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

Investigational Product Number:	PF-07081532
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	N/A
Protocol Number:	C3991002
Phase:	1

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

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	16 January 2020	Not applicable (N/A)

TABLE OF CONTENTS

LIST OF TABLES

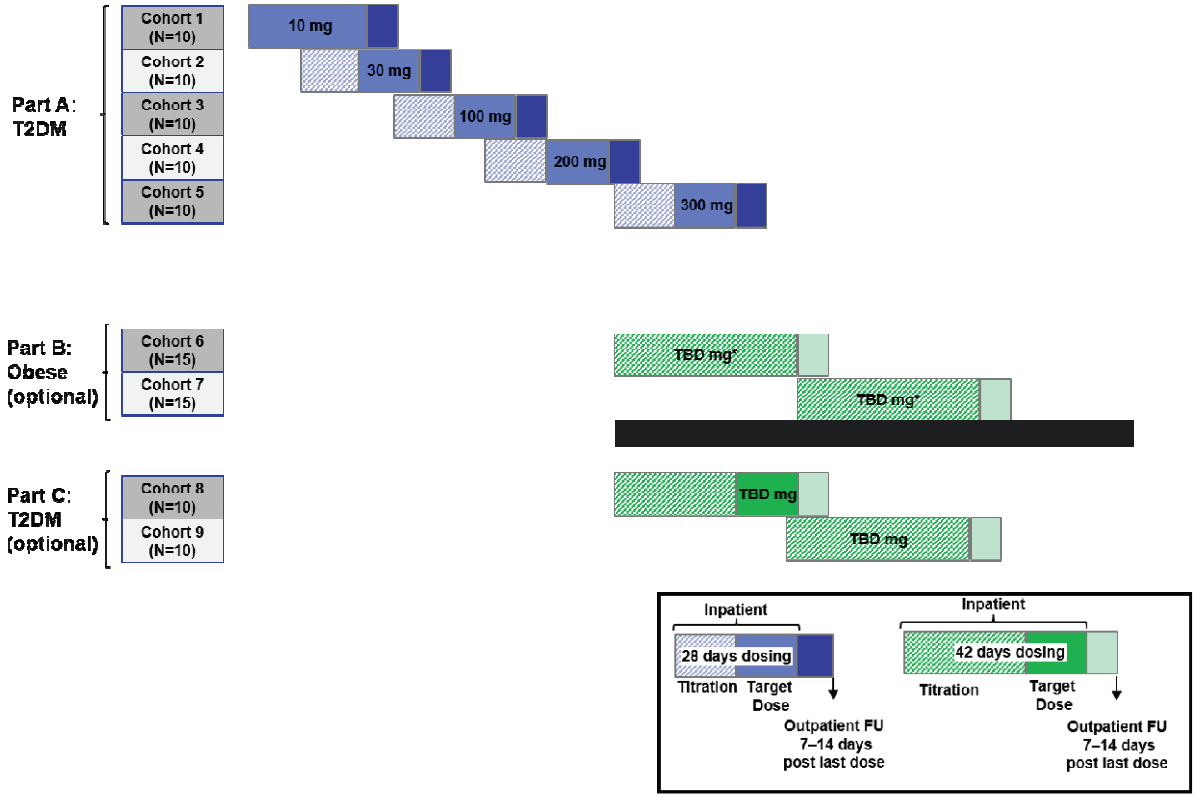
1. PROTOCOL SUMMARY

1.1. Synopsis

Not Applicable.

1.2. Schema

This schema is provided <u>for illustrative purposes only</u>.



<u>TBD: To Be Determined; N: number of participants randomized; FU: follow-up</u>

Dose levels represent PF-07081532 or matching placebo. Dose levels provided here may be adjusted based on emerging data and doses for Parts B and C, if conducted, will be determined based on emerging data.

Some cohorts may have titration schedules of less than, or more than, 14 days.

Based on emerging data, some cohorts (of Parts A, B, and/or C) may be run concurrently.

1.3. Schedule of Activities (SoA)

The tables below provide an overview of the protocol visits and procedures that are tailored for specific cohorts as follows:

Part A: Table 1 and Table 2

Part B: Table 3 and Table 4

Part C: Table 5 and Table 6

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 tables, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1. Part A (4-week in T2DM): Overall Visit Schedule and List of Procedures (use with Table 2 for full details)

	Screen	Study Day (all activities at 0H [prior to dosing] unless otherwise specified)																							Follow-up		Early Termination
		-2	-1	1	2	3	4	5-7	8	9-10	11	12-13	14	15	16-17	18	19-20	21	22	23-24	25	26-27	28	29	30	31	35-42	56-63[a]	
Outpatient visit (after ≥8H fast)	x																									x		
Informed consent	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
Adverse event monitoring	x	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x	x	x	x
Review contraception use/requirement	x	x																							x	x	x	x
Physical examination[b]	x	x											x										x					x
Body weight	x			x					x				x						x				x			x		x
Blinded IP administration[c]				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Supine 12-lead ECG[d]	x		See Table 2	See Table 2	x[e]		x		x		x		See Table 2	x[e]		x		See Table 2	x[e]		x		See Table 2	x	x	x	x		x
Supine vital signs (blood pressure and pulse rate)[f]	x				x[e]		x		x		x			x[e]		x			x[e]		x			x	x	x	x		x
Fasting fingerstick blood glucose measurement[g]		x			x	x	x	x	x	x	x	x		x	x	x	x		x	x	x	x		x	x	x			
Standardized meals/snacks[h]		x			x	x	x	x	x	x	x	x		x	x	x	x		x	x	x	x		x	x	x			
Blood Sampling for:																													
Safety laboratory tests[i]	x						x		x							x										x	x		x
FSH[j], HIV, HepBsAg, HepBcAb, HCVAb	x																												
CCI [redacted]	[redacted]																									[redacted]			
PF-07081532 PK					x[e]		x		x					x[e]		x			x[e]					x[e,k]	x[k]	x[k]			x
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. **Dose** administration to occur with breakfast or mixed meal daily from Day 1 to Day 28, inclusive; see Section 5.3 and Section 6.
d. Single 12-lead **ECG** at Screening, follow-up and Early Termination (if applicable). Measure in triplicate at all other times indicated.
e. 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).
f. Single **vital signs** at Screening, follow-up and Early Termination (if applicable). Measure in triplicate at all other times indicated.
g. **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.
h. **Meals** to be provided at approximately 0H, 4H, and 10H relative to dosing; snacks to be provided. Refer to Section 5.3.
i. See Appendix 2 for **safety lab** tests to be collected at each timepoint and Section 5.3 for fasting requirements. CCI [redacted]
j. **FSH** in females to confirm postmenopausal status only.
k. **PK** samples on Days 29, 30 and 31 to be collected 24H, 36H, 48H, and 72H after the final dose on Day 28.

Table 2. Part A (4-week in T2DM): 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 28. plus Day 14 **or** Day 21[k]	x			x		x		x		x		x		x
Triplicate, supine vital signs (blood pressure and pulse)	Days -1, 1, and 28 plus Day 14 **or** Day 21[k]	x			x		x		x		x		x		x
Fasting fingerstick blood glucose measurement[b,c]	All inpatient days	x													
CCI															
Standardized meal/snack[d]	All inpatient days	x[e]							x			x		x	
Blinded investigational product administration	Daily: Day 1 to Day 28	x[f]													
Blood sampling for:															
- Safety laboratory tests[g]	Days -1, 14, 21, and 28	x[h]													
CCI															
- HbA1c, TSH	Days -1 and 28	x													
CCI															
- PF-07081532 PK	Days 1 and 28 plus Day 14 **or** Day 21[k]	x		x	x		x		x	x	x	x	x	x	x
CCI															
Urine sampling for:															
- Urinalysis and microscopy, as appropriate	Days -1, 14, 21, and 28	x													
- PK predose spot urine (urine blank)	Day 1 only	x													
- PF-07081532 PK[m]	Day 28 only	x	→	→	→	→	→	→	→	x	→	→	x	→	x

a. Day -1, time of 0H procedures to match approximate planned clock time of collection on Day 1. All other days, 0H procedures completed pre-dose.
b. The 24H sample/measurement is to be collected prior to dosing on the following morning, as indicated in Table 1.
c. Obtain fasting fingerstick blood glucose measurement via glucometer before breakfast on all days while inpatient.
d. Standardized meals/snacks to be provided on all days while inpatient; CCI
f. Dosing to occur with breakfast CCI daily from Day 1 to Day 28, inclusive.
g. See Appendix 2: Clinical Laboratory Tests for safety lab tests to be collected at each timepoint.
h. See Section 5.3 for fasting requirements.
CCI
k. Decision to conduct the indicated procedures on Day 14 **or** Day 21 will be provided in writing prior to initiation of dosing for each cohort.
CCI
m. Urine collection for PF-07081532 PK to occur over 0-6H, 6-12H, and 12-24H. Participants should void and discard the sample prior to the first sampling interval and void at the end of each sampling interval for inclusion in the volume collected over that interval.

Table 3. Part B (6-week in Obese): Overall Visit Schedule and List of Procedures (use with Table 4 for full details)

Protocol Activity	Screen	Study Day (all activities at 0H [prior to dosing] unless otherwise specified)																					Follow-up		Early Term
		-3[a]	-2	-1	1	2	3-7	8	9-13	14	15-21	22	23-27	28	29	30-35	36	37-40	41	42	43	44	45	49-56	70-77[b]	
Outpatient visit (after ≥8H fast)	x																						x		
Informed consent	x																								
Demography and height	x																								
Inpatient stay at CRU[a]		x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x			
Medical history	x	x																							
Review drug, alcohol, tobacco use	x	x																					x		
Review prior/concomitant treatments	x	x																					x	x	x
Adverse event monitoring	x	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x	x	x	x
Review contraception use/requirement	x	x																					x	x	x
Physical examination[c]	x	x										x									x				x
Body weight	x				x			x		x		x			x		x				x			x	x
Blinded IP administration[d]					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Supine 12-lead ECG[e]	x		See Table 4			x[f]		x		x		x		See Table 4	x[f]		x		See Table 4	See Table 4	x[f]	x	x	x		x
Supine vital signs (blood pressure and pulse)[g]	x					x[f]		x		x		x			x[f]		x				x[f]	x	x	x		x
Fasting fingerstick blood glucose[h]		x				x	x	x	x	x	x	x	x		x	x	x	x			x	x	x			
Standardized meals/snacks[i]		x				x	x	x	x	x	x	x	x		x	x	x	x			x	x	x			
Blood Sampling for:																										
- Safety laboratory tests[j]	x							x		x							x						x	x		x
- FSH,[k] CCI HIV, HepBsAg, HepBcAb, HCVAb, HbA1c	x																									
CCI																										
- PF-07081532 PK						x[f]		x		x		x			x[f]		x				x[f,l]	x[l]	x[l]			x
Urine Sampling for:																										
- Urine drug test	x	x																								
- Urinalysis (and microscopy, as appropriate)	x							x		x							x						x	x		x

CCI

b. This follow-up contact may be conducted as a phone call
c. Full **physical exam** at times indicated; limited exam for previous findings, new/open AEs, or investigator discretion.
d. **Dose** administration to occur with breakfast daily from Day 1 to Day 42, inclusive; see Table 4, Section 5.3 and Section 6.
e. Single 12-lead **ECG** at Screening, follow-up and Early Termination (if applicable). Measure in triplicate at all other times indicated.
f. Measurement/sample at 0H corresponds to the 24H timepoint as detailed in Table 4 (ie, listed in both tables, but only one sample/measurement should be collected).
g. Single **vital signs** at Screening, follow-up and Early Termination (if applicable). Measure in triplicate at all other times indicated.
h. **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.
i. **Meals** to be provided at approximately 0H, 4H, and 10H relative to dosing; snacks may be provided. Refer to Section 5.3.
j. See Appendix 2 for **safety lab** tests to be collected at each timepoint, see Section 5.3 for fasting requirements. CCI
k. **FSH** in females to confirm postmenopausal status only. CCI
l. **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 4. Part B (6-week in Obese): 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, 28, and 42	x			x		x		x		x		x		x
Triplicate, supine vital sign (blood pressure and pulse rate)	Days -1, 1, 28, and 42	x			x		x		x		x		x		x
Fasting fingerstick blood glucose measurement[c]	All inpatient days	x													
Standardized meal/snack[d]	All inpatient days	x							x			x		x	
Blinded investigational product administration	Daily: Day 1 to 42	x[e]													
CCI															
Blood sampling for:															
- Safety laboratory tests[g]	Days -1, 28, and 42	x[h]													
CCI															
- PF-07081532 PK	Days 1, 28, and 42 Day 41 0H only[f,k]	x		x	x		x		x	x	x	x	x	x	x
CCI															
Urine sampling for:															
- Urinalysis and microscopy, as appropriate	Days -1, 28, and 42	x													

a. Day -2 and Day -1, time of 0H procedures to match approximate planned clock time of collection on Day 1. All other days, 0H procedures completed pre-dose.
b. The 24H sample is to be collected prior to dosing on the following morning, as indicated in Table 3.
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. Standardized meals/snacks to be provided on all days while inpatient. Refer to Section 5.3.
e. Dosing to occur with breakfast daily from Day 1 to Day 42, inclusive.
CCI
g. See Appendix 2: Clinical Laboratory Tests for safety lab tests to be collected at each timepoint.
h. See Section 5.3 for fasting requirements.
CCI

Table 5. Part C (6-week in T2DM): Overall Visit Schedule and List of Procedures (use with Table 6 for full details)

Protocol Activity	Screen	Study Day (all activities at 0H [prior to dosing] unless otherwise specified)																			Follow Up		Early
		-2	-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]	Termination
Outpatient visit (after ≥8-H fast)	x																					x		
Informed consent	x																							
Demography and height	x																							
Inpatient stay at CRU		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x			
Medical history	x	x																						
Review drug, alcohol, tobacco use	x	x																				x		
Review prior/concomitant treatments	x	x																				x	x	x
Adverse event monitoring	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
Blinded IP administration[c]				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Supine 12-lead ECG[d]	x		See Table 6	See Table 6	x[e]		x		x		x		See Table 6	x[e]		x		See Table 6	x[e]	x	x	x		x
Supine vital signs (blood pressure and pulse)[f]	x				x[e]		x		x		x			x[e]		x			x[e]	x	x	x		x
Fasting fingerstick blood glucose measurement[g]		x			x	x	x	x	x	x	x	x		x	x	x	x		x	x	x			
Standardized meals/snacks[h]		x			x	x	x	x	x	x	x	x		x	x	x	x		x	x	x			
Blood Sampling for:																								
- Safety laboratory tests[i]	x						x		x							x					x	x		x
- FSH,[j] HIV, HepBsAg, HepBcAb, HCVAb	x																							
CCI [redacted]	[redacted]																					[redacted]		
- PF-07081532 PK					x[e]		x		x		x			x[e]		x			x[k]	x[k]	x[k]			x
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. **Dose** administration to occur with breakfast CCI [redacted] daily on Days 1 to 42, inclusive, see Section 5.3 and Section 6.
d. Single 12-lead **ECG** at Screening, follow-up and Early Termination (if applicable). Measure in triplicate at all other times indicated.
e. Measurement/sample at 0H corresponds to the 24H timepoint as detailed in Table 6 (ie, listed in both tables, but only one sample/measurement should be collected).
f. Single **vital signs** at Screening, follow-up and Early Termination (if applicable). Measure in triplicate at all other times indicated.
g. **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..
h. **Meals** to be provided at approximately 0H, 4H, and 10H relative to dosing; snacks may be provided. Refer to Section 5.3.
i. See Appendix 2 for **safety lab** tests to be collected at each timepoint, see Section 5.3 for fasting requirements. CCI [redacted]
j. **FSH** in females to confirm postmenopausal status only.
k. **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 6. Part C (6-week in T2DM): 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, 28, and 42	x			x		x		x		x		x		x
Triplicate, supine vital sign (blood pressure and pulse)	Days -1, 1, 28, and 42	x			x		x		x		x		x		x
Fasting fingerstick blood glucose measurement[b,c]	All inpatient days	x													
CCI															
Standardized meal/snack[d]	all inpatient days	x[e]							x			x		x	
Blinded investigational product administration	Daily: Day 1 to Day 42	x[f]													
Blood sampling for:															
- Safety laboratory tests[g]	Days -1, 28, and 42	x[h]													
CCI															
- HbA1c, TSH	Days -1, 28, and 42	x													
CCI															
- PF-07081532 PK	Days 1, 28, and 42	x		x	x		x		x	x	x	x	x	x	x
CCI															
- Urine sampling for:															
- Urinalysis and microscopy, as appropriate	Days -1, 28, and 42	x													
- PK predose spot urine (urine blank)	Day 1 only	x													
- PF-07081532 PK	Day 42 only[k]	x	→	→	→	→	→	→	→	x	→	→	x	→	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 5.
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. Standardized meals/snacks to be provided on all days while inpatient; CCI
f. Dosing to occur with breakfast CCI daily from Day 1 to day 42, inclusive.
g. See Appendix 2: Clinical Laboratory Tests for safety lab tests to be collected at each timepoint.
h. See Section 5.3 for fasting requirements.
CCI
k. Urine collection for PF-07081532 PK to occur over 0-6H, 6-12H, and 12-24H. Participants should void and discard the sample prior to the first sampling interval and void at the end of each sampling interval for inclusion in the volume collected over that interval.
CCI

2. INTRODUCTION

Glucagon-like peptide-1 (GLP-1) is a neuroendocrine hormone that is predominantly released from the small intestine in response to food intake.[1] Activation of the GLP-1 receptor (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 type 2 diabetes mellitus (T2DM).

2.1. Study Rationale

The purpose of this study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of multiple oral doses of PF-07081532 in participants with inadequately controlled T2DM on metformin and optionally in non-diabetic obese participants. CCI [redacted]

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 glycated hemoglobin (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 the majority of currently available peptidic GLP-1R agonists. CCI [redacted]

CCI

[redacted]

CCI

[redacted]

[redacted]

[redacted]

2.2.3. 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. The cynomolgus monkey is the only pharmacologically relevant

nonclinical species (PF-07081532 activates the GLP-1 receptor), therefore rat was used to characterize off-target activity of the molecule.

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. CCI [redacted]

A 6-week oral gavage toxicity study was conducted in Wistar Han rats at PF-07081532 doses of 30, 100, and 300 mg/kg/day. CCI [redacted]

The NOAEL in the pivotal 8-week toxicity study in monkeys was 100 mg/kg/day CCI [redacted] and the NOAEL in the pivotal 6-week toxicity study in rats was 100 mg/kg/day CCI [redacted]

PF-07081532 was not mutagenic or clastogenic in in vitro studies and was negative in an in vivo rat micronucleus study. Based on the molar extinction coefficient for PF-07081532, the phototoxic risk was evaluated in the 3T3 Neutral Red assay described in International Council for Harmonisation (ICH)S10 and was found to be negative for phototoxic potential.

Safety pharmacology studies that were 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]

Further details of the nonclinical safety program are provided in the current IB.

2.2.4. Clinical Experience with PF-07081532

PF-07081532 is currently being evaluated in an ongoing Phase 1 single ascending dose First-in-Human study, C3991001. C3991001 is an investigator- and participant-blinded, sponsor-open, randomized, single-ascending oral dose, 4-period crossover, placebo substitution design in 2 interleaving cohorts of healthy adult participants. The following is a

blinded interim draft summary of the emerging clinical safety and PK data available to date (7th January 2020). All data provided below should be considered preliminary and subject to update on final reporting of this study's results.

Sixteen (16) participants have been randomised to participate in C3991001. Preliminary, draft data from the first 3 doses in this study are currently available and described below. At each of the 3 dose levels for which data are currently available, 6 participants received PF-07081532 and 2 participants received placebo. PF-07081532 or matching placebo was orally administered as a solution formulation in the fasted state.

Over the dose range of 10 mg to 100 mg, there have been no clinically significant adverse trends observed in any safety parameter, including laboratory test, vital signs and ECG. There have been no deaths, no suspected unexpected serious adverse reactions (SUSARs), and no adverse events (AEs) of severe intensity reported. The most frequently reported AEs have been in the gastrointestinal system, consistent with marketed GLP1-R agonists. 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, obese participants 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 the 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; data gathered during nonclinical studies with PF-07081532 are summarized in Section 2.2.3, and preliminary data emerging from the ongoing FIH study are given in Section 2.2.4. The clinical impact of any potential risks will be minimized through cautious dose-escalation, that is, higher doses of PF-07081532 will be administered only after lower doses have been found to be well tolerated with an acceptable safety profile (see Section 4.2 for study design rationale, Section 4.3 for justification of the selected dose levels, and Section 6.6.1 for dose escalation and stopping rules). In addition, this study includes standard, intensive, inpatient monitoring of the participants following administration of multiple, oral doses of the investigational product (IP). Clinical safety laboratory tests, thorough assessments of vital signs and electrocardiograms (ECGs), physical examinations and adverse event (AE) monitoring will provide essential data to evaluate the safety and tolerability of PF-07081532.

The potentially important risks of marketed injectable GLP-1R agonists, based on the approved labeling (United States Package Insert and European Union (EU) Summary of Product Characteristics) are summarized in the current PF-07081532 IB. Although there is no evidence to date to suggest that PF-07081532 would cause a hypersensitivity reaction, as a precaution, participants with a history of a known hypersensitivity reaction to any GLP-1R agonist should not be enrolled in studies with PF-07081532, see Section 5.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-07081532 may be found in 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 AND ENDPOINTS

Primary Objective:	Primary Endpoints:
• To evaluate the safety and tolerability of escalating, multiple doses of PF-07081532, orally administered to adult participants with T2DM inadequately controlled by metformin and, if conducted, to non-diabetic obese participants.	• Assessment of AEs, safety laboratory tests, vital signs and 12-lead ECGs.
Secondary Objectives:	**Secondary Endpoints:**
• To characterize plasma PK of PF-07081532 following multiple doses administered orally to adult participants with T2DM inadequately controlled on metformin and, if conducted, to non-diabetic obese participants.	• PF-07081532 plasma PK parameters* AUC_{24}, C_{max}, T_{max}, $t_{½}$ on Day 1 and following multiple, oral dose administration, as data permit.
• To characterize the urine PK of PF-07081532 following multiple doses administered orally to adult participants with T2DM inadequately controlled on metformin.	• Urine PK parameters* for PF-07081532, as data permit: Ae_{24}, Ae_{24}%, and CLr following multiple, oral dose administration, as data permit.
CCI [redacted]	[redacted]
[redacted]	[redacted]

* Parameters are defined in Table 11, Table 12, Table 13 and/or Appendix 8: Abbreviations.

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.

There may be 2 participant populations enrolled in this study: participants enrolling with T2DM (as indicated by HbA1C level at screening, see Section 5) and non-diabetic obese participants (as indicated by BMI at screening, see Section 5). The study will be conducted in up to 3 parts, portions of which (see Section 4.3) may be conducted concurrently.

Part A: adult participants with T2DM inadequately controlled on metformin who will receive PF-07081532 or placebo daily for 28 days. Up to 5 such cohorts will be enrolled, with approximately 10 participants (8 PF-07081532: 2 placebo) per cohort. For individual participants in Part A, the duration of the study from the Screening visit to the on-site follow-up visit will be approximately 10 weeks of which approximately 33 days will be inpatient at the CRU.

Part B (optional): obese (non diabetic) adult participants who will receive PF-07081532 or placebo daily for 42 days. This is an optional study part for which up to 2 cohorts may be enrolled with approximately 15 obese participants (12 PF-07081532: 3 placebo) per cohort. CCI [redacted] For individual participants in Part B, the duration of the study from the Screening visit to the on-site follow-up visit will be approximately 12 weeks of which approximately 48 days will be inpatient at the CRU.

Part C (optional): adult participants with T2DM inadequately controlled on metformin who will receive PF-07081532 or placebo daily for 42 days. Up to 2 cohorts of 10 participants (8 PF-07081532: 2 placebo per cohort) may be enrolled if judged necessary to meet the study objectives. For individual participants in Part C, the duration of the study from the Screening visit to the on-site follow-up visit will be approximately 12 weeks of which approximately 47 days will be inpatient at the CRU.

In all study parts, participants will initially return to the clinical research unit (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 study will be conducted in the US. Where more than 1 site participates in a given cohort, an attempt will be made to have at least 1 participant randomized to placebo per participating site, which will be facilitated through block randomization. Participants who discontinue prior to completion of the study may be replaced, at the discretion of the principal investigator (PI) and sponsor.

4.2. Scientific Rationale for Study Design

The primary purpose of this study is to evaluate the safety, tolerability, and PK of multiple escalating oral doses of PF-07081532 in adult participants with T2DM.

4.2.1. Population(s)

The population planned for this study will be male and female adult participants. Female participants will be women of non-childbearing potential (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).

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.[11] At screening, this study requires that participants 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 organic cation transporter (OCT)2, and the risk of a clinical interaction is deemed negligible.

There is precedent for a GLP-1R agonist being indicated for obesity (Saxenda®, liraglutide 3 mg). PF-07081532 may also be assessed in non-diabetic obese participants in this study. This would afford the opportunity to assess the safety, tolerability, pharmacokinetics, CCI [redacted] in an obese population. The PK CCI [redacted] data collected in these cohorts may be used to select doses and titration algorithms for future studies of PF-07081532 in obesity.

CCI [redacted]

4.2.2. IP Administration

The total duration of dosing for PF-07081532 or placebo in this study will be up to 42 days, as supported by completed nonclinical toxicity studies (Section 2.2.3). All participants will be confined to the clinical research unit (CRU) during dosing periods as detailed in the Schedule of Activities.

Due to the anticipated gastrointestinal-related tolerability issues associated with GLP-1 antagonism[12] that have been shown to tolerate with repeated dosing, a dose titration approach will be taken in this study. This may not be necessary for all cohorts (see Section 4.3.5).

Multiple escalating daily oral doses of PF-07081532 will be administered to participants with T2DM for 28 days in study Part A. It is expected that these cohorts will require up to approximately 2 weeks of titration, in addition to at least 14 days of dosing at the target dose level. This duration is anticipated to be sufficient to assess safety, tolerability, PK, CCI [redacted] of PF-07081532 at each dose escalation step. However, if necessary to enhance tolerability or enable exploration of a wider dose range, the duration of titration, and therefore the total duration of dosing, in participants with T2DM, may be increased to up to 42 days in study Part C.

In Part B of this study, if conducted, non-diabetic obese participants may be enrolled for 42 days of dosing. The duration of dose administration in this cohort is based on anticipated time needed to titrate to higher doses of PF-07081532 that may be needed to treat obesity CCI [redacted]

Dosing of investigational product (IP) is planned to occur in the fed state, ie, with breakfast. While, based on physicochemical properties and in silico predictions, food is not expected to have a significant impact on PF-07081532 exposure, if thought necessary to achieve study objectives (eg, to assess tolerability or exposure), the timing of meals or snacks relative to study treatment administration may be altered during any of the study cohorts; should this be necessary, details will be provided to investigators in writing.

4.2.3. Study Blinding

To permit an unbiased assessment of safety the participants' treatment assignments (active treatment versus placebo) 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 9.5).

4.2.4. Endpoints

4.2.4.1. Safety

Given that the current study is the first to administer repeated doses of PF-07081532 to humans, an escalating design with careful on-going review of safety and PK of PF-07081532 is planned. Doses and dose titration schemes (if used) in the escalation sequence may be modified or repeated as guided by emerging safety, tolerability, and PK data and will be provided to investigators in writing prior to initiation of dosing.

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. CCI [redacted]

While GLP-1R agonists typically are not associated with hypoglycemia unless co-administered with anti-diabetic agents that can cause hypoglycemia (such as insulin or sulfonylureas), blood glucose concentrations will be monitored throughout the study via a glucometer at least once daily (pre-breakfast), and careful monitoring of symptomatic hypoglycemic AEs will be performed.

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

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

4.2.4.2. Characterization of PF-07081532 Pharmacokinetics

As is typical for multiple ascending dose (MAD) studies with investigational agents, this study will include sampling to examine the Day 1 and steady-state plasma PK of PF-07081532. Urine samples will also be collected at steady-state in Parts A and C to evaluate the proportion of drug excreted via renal elimination. CCI [redacted]

CCI [redacted]

4.3. Justification for Dose

The doses proposed for this study were determined considering all relevant information obtained from nonclinical safety studies along with preliminary safety, tolerability, and PK data observed in the ongoing Study C3991001.

CCI [redacted]

4.3.1. Dose Selection -- Part A

In Part A of this study, a starting dose of 10 mg QD PF-07081532 is planned. CCI [redacted]

Due to potential toleration of gastrointestinal adverse events that have been shown to occur with GLP-1 agonists, doses of PF-07081532 within a cohort may be titrated from a low dose up to the target dose that is expected to be obtained by the conclusion of the dosing period.

Beyond the starting dose. the planned dose escalation procedure will be dictated by the rules summarized in Section 6.6.1 and is aimed to occur initially in incremental increases of approximately ≤½-log (ie, approximately 3.3-fold) based on predicted exposure. These increments may be adjusted based on emerging safety tolerability and PK data. Dose-escalation is envisioned to proceed up to the highest dose deemed to be well tolerated with an acceptable safety profile, achievement of plasma exposures equivalent to the PK stopping limits (see Section 6.6.1).

4.3.2. Dose Selection -- Part B

Part B in obese non-diabetic participants is optional. Dosing in Part B may occur after data from at least 2 cohorts in Part A are reviewed by the study team (Day 28 safety, Day 14 or 21 PK). Part B of the study enrolls a different population that may have a different tolerability profile relative to T2DM and allows for a longer titration period than Part A (up to 6 weeks). This may afford the opportunity to achieve higher target doses in Part B. The target dose in Part B (Cohort 1) will be no greater than approximately 3.3-fold higher than a dose previously tested in the study that was deemed to be adequately tolerated and has exposures projected to be less than the PK stopping limits. Doses in Part B are expected to be titrated to the target dose over the 42 days of the treatment period.

4.3.3. Dose Selection -- Part C

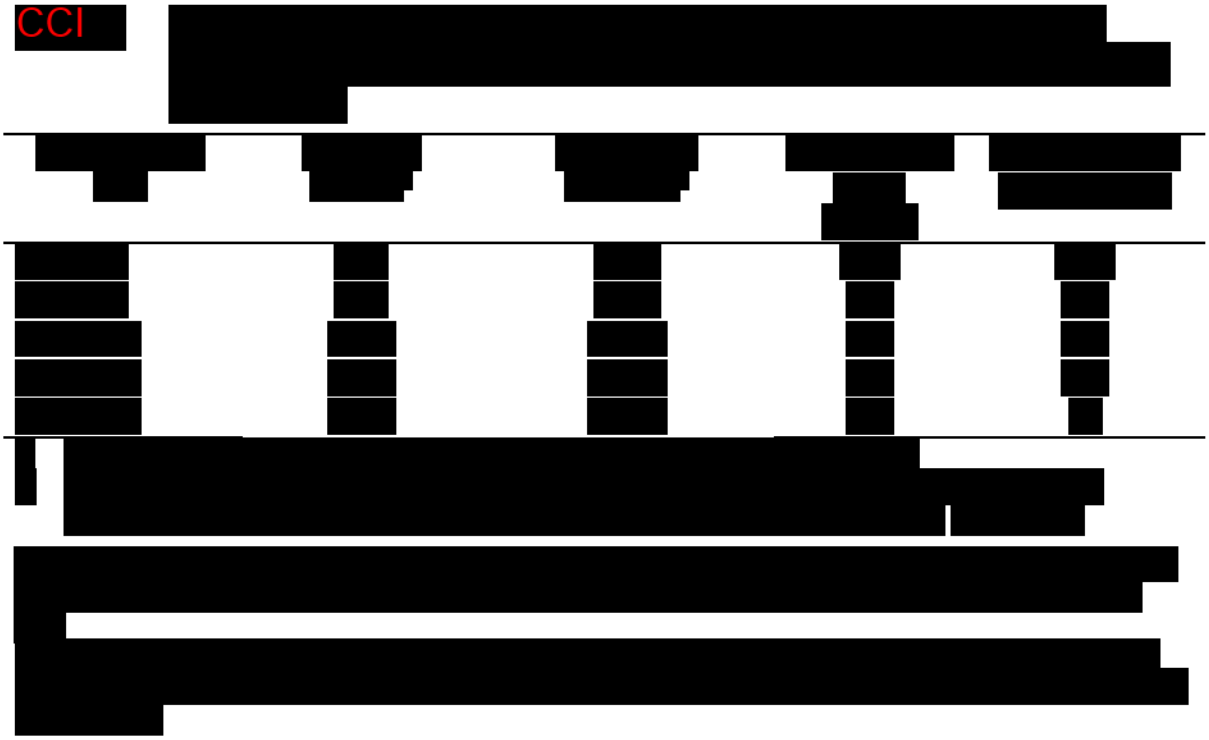
Part C in T2DM is optional. Dosing in Part C may occur after data from at least 2 cohorts in Part A are reviewed by the study team (Day 28 safety, Day 14 or 21 PK). Part C of the study allows for a longer titration period (up to 6 weeks) and therefore may allow for attaining higher target doses in Part C, relative to Part A. The target dose in Part C (Cohort 1) will be no greater than approximately 3.3-fold higher than a dose previously tested in the study that was deemed to be adequately tolerated and has exposures projected to be less than the PK stopping limits. Doses in Part C are expected to be titrated to the target dose over the 42 days of the treatment period.

4.3.4. Dose Range and Margins

The planned dose range for this study (10-300 mg QD, but with the potential to escalate up to 1000 mg QD depending upon observations at lower doses) was chosen in order to appropriately bracket the projected efficacious dose to cover the potential impact of uncertainty in projection of efficacious concentration or of unanticipated factors on drug exposure, while accommodating feasibility considerations. CCI [redacted]

Predicted exposure levels and safety margins for a range of anticipated doses for this study are provided in Table 8 below. All exposure-based safety margins were calculated using unbound concentrations. This table gives an overview of the potential dose levels; however, doses may be adjusted as long as the the projected increment of C_{max} and AUC_{24} between dose levels is no greater than approximately 3.3-fold and the projected exposure is not expected to exceed the PK stopping limits.

It is anticipated that dose titration will be required in this study; details are provided in Section 4.3.5.



4.3.5. Dose Titration

The dose titration schedule for each cohort will be provided in writing prior to its initiation.

Study Part A: it is expected that these cohorts will require up to 2 weeks of titration, followed by at least 14 days of dosing at the target dose level. A sample dose titration scheme is provided in Table 9 for illustrative purposes only. The dose levels and dose titration schemes outlined in Table 9 may be modified based on the emerging safety, tolerability, or PK data. Additional titration schemes, including up to 4 weeks of dose titration without a stable dosing period at a target dose level, may be explored. The total duration of dose administration to any given participant in Part A will not exceed 28 days.

Study Parts B and C: the titration scheme to be used in Parts B and C will be determined based on data emerging from Part A and may or may not include a stable dosing period. The total duration of dose administration to any given participant in Parts B or C will not exceed 42 days.

During the titration period, if a participant does not tolerate titration 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, and dose titration to the next higher dose may be delayed by 1 to 2 days or longer, as needed. Following down-titration, 2 separate attempts at up-titration 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 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 maximum tolerated dose (MTD), as judged to be appropriate by the PI and sponsor. For Cohorts with a stable dosing period, dose adjustments/titration will ***not*** be permitted during this period and participants should remain on the same dose (even if lower than the target dose).

Table 9. Sample Titration Scheme and Dosing Paradigm for Study Part A

Cohort[a]	Study Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 through 28[b]
1	10 mg		10 mg		10 mg		10 mg		10 mg		10 mg		10 mg		10 mg
2	10 mg		10 mg		20 mg		20 mg		30 mg		30 mg		30 mg		30 mg
3	10 mg		20 mg		30 mg		40 mg		50 mg		60 mg		80 mg		100 mg or MTD[c]
4	10 mg		30 mg		50 mg		80 mg		100 mg		120 mg		150 mg		200 mg or MTD[c]
5	10 mg		30 mg		50 mg		100 mg		150 mg		200 mg		250 mg		300 mg or MTD[c]

NOTE that this is provided as a sample only. Other than for Part A, Cohort 1, the titration scheme and target dose level for each cohort will be provided to the investigator(s) in writing prior to initiation of each cohort.

a. Doses and dose titration approaches for additional cohorts/study parts to be determined.

b. Stable dose to be administered from at least Day 15 through 28.

c. For participants not able to reach to target dose of that cohort, the individual MTD for that participant may be permitted.

For all dosing and titration regimens, matching placebo will also be administered.

CCI [redacted]

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date the investigator reviews the last participant's final data and determines that no further evaluation is required for the participant to complete the trial.

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 informed consent document (ICD). 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).

Type of Participant and Disease Characteristics:

2. **Parts A and C only:** Participants enrolling with **T2DM** 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, including dose, for at least 2 months prior to the screening visit. For further information, see Section 6.5.

3. **Parts A and C only:** For participants enrolling with **T2DM**: HbA1c ≥7.0% and ≤10.5% at screening (confirmed by a single repeat, if necessary).

    Part B only: For participants enrolling as non-diabetic **obese**: HbA1c <6.5% at screening.

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

Weight:

5. A total body weight >50 kg (110 lbs).

6. **Parts A and C only:** For participants enrolling with **T2DM**: body mass index (BMI) of ≥24.5 to ≤45.5 k/m^2.

7. **Part B only:** For participants enrolling as non-diabetic **obese**: BMI >30.5 to ≤45.5 kg/m^2.

Informed Consent:

8. 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 6.5 for further information on concomitant medications.

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

3. **Part B only**: Participants enrolling as non-diabetic **obese** may not have medical history of type 2 diabetes mellitus.

4. 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.

5. 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.

6. Acute pancreatitis or history of chronic pancreatitis.

7. Acute gallbladder disease.

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

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

CCI [redacted]

11. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or IP administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

12. See inclusion criterion #2, exclusion criterion #1 and Section 6.5 for details on concomitant medications.

Prior/Concurrent Clinical Study Experience:

13. 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 IP used in this study (whichever is longer).

14. 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 1 Cohort/Part of this study.

Diagnostic Assessments:

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

16. Positive testing at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb) or hepatitis C antibody (HCVAb). As an exception a positive HBsAb due to hepatitis B vaccination is permissible.

17. Screening supine blood pressure (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.

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

    If QTcF exceeds 450 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.

19. 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:

    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level ≥1.5 times the upper limit of normal (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.

20. **Parts A and C** (participants with T2DM): Fasting blood glucose >270 mg/dL at screening or admission, confirmed by a single repeat test if deemed necessary.

CCI [redacted]

22. At Screening, participants with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 as calculated by the modification of diet in renal disease equation (MDRD, see Appendix 2: Clinical Laboratory Tests), and confirmed via a single repeat, if deemed necessary.

Other Exclusions:

23. History of alcohol abuse or binge drinking and/or any illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces ([240 mL] beer, 1 ounce [30 mL] of 40% spirit or 3 ounces [90 mL] of wine).

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

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

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

CCI [redacted]

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

29. 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 first blood sample at the outpatient **Screening** and **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 fingerstick blood glucose (FSBG), safety laboratory, PK, CCI 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, fruit 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 CCI
- **Lunch** will be provided approximately 4 hours after dosing (approximately 1200 hours) and at approximately the same time on each inpatient day. CCI
- **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 CCI .

[redacted]

5.3.2. Alcohol, Caffeine and Tobacco

- Participants will abstain from alcohol for 24 hours (or as specified above for red wine) prior to **admission** to the clinical research unit (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 all vital signs and ECG measurements conducted throughout study participation (from screening to the final follow-up visit).
- CCI [redacted]

- 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 CCI [redacted] 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.
- 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 (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, 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 investigational product/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened, CCI [redacted]

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(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.

6.1. Study Intervention(s) Administered

For this study, the investigational product is PF-07081532 (or matching placebo). PF-07081532 and matching placebo will be provided by Pfizer as bulk powder for extemporaneous preparation of oral solution at the site. PF-07081532 and matching placebo will be presented to the participants in individual dosing containers. In addition, PF-07081532 and matching placebo may also be supplied by Pfizer as tablets. If provided, tablets will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

CCI [redacted]

6.1.1. Administration

On Day 1, participants will receive IP at approximately 0800 hours (plus or minus 2 hours). Details on meals and dietary requirements and activity restrictions are given in Section 5.3.

PF-07081532 oral solution: IP (ie, PF-07081532 and placebo) will be administered according to the extemporaneous dispensing record (EDR). Investigator site personnel will administer investigational product with ambient temperature water to a total volume of approximately 240 mL (100 mL investigational product solution plus approximately 140 mL rinse). The entire volume of liquid must be consumed by the participant.

PF-07081532 Tablet formulation: 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.

CCI [redacted]

Metformin and other Permitted Concomitant Medications: 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.

Participants will not be provided with metformin during the study. Participants enrolled in Parts A and C of this study 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.

6.2. Preparation/Handling/Storage/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, as applicable for temperature-monitored shipments.

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 temperature since previously documented for all site storage locations upon return to business.

3. 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). All study interventions will be accounted for using an IP accountability form/record.

4. Further guidance and information for the final disposition of unused study interventions are provided in the study documentation.

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

6. Study interventions should be stored in their original containers and in accordance with the labels.

7. See the extemporaneous dispensing record *(*EDR) for storage conditions of the study intervention once reconstituted and/or diluted for administration as an oral solution, or the investigational product manual if oral tablets are provided.

8. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer upon discovery. 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. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. 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 study documentation.

9. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). 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, and all destruction must be adequately documented.

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

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

PF-07081532 and placebo oral dosing solutions will be prepared in the CRU by 2 operators, 1 of whom is a pharmacist. Doses will be prepared by qualified unblinded site personnel. Blinded IP will be administered to the participant. Details of dose preparation will be given in a separate extemporaneous dispending record (EDR). Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

PF-07081532 and placebo tablets, if used, will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

CCI [redacted]

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

Participants will be randomly assigned to receive investigational product from a central randomization scheme. Investigators will remain blinded to each participant's assigned investigational product throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party (for example, pharmacist) will be responsible for the preparation and dispensing of all investigational product according to the randomization schedule and assigned treatment for the individual participant.

Allocation of participants to treatment groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The unblinded dispensing personnel will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the participant number. The unblinded dispenser will then be provided with a randomization number, product assignment, and dispensable unit (DU) or container number when investigational

product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be retained by the unblinded dispenser in the unblinded site files. Investigational product will be dispensed at the study visits as summarized in the Schedule of Activities. Returned investigational product must not be redispensed to the participants.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. 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. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF).

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the participant. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF)/data collection tool (DCT).

Blood specimens will be obtained from all participants for PK analysis to maintain the study blind at the investigator site. Only the investigator site staff and blinded study monitor, if assigned, will be blinded to study treatment. Other Pfizer personnel will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data, and provide information necessary to potentially alter the dose-escalation sequence. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for the study has been completed. Specimens from participants randomized to placebo will not be routinely analyzed for PF-07081532 PK. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer unblinded personnel and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

6.4. Study Intervention Compliance

Investigational product will be administered under the supervision of investigator site personnel. The oral cavity of each participant will be examined following dosing to ensure the investigational product was taken.

6.5. Concomitant Therapy

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.

Treatments taken within 28 days before the first dose of IP will be documented as a prior treatment. Treatments taken after the first dose of IP will be documented as concomitant treatments. All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

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

6.5.1. Medications for Glycemic Control: Parts A and C only

All participants enrolling with T2DM (Parts A and C) are required to be taking metformin monotherapy. At screening, this study requires (Section 5.1) that participants have been taking a minimum metformin dose of ≥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, the Follow-up visit).

Use of other medications for glycemic control is **not permitted** in this study (see Section 6.5.4).

6.5.2. Antihypertensive and Lipid-Modifying Agents: Parts A, B, and C

The use of background antihypertensive and/or lipid-modifying agent(s) is permitted (unless noted in Section 6.5.4). 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).

6.5.3. 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.

6.5.4. Prohibited Medications

Medications Not Permitted during study conduct

CCI [redacted]

Medications Not Permitted within 3 Months of Screening

The use of the following classes of agents is not permitted within 3 months prior to screening and for the duration of participation in the study:

- Thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone;
- Subcutaneously administered agents for glycemic control (eg, insulin, exenatide, liraglutide, pramlintide).

Medications Not Permitted within 4 Weeks of Screening

In addition to the above, the following medications are not permitted within 4 weeks prior to screening and for the duration of participation in the study:

- Other oral anti-diabetic medications, including:
  - Sulfonylureas such as acetohexamide, chlorpropamide, tolazamide, tolbutamine;
  - Glimepiride, glipizide, glyburide;
  - Meglitinide analogues such as repaglinide, nateglinide;
  - Dipeptidyl peptidase-4 inhibitors (DPP-4i) such as sitagliptin, saxagliptin;

- Vildagliptin;
- α-glucosidase inhibitors such as acarabose, miglitol;
- Sodium-glucose cotransporter-2 (SGLT2) inhibitors such as canagliflozin.

- Systemic glucocorticoids such as prednisone, dexamethasone, triamcinolone, budesonide, betamethasone.

  Note: As an exception, steroid-containing inhalers, nasal sprays, and topical formulations are permitted.

- Immunosuppressants such as cyclosporine and tacrolimus.
- Appetite- or weight-modifying medications, including non-prescription or herbals.
- Pharmacological agents with approved indication for weight loss such as orlistat and sibutramine.
- (Medical-grade) marijuana, regardless of medical indication.
- Anti-psychotic medications such as olanzapine, risperidone.
- Antidepressant medications such as 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.

[redacted]

6.5.5. Rescue Medicine

There is no rescue therapy to reverse adverse events (AEs) observed with PF-07081532; standard medical supportive care must be provided to manage any AEs (see Section 6.5.3 Management of Nausea and Vomiting).

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.

6.6. Dose Modification

6.6.1. Dose Escalation and Stopping Rules

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

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

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

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

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

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

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

- If, at any dose level, the average exposure reaches or exceeds the pharmacokinetic (PK) stopping limits of:

  [redacted]

  [redacted]

  These stopping limits are based on the unbound exposures at the NOAEL in the non-human primate (NHP) toxicity study (see Section 2.2.3) after accounting for protein binding in humans.

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

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

Data required for dose escalation evaluation will be determined by cohort and will be based on review of safety and PK data through a minimum of 14 days of dose administration, with at least 7 of these days at the previous target dose level. Each dose escalation will be based on review of available safety and PK data for at least 7 participants from that cohort. Details on safety assessments included in dose escalation review are provided in Section 8.2 and Appendix 2.

The timing of safety and PK required for dose escalation will be provided in writing prior to initiation of dosing for each such cohort.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

This is a multiple dose study in which study participants may receive up to 42 days of dosing. In rare instances, it may be necessary for a participant to permanently discontinue investigational product. Discontinuation of dosing does not necessarily represent withdrawal from the study (see Section 7.2). If investigational product is permanently discontinued, the participant may remain in the study to be evaluated for the remainder of the study. At a minimum, an early termination visit will be conducted. See the Schedule of Activities for data to be collected at the time of intervention discontinuation (early termination) and follow-up and for any further evaluations that need to be completed. Additional follow-up may be required for safety evaluation, at the discretion of the investigator.

ECG Changes

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

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

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Adverse Events

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

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

Laboratory Abnormalities

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

- Hyperglycemia: see Section 6.5.5;
- Creatine kinase >10 x ULN;

  Note: Urine myoglobulin and serum creatinine (SCr) will be performed as reflex testing for any participant with creatine kinase >10 x ULN.

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

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

Potential Cases of Acute Kidney Injury

Abnormal values in serum creatinine (SCr) concurrent with presence or absence of increase in blood urea nitrogen (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.

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 or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the Schedule of Activities 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 randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

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

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) 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. When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment 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 investigational product 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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not 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.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Participants will be screened within 28 days prior to administration of the investigational product to confirm that they meet the study population criteria for the study. The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD **before performing any study-specific procedures**. 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. CCI [redacted]

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

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the Schedule of Activities, 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.

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 (refer to 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 (refer to 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 (refer to Section 8.6.3);
- *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).

Note that if an IV catheter is placed for serial blood sample collections, ECGs and vital signs (pulse rate, BP) assessments should be either collected prior to the insertion of the catheter or sufficient rest period after catheter insertion introduced to minimize impact of catheter placement on these assessments.

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

The total blood sampling volume for individual participants in **Part A** of this study is approximately 535 mL.

The total blood sampling volume for individual participants in **Part B** of this study is approximately 420 mL.

The total blood sampling volume for individual participants in **Part C** of this study is approximately 525 mL.

The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

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

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, throat/mouth, neck, skin, cardiovascular, respiratory, gastrointestinal, lymphatic, 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.

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 supine 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 required (see Schedule of Activities), they will be obtained approximately 3 minutes (±1 minute) apart; the average of the triplicate measurements 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 twelve (12)-Lead ECGs should be collected at times specified in the Schedule of Activities section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 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. 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 ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTcF 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 QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a postdose QTcF interval remains ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or 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 criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

ECG data will be submitted to a blinded central reader for assessment. The final ECG report from the central reader should be maintained in the participant's source documentation and be the final interpretation of the ECG recording.

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 QTcF 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 Schedule of Activities for the timing and frequency.

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.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

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

8.2.4.1. Fasting Fingerstick Blood Glucose (via Glucometer)

Investigators will monitor fasting fingerstick blood glucose (FSBG) using a glucometer at the times specified in the Schedule of Activities. While the participant is confined to the CRU, FSBG measurements should be taken each morning before breakfast.

FSBG readings will be maintained at the sites 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 for the purpose of dose-escalation decisions, but these data will be stored in the sites' source documents unless related to an AE as described in Section 8.2.4.2 below.

If an FSBG result is ≤70 mg/dL, a second FSBG should be obtained to confirm the glucose value, 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 and Serious Adverse Events

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

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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 it meets the criteria for classification as an SAE or that caused the participant to discontinue the study intervention (see Section 7).

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 investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

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

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately 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.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

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/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 towards 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, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until the last follow-up visit.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. 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's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported 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 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 is maintained in the investigator site file.

8.3.6. Medication Errors

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

Exposures to the investigational product 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 investigational product;
- 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 immediately.

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 an 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. Treatment of Overdose

For this study, any dose of PF-07081532 greater than that projected to result in exposures greater than the defined PK stopping limit CCI [redacted] within a 24-hour time period will be considered an overdose.

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

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until PF-07081532 can no longer be detected systemically (at least 5 days).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to 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.

8.5. Pharmacokinetics

8.5.1. 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 dipotassium ethylenediaminetetraacetic acid (K_2EDTA) for measurement of plasma concentrations of PF-07081532 at times specified in the Schedule of Activities. 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 amendment.

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 standard operating procedures (SOPs).

CCI [redacted]

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.

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8.5.3. Urine for Analysis of PF-07081532

Urine will be collected at times specified in the Schedule of Activities.

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

- ***Following dosing*** on Days Specified in the Schedule of Activities, each void post dose will be collected and saved in a container and stored in refrigerated conditions (ie, 2-8°C) for the duration of the collection intervals, as specified in the Schedule of Activities.

  - Just prior to the first collection interval, participants will complete a forced void and the urine will be discarded;

  - At the end of each collection interval, participants must complete a forced void with this complete void included as part of the interval collection;

  - The urine container will be mixed thoroughly and total volume plus weight of the urine collected during the interval recorded;

  - An **aliquot** (approximately 20 mL) will be labeled and stored frozen for the potential measurement of drug concentrations CCI [redacted] per detailed instructions offered in a laboratory manual prior to the start of the study; and the remaining urine discarded.

Details regarding the processing, storage and shipping of the samples will be provided in the lab manual. The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study. The urine samples must be processed as indicated to maintain sample integrity. Any deviations from the urine sample processing steps given in the protocol or lab manual, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of

established stability, or of questionable integrity, will be considered a protocol deviation. Samples for analysis of PF-07081532 PK will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

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8.6.3. Body Weight

Body weight measurements will be obtained at the time points outlined in the Schedule of Activities. 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 Schedule of Activities 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 Schedule of Activities. 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.

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[redacted]

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (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.

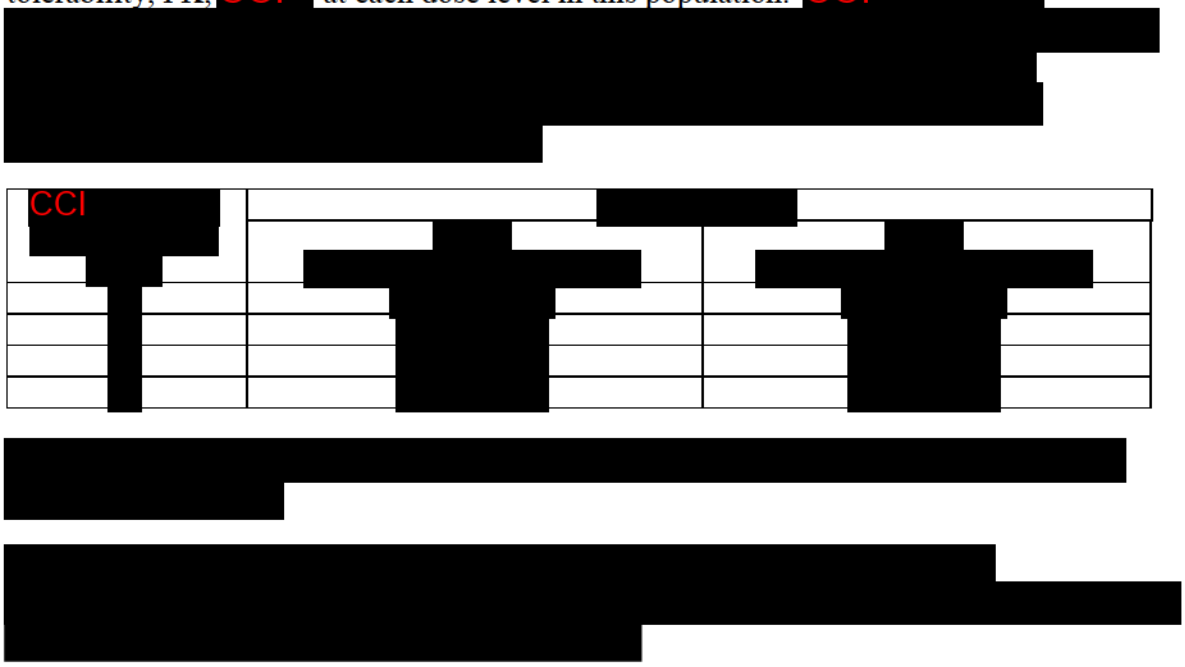
9.1. Statistical Hypotheses

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

9.2. Sample Size Determination

Part A and Part C (if conducted), participants with T2DM: a sample size of up to approximately 10 participants per cohort (8 active, 2 placebo) has been selected to minimize exposure to humans to a new chemical entity while allowing adequate characterization of safety and tolerability, PK, CCI at each dose level in this population.

Part B (if conducted), obese participants: a sample size of up to approximately 15 participants per cohort (12 active, 3 placebo) has been selected to minimize exposure of humans to a new chemical entity while allowing adequate characterization of safety and tolerability, PK, CCI at each dose level in this population. CCI



9.3. Populations for Analysis

For purposes of analyses the following populations are defined:

Table 10. Populations for Analysis

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to investigational product	All participants randomly assigned to investigational product regardless of whether or not the investigational product was administered.
Evaluable	All participants randomly assigned to investigational product and who take at least 1 dose of investigational product. Participants will be analyzed according to the product they actually received.
Safety	All participants randomly assigned to investigational product and who take at least 1 dose of investigational product. 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.
CCI [redacted]	[redacted]

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

An efficacy analysis is not applicable to this study.

9.4.2. Safety Analyses

All participants who received at least 1 dose of study medication 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: CCI [redacted] TBA CCI [redacted] will be reported.

9.4.2.1. Electrocardiogram Analyses

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

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

Safety QTcF Assessment

Prolongation	Mild	Moderate	Severe
Absolute value (msec)	>450-480	>480-500	>500
Increase from baseline in QTcF (msec)		30-60	>60

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

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 will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK[CCI] modeling approach. The results of such analyses will not be included in the CSR.

9.4.3. Pharmacokinetic Analyses

9.4.3.1. PF-07081532 Pharmacokinetics

The populations for PK concentration and PK parameter analyses are defined in Table 10.

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 11 and Table 12. 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. Additional detail on PK parameter definition for titrated and non-titrated cohorts will be provided in the SAP.

Table 11. Definition of Plasma PK Parameters for PF-087081532

Parameter	Day 1 (D1) or Steady State (SS)	Definition	Method of Determination
C_{max}	D1 & SS	Maximum plasma concentration observed from time zero to 24 hours	Observed directly from data
T_{max}	D1 & SS	Time for C_{max}	Observed directly from data as time of first occurrence
C_{max} (dn)	D1 & SS	C_{max} normalized to a 1 mg dose	C_{max}/Dose
AUC_{24}	D1 & SS	Area under the plasma concentration-time profile from time zero to time 24 hours	Linear/Log trapezoidal method
AUC_{24} (dn)	D1 & SS	AUC_{24} normalized to a 1 mg dose	AUC_{24}/Dose
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$t_{½}$[a]	SS	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.
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a. If data permit.

Table 12. Definition of Urine PK Parameters for PF-087081532

Parameter	Steady State (SS)	Definition	Method of Determination
Ae_{24}	SS	Amount of unchanged drug recovered in urine over 24 hours	Sum of [urine concentration* sample volume[a]] for each collection over the dosing interval
Ae_{24}%	SS	Percent of dose recovered in urine as unchanged drug	100* Ae_{24}/Dose
CL_r	SS	Renal clearance	Ae_{24}/AUC24

a. sample volume = (Urine weight in g/1.020), where 1.020 g/mL is the approximate specific gravity of urine.

The plasma and urine PK parameters will be summarized descriptively by actual dose received (and treatment, if applicable), in accordance with Pfizer standards. 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 24hr [AUC_{24} (dn)] and dose-normalized C_{max} [C_{max} (dn)] will be plotted against dose (potentially on a logarithmic scale depending on the extent of the dose range) (and treatment, if applicable), and will include individual participant values and the geometric means for each dose (and treatment, if applicable). These plots will be used to help understand the relationship between the PK parameters and dose (and treatment, if applicable).

Plasma concentrations of PF-07081532 will be listed and descriptively summarized by nominal PK sampling time and dose (and treatment, if applicable). Individual participant and median profiles of the plasma concentration-time data will be plotted by dose (and treatment, if applicable) using actual and nominal times, respectively. Median profiles will be presented on both linear-linear and log-linear scales.

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CCI [redacted]

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CCI

[redacted]

[redacted]

[redacted]

CCI [redacted]

9.5. Interim Analyses

As this is a sponsor-open study, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and facilitating dose-escalation decisions. In addition, these reviews may facilitate PKCCI modeling and/or supporting clinical development.

9.5.1. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

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 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, investigator's brochure (IB), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and 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.

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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (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 investigational product, 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 ICH GCP 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 to the participant or his/her legally authorized representative and answer all questions regarding the study.

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, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that 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.

The participant 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 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 the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the 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.

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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 shall 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 natural persons 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. 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.

10.1.4. 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 European Clinical Trials Database (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 standard operating procedures (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 US Basic 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. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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 US Basic Results document is 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 European Medicines Agency (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 contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 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.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

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 (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, remote, or on-site monitoring), are provided in the monitoring plan.

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

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, and all applicable regulatory requirements.

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

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

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.6. 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 electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the investigator site file.

10.1.7. Study and Site Closure

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 contract research organization (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 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 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) system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator

staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the participant directly, and if a participant calls that number, 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 Schedule of Activities. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Investigators must document their review of each laboratory safety report.

Table 14. 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 (TBA)	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[b]	<u>At screening only:</u> • FSH[c] • Hepatitis B surface antigen (HbsAg) • Hepatitis C (HCV) antibody • Hep B core antibody (HbcAb) • Human immunodeficiency virus (HIV) [redacted] <u>At times specified</u> in the Schedule of Activities: • Urine drug screening[e]

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CO_2 = carbon dioxide; FSH = follicle-stimulating hormone; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; qual = qualitative; RBC = red blood cell; WBC = white blood cell.

a. Glomerular Filtration Rate (GFR) will be calculated using the modification of diet in renal disease (MDRD) equation:
GFR (ml/min/1.73m^2) = 175 x standardized Serum Creatinine-1.154 x age-0.203 x 1.212 [if black] x 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.

[redacted]

e. The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).

Reflex testing may be conducted at investigator discretion; such tests may include PT/INR/partial thromboplastin time (PTT), myoglobin, creatine kinase.

In addition to the safety laboratory tests listed in the table above, blood samples will be collected and analyzed for additional tests as specified in the Schedule of Activities.

All available results of the safety laboratory tests listed in the preceding table will be reviewed as part of dose escalation. Note that review of the following laboratory data is not required prior to dose escalation or progression to the next cohort/study part; results will be reviewed as they become available.

- CCI [redacted] TBA.

Laboratory/analyte results that could unblind the study CCI [redacted] will not be reported to investigator sites or other blinded personnel until the study has been unblinded; see also Section 9.5.

CCI [redacted]

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions 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/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 which 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 SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

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 detained (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 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. **Is a congenital anomaly/birth defect**
f. **Other situations:** • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but 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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the investigational product 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 investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/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/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/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/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: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  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/SAE.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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 investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/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 investigational product caused the event, then the event will be handled as "related to investigational product" 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 professionals.

- 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 completed CRF.
- 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) in order 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 Guidance and Collection of Pregnancy Information

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 will be considered in woman of childbearing potential (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, or a WOCBP (see definitions below in Section 10.4.3).

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential (WOCBP)

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 age 60 years or older or no menses for 12 months without an alternative medical cause.
  - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
  - 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

The following contraception methods are be used by women of childbearing potential who are partners of male participants in this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device (IUD).
3. Intrauterine hormone-releasing system (IUS).
4. Bilateral tubal occlusion.
5. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.
   - Oral;
   - Intravaginal;
   - Transdermal;
   - Injectable.
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).

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, 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. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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).

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 includes 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 investigational product.

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.

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[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 drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (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 cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), TBA, 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 (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, 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 and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen 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 liver function test (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 Adverse Events (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 premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as Serious Adverse Events (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 participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
• Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and

monomorphic/polymorphic ventricular tachycardia >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 Serious Adverse Events
• 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: Abbreviations

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

Abbreviation	Term
Abs	Absolute
AE	Adverse event
Ae_{24}	Amount of unchanged drug recovered over 24 hours
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the concentration-time curve from time zero to infinity
AUC_{last}	Area under the concentration-time profile from time zero to the time of the last quantifiable concentration
CCI [redacted]	[redacted]
AUC_4	Area under the curve over 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
CCI [redacted]	[redacted]
β-hCG	Beta-human chorionic gonadotropin
BMI	Body mass index
BP	Blood pressure
Bpm	Beats per minute
BUN	Blood urea nitrogen
CCI [redacted]	[redacted]
CFR	Code of Federal Regulations
CCI [redacted]	[redacted]
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CCI [redacted]	[redacted]
CLr	Renal clearance
CCI [redacted]	[redacted]
C_{max}	Maximum observed concentration
CO_2	Carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
CCI [redacted]	[redacted]
CRF	Case report form
CRO	Contract research organization

Abbreviation	Term
CRU	Clinical research unit
CSR	Clinical study report
CT	Clinical trial
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
DCT	Data collection tool
CCI [redacted]	[redacted]
DILI	Drug-induced liver injury
DMC	Data monitoring committee
CCI [redacted]	[redacted]
DPP-4i	Dipeptidyl peptidase-4 inhibitors
DU	Dispensable unit
EC	Ethics committee
CCI [redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic case report form
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
CCI [redacted]	[redacted]
FSBG	Fingerstick blood glucose
FSH	Follicle-stimulating hormone
FU	Follow-up
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
H or hr	Hour
HbA1c	Glycated hemoglobin
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCVAb	Hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
[redacted]	[redacted]
HRT	Hormone replacement therapy

Abbreviation	Term
IB	Investigator's brochure
ICD	Informed consent document
ICH	International Council for Harmonisation
ID	Identification
IND	Investigational new drug application
INR	International normalized ratio
IP	Investigational product
IP manual	Investigational product manual
IRB	Institutional review board
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
CCI	[redacted]
IWR	Interactive Web-based response
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
Kg	Kilogram
CCI	[redacted]
LBBB	Left bundle branch block
LFT	Liver function test
MAD	Multiple ascending dose
CCI	[redacted]
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
CCI	[redacted]
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 or minimum
CCI	[redacted]
Msec	Millisecond
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
CCI	[redacted]
N/A	Not applicable
N	Number
NC	Not calculated
NHP	Non-human primate
nM	Nanomolar
NOAEL	No-observed-adverse-effect level

Abbreviation	Term
NSAIDs	Non-steroidal anti-inflammatory drugs
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
PCD	Primary completion date
CCI [redacted]	[redacted]
PGx	Pharmacogenomic(s)
PI	Principal investigator
PK	Pharmacokinetic(s)
PT	Prothrombin time
CCI [redacted]	[redacted]
PTT	Partial thromboplastin time
PVC	Premature ventricular contraction/complex
QD	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	Corrected QT (Fridericia method)
Qual	Qualitative
CCI [redacted]	[redacted]
RBC	Red blood cell
CCI [redacted]	[redacted]
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
SSRIs	Selective serotonin reuptake inhibitors
SToD	Study team on demand
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Half life
T2DM	Type 2 diabetes mellitus
[redacted]	[redacted]
TBD	To be determined
TBA	Total bile acids
TBili	Total bilirubin

Abbreviation	Term
THC	Tetrahydrocannabinol
CCI [redacted]	[redacted]
T_{max}	Time to maximum concentration
TSH	Thyroid stimulating hormone
TZDs	Thiazolidinediones
CCI [redacted]	[redacted]
ULN	Upper limit of normal
US	United States
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
WBC	White blood cell
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential

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