculated using the MDRD equation: GFR (ml/min/1.73m^2) = 175 × standardized Serum Creatinine-1.154 × age-0.203 × 1.212 [if Black] × 0.742 [if female].
b. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
c. For confirmation of postmenopausal status in female participants only.
d. C-peptide is collected as part of safety laboratory tests at Screening (collected as part of MMTT at other times indicated in Table 1and Table 2).
e. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).

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.

Safety/laboratory/analyte results obtained following first dose of the study intervention (Day 1) that could unblind the study (ie, glucose, insulin, glucagon, C-peptide, HbA1c, and PK),

will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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 <u>Meeting</u> 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 either an increase in 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, is considered serious.
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 or SAEs associated with exposure during pregnancy or breastfeeding **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 non-participant (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 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: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

- 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 his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has 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 his/her 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 Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool 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 data collection tool 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 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, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention.

- Refrain from donating sperm.

PLUS either**:**

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

OR

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

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

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding and is not a WOCBP (see definitions below in Section 10.4.3).

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 an alternate 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 nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they 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.

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 (eg, bilateral tubal ligation).

5. Vasectomized partner.

   - A 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

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

One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent:

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

CCI [redacted]

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili 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 TBili 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 TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili 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** TBili 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 TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili 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 TBili 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 TBili 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: 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 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec 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 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free patients 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 patients 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 (heart rate <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.

10.8. Appendix 8: 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 judgement 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.

Drug Category	Drugs (Therapeutic Class)	Washout Period Requirement Prior to the First Dose of Study Intervention
CYP3A Inhibitor (strong)	Boceprevir (Antiviral), Ceritinib (Kinase Inhibitor), Clarithromycin (Antibiotic), Cobicistat (Pharmacokinetic Enhancer), Conivaptan (Diuretic), Danoprevir and Ritonavir (Antiviral), Elvitegravir and Ritonavir (Treatment of AIDS), Grapefruit juice (Food Product), Idelalisib (Kinase Inhibitor), Indinavir (Protease Inhibitor), Indinavir and Ritonavir (Protease Inhibitor), Itraconazole (Antifungal), Ketoconazole (Antifungal), LCL161 (Cancer Treatment), Lopinavir and Ritonavir (Protease Inhibitor), Mibefradil (Calcium Channel Blocker), Mifepristone (Antiprogestin), Nefazodone (Antidepressant), Nelfinavir (Protease Inhibitor), Posaconazole (Antifungal), Ribociclib (Kinase Inhibitor), Ritonavir (Protease Inhibitor), Saquinavir (Protease Inhibitor), Saquinavir and Ritonavir (Protease Inhibitor), Telaprevir (Antiviral), Telithromycin (Antibiotic),	5 half-lives plus 14 days

Drug Category	Drugs (Therapeutic Class)	Washout Period Requirement Prior to the First Dose of Study Intervention
	Tipranavir and Ritonavir (Protease Inhibitor), Troleandomycin (Antibiotic), Tucatinib (Kinase Inhibitor), Viekira Pak (Antiviral), Voriconazole (Antifungal)	
CYP3A Inducer (strong)	Apalutamide (Antiandrogen), Avasimibe (Antilipemic), Carbamazepine (Anticonvulsant), Enzalutamide (Antiandrogen), Ivosidenib (Cancer Treatment), Lumacaftor (Cystic Fibrosis Treatment), Mitotane (Antineoplastic), Phenobarbital (Anticonvulsant), Phenytoin (Anticonvulsant), Rifampin (Antibiotic), Rifapentine (Antibiotic), St. John's wort extract (Herbal Medication)	5 half-lives plus 14 days
OATP (1B1/1B3) Inhibitor	Atazanavir and Ritonavir (Protease Inhibitor), Clarithromycin (Antibiotic), Cyclosporine (Immunosuppressant), Erythromycin (Antibiotic), Gemfibrozil (Fibric Acid Derivative), Lopinavir and Ritonavir (Protease Inhibitor), Rifampin (Antibiotic), Simeprevir (Antiviral)	2 weeks or 5 half-lives, whichever is longer
CYP2C19 Substrate	BMS-823778 (Diabetes Treatment), Clobazam (Benzodiazepine), Clopidogrel (Antiplatelet), Diazepam (Benzodiazepine), Gliclazide (Sulfonylurea), Hexobarbital (Hypnotic – Sedative), Lansoprazole (Proton Pump Inhibitor), Mephobarbital (Anticonvulsant), Omeprazole (Proton Pump Inhibitor), Pantoprazole (Proton Pump Inhibitor), Proguanil (Antimalarial), Rabeprazole (Proton Pump Inhibitor), S-mephenytoin (Anticonvulsant), Tilidine (Treatment of Pain & Inflammation), Voriconazole (Antifungal)	2 weeks or 5 half-lives, whichever is longer

Investigators should consult the SRSD for active comparator for information regarding medication that is prohibited for concomitant use.

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

10.9. Appendix 9: Prohibited Medications Not Permitted From Screening

Drug class/Name	Duration Not Permitted from Screening
TZDs: eg, pioglitazone; rosiglitazone	Within 3 Months of Screening
Subcutaneously administered agents for glycemic control: eg, insulin, exenatide, liraglutide, pramlintide	
Other oral anti-diabetic medications: • Sulfonylureas: eg, acetohexamide, chlorpropamide, tolazamide, tolbutamine; • Glimepiride, glipizide, glyburide; • Meglitinide analogues, eg, repaglinide, nateglinide; • DPP-4i eg, sitagliptin, saxagliptin; • Vildagliptin; • α-glucosidase inhibitors, eg, acarabose, miglitol; • SGLT2 inhibitors, eg, canagliflozin.	Within 4 Weeks of Screening
Systemic glucocorticoids, eg, prednisone, dexamethasone, triamcinolone, budesonide, betamethasone. Note: As an exception, steroid-containing inhalers, nasal sprays, and topical formulations are permitted.	
Immunosuppressants, eg, cyclosporine and tacrolimus.	
Appetite- or weight-modifying medications, including non-prescription or herbals.	
Pharmacological agents with approved indication for weight loss, eg, orlistat and sibutramine.	
(Medical-grade) marijuana, regardless of medical indication.	
Anti-psychotic medications, eg olanzapine, risperidone.	
Antidepressant medications, eg tricyclic agents, selective serotonin reuptake inhibitors, and serotonin/norepinephrine reuptake inhibitors.	
Coumarin-type anticoagulants or other anticoagulants (eg, dabigatran).	
Anticonvulsants, if prescribed for a seizure disorder.	
Opioids.	
Antiarrhythmics.	
Non-selective β-blockers.	
Thiazide diuretics >25 mg per day.	
Sympathomimetic agents.	

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
%CV	percent coefficient of variation
Abs	absolute
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time profile from time 0 to the time of the last quantifiable concentration
$AUC_{(0-4)}$	area under the curve from 0 to 4 hours
AUC_{24}	area under the concentration-time curve over 24 hours
AUC_{inf}	area under the concentration-time curve to infinity
AV	atrioventricular
BBS	Biospecimen Banking System
BCRP	Breast Cancer Resistance Protein
BMI	body mass index
BP	blood pressure
Bpm	beats per minute
BUN	blood urea nitrogen
cAMP	3'-5'-cyclic adenosine monophosphate
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL	clearance
CL/F	apparent clearance
CL_p	plasma clearance
C_{av}	average concentration
C_{min}	minimum observed concentration
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial

Abbreviation	Term
CV	co-efficient of variation
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DPP-4i	dipeptidyl peptidase-4 inhibitors
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FPG	fasting plasma glucose
FPI	fasting plasma insulin
FSBG	fingerstick blood glucose
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
H	hour
HbA1c	Glycated hemoglobin
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment of insulin resistance
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document

Abbreviation	Term
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous(ly)
IVGTT	intravenous glucose tolerance test
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
k_{el}	terminal phase rate constant
kg	kilogram
Ki	mean binding inhibition constant
LBBB	left bundle branch block
LDL	low density lipoprotein
LFT	liver function test
Log_e	natural logarithm with the base e
MATE	multi-drug and toxin extrusion protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDG	mean daily glucose
MEN2	multiple endocrine neoplasia syndrome type 2
mg/dL	milligram(s) per deciliter
µmol/L	micromole per liter
MDRD	modification of diet in renal disease
min	minute; minimum
MMTT	mixed meal tolerance test
msec	millisecond
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
MDR1	multidrug resistance protein 1
N/A	Not applicable
N	total number
NC	not calculated
NHP	non-human primate
nM	nanomolar
NOAEL	no observed adverse effect level
NSAID	non-steroidal anti-inflammatory drug
OAT	organic anion transporter
OATP	organic anion transporting polypeptide

Abbreviation	Term
OCT	organic cation transporter
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PI	Principal Investigator
PK	pharmacokinetic(s)
PT	prothrombin time
PTR	peak-to-trough ratio
PVC	premature ventricular contraction
QD	once daily
QT	duration of ventricular depolarization and subsequent repolarization. Duration resides between beginning of QRS complex to end of the T wave
QTc	corrected QT
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
R_{ac}	accumulation ratio based on AUC (observed)
$R_{ac,Cmax}$	C_{max} accumulation ratio
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCr	serum creatinine
SD	standard deviation
SGLT2	sodium-glucose cotransporter-2
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SS	steady state
SSID	single subject identifier
SToD	Study Team on Demand
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal phase half life
T2DM	type 2 diabetes mellitus
T4	free thyroxine
TBD	to be determined
TBA	total bile acids
TBili	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time to reach C_{max}
TSH	thyroid stimulating hormone
TZD	thiazolidinedione
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal

Abbreviation	Term
US	United States
V_{ss}	steady-state volumes of distribution
V_z/F	apparent volume of distribution for extravascular dosing
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non-childbearing potential

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