Title Page

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, DOSE RANGING, DOSE FINDING, PARALLEL GROUP STUDY TO ASSESS EFFICACY AND SAFETY OF PF-07081532, AND OPEN LABEL ORAL SEMAGLUTIDE, IN ADULTS WITH TYPE 2 DIABETES MELLITUS (T2DM) INADEQUATELY CONTROLLED ON METFORMIN, AND SEPARATELY PF-07081532 COMPARED TO MATCHING PLACEBO IN ADULTS WITH OBESITY BUT WITHOUT T2DM

Study Intervention Number:	PF-07081532; Oral semaglutide
Study Intervention Name:	NA; Rybelsus
US IND Number:	147045 (PF-07081532)
EudraCT Number:	2022-002834-15
ClinicalTrials.gov ID:	Not available
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C3991004
Phase:	2

Brief Title:

Trial to Learn About the Study Medicine (PF-07081532) and Rybelsus in People With T2DM and Separately PF-07081532 in People With Obesity

Document History

Document	Version Date
Original protocol	13 September 2022

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Dose-Finding, Parallel Group Study to Assess Efficacy and Safety of PF-07081532, and Open-Label Oral Semaglutide, in Adults with Type 2 Diabetes Mellitus (T2DM) Inadequately Controlled on Metformin, and Separately PF-07081532 Compared to Matching Placebo in Adults with Obesity but Without T2DM.

Brief Title: Trial to Learn About the Study Medicine (PF-07081532) and Rybelsus in People With T2DM and Separately PF-07081532 in People With Obesity

Regulatory Agency Identification Number(s):

US IND Number:	147045 (PF-07081532)
EudraCT Number:	2022-002834-15
ClinicalTrials.gov ID:	Not available
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C3991004
Phase:	2

Rationale: The current study is the first study in the clinical program with PF-07081532 powered to evaluate the efficacy of a range of PF-07081532 doses compared to matching placebo in adults with T2DM inadequately controlled on metformin and separately adults with obesity but without T2DM. PF-07081532 is an orally administered, potent and selective GLP-1R agonist in development as an adjunct to diet and exercise, to improve glycemic control in T2DM, and for chronic weight management in a population that is overweight with co-morbidities or who have obesity. The study includes open-label administration of Rybelsus (oral semaglutide), an orally administered peptidic GLP-1R agonist, as an internal reference standard evaluated in the population with T2DM.

The population enrolled will be stratified as follows:

- **Stratum 1:** participants with T2DM inadequately controlled on metformin
- **Stratum 2:** participants with obesity (defined as BMI ≥30 kg/m^2) without T2DM

Additionally, randomization will be further stratified with the aim of randomizing ≥30% male (and hence ≤70% female) participants, in ***each*** of stratum 1 (T2DM) and stratum 2 (obesity).

Objectives, Endpoints, and Estimands: The ***key*** primary and secondary endpoints of focus in this study include –

Objectives	**Endpoints**	**Estimands**
Primary:	**Primary:**	**Primary:**
To evaluate the efficacy of a range of PF-07081532 doses compared to placebo, ***in participants with T2DM inadequately controlled on metformin***	Placebo-adjusted, change from baseline in ***HbA1C*** at Week 32	The population average treatment effect on the change from baseline in HbA1C at Week 32 of PF-07081532 compared to placebo in the absence of glycemic rescue medication while on treatment • Measurements after initiation of glycemic rescue medication or discontinuation of study intervention will be censored and treated as missing data • Missing data due to censoring, study withdrawal or other reasons (eg, laboratory failure) will have data imputed based on a MAR assumption • Participants with inadequate compliance will have their HbA1C values used as-is in the analysis • The population-based treatment effect will be the difference in the mean change from baseline in each PF-07081532 arm compared to placebo
To evaluate the efficacy of a range of PF-07081532 doses compared to placebo, ***in participants with obesity but without T2DM***	Placebo-adjusted, percent change from baseline in ***body weight*** at Week 32	The population average treatment effect on the percent change from baseline in body weight at Week 32 of PF-07081532 compared to placebo while on treatment • Measurements after discontinuation of study intervention will be censored and treated as missing data • Missing data due to censoring, study withdrawal or other reasons (eg, equipment failure) will have data imputed based on a MAR assumption • Participants with inadequate compliance will have their body weight values used as-is in the analysis • The population-based treatment effect will be the difference in the mean percent change from baseline in each PF-07081532 arm compared to placebo
Secondary:	**Secondary:**	**Secondary:**
To assess the effect of a range of PF-07081532 doses compared to placebo on various parameters, ***in participants with T2DM inadequately controlled on metformin***	Proportion of participants who achieve ***HbA1C*** <7% (<53 mmol/mol) at Week 32	The odds ratio (PF-07081532 relative to placebo) of achieving HbA1C <7% (<53 mmol/mol) at Week 32 in the absence of glycemic rescue medication while on treatment • Measurements after initiation of glycemic rescue medication or discontinuation of study intervention will be censored and treated as missing data • Missing data will not be imputed. Participants with inadequate compliance will have their HbA1C values used as-is in the analysis • The population-based treatment effect will be the odds ratio of PF-07081532 arm relative to placebo

Objectives	Endpoints	Estimands
	Placebo-adjusted, change from baseline in ***FPG*** at Week 32	The estimand for placebo-adjusted, change from baseline in ***FPG*** at Week 32 endpoint will be constructed in a similar manner as Placebo-adjusted, change from baseline in ***HbA1C*** at Week 32
	Placebo-adjusted, percent change from baseline in ***body weight*** at Week 32	The estimand for the placebo-adjusted, percent change from baseline in ***body weight*** at Week 32 endpoint will be constructed in a similar manner as Placebo-adjusted, change from baseline in ***HbA1C*** at Week 32
To compare the efficacy of PF-07081532 and Rybelsus relative to placebo, ***in participants with T2DM inadequately controlled on metformin***	Placebo-adjusted, change from baseline in ***HbA1C*** at Week 32	The population average treatment effect on the change from baseline in HbA1C at Week 32 of each arm of PF-07081532 and of Rybelsus compared to placebo in the absence of glycemic rescue medication while on treatment • Measurements after initiation of glycemic rescue medication or discontinuation of study intervention will be censored and treated as missing data • Missing data due to censoring, study withdrawal or other reasons (eg, laboratory failure) will have data imputed based on a MAR assumption • Participants with inadequate compliance will have their HbA1C values used as-is in the analysis • The population-based treatment effect will be the difference in the mean change from baseline in each PF-07081532 arm and Rybelsus arm compared to placebo
To assess the effect of a range of PF-07081532 doses compared to placebo on various parameters ***in participants with obesity but without T2DM***	• Proportion of participants achieving ≥5%, ≥10%, and ≥15% ***body weight loss*** at Week 32 relative to baseline • Placebo-adjusted, ***absolute*** change from baseline in ***waist circumference*** at Week 32 • Placebo-adjusted, ***absolute*** change from baseline in ***waist-to-hip ratio*** at Week 32 • Placebo-adjusted, change from baseline in ***HOMA-IR*** at Week 32 • Placebo-adjusted, change from baseline in ***HOMA-S*** at Week 32	• The odds ratio (PF-07081532 relative to placebo) of achieving HbA1C <7% (<53 mmol/mol) at Week 32 in the absence of glycemic rescue medication while on treatment ◦ Measurements after discontinuation of study intervention will be censored and treated as missing data ◦ Missing data will not be imputed ◦ Participants with inadequate compliance will have their body weight values used as-is in the analysis ◦ The population-based treatment effect will be the odds ratio of PF-07081532 arm relative to placebo • The estimand for each of the continuous endpoints will be constructed in a similar manner as the primary endpoint Placebo-adjusted, percent change from baseline in ***body weight*** at Week 32
To assess the safety and tolerability with a range of PF-07081532 doses compared to placebo, ***in participants with T2DM inadequately controlled on metformin*** and separately ***participants***	In ***each*** population randomized – • Number (and percent) of participants with: ◦ TEAEs ◦ SAEs ◦ AE leading to permanent discontinuation from study intervention or study	

Objectives	Endpoints	Estimands
with obesity but without T2DM	• Hypoglycemia • AESIs • Clinical laboratory abnormalities • Vital sign abnormalities • 12-lead ECG abnormalities • And TEAEs, presented in descending order of frequency	
To assess the safety and tolerability with a range of PF-07081532 doses compared to placebo, ***in participants with obesity but without T2DM***	Assessment of mental health as determined by – • C-SSRS	

In all cases, baseline defined as the evaluable result closest prior to dosing on Day 1/Visit 3

Overall Design: This is a multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled, dose-ranging, dose-finding, parallel-group study to assess efficacy and safety/tolerability of PF-07081532, and open-label Rybelsus, in adults with T2DM inadequately controlled on metformin, and separately PF-07081532 compared to matching placebo in adults with obesity but without T2DM. For additional details, refer to Schema in Section 1.2.

The study will employ an IRC who will be responsible for ongoing review of unblinded safety and tolerability according to an IRC Charter. In addition, an interim analysis to ***assess efficacy and safety/tolerability*** in the Stratum that achieves PCD early may be performed.

Number of Participants: Approximately 780 participants (60/arm) will be enrolled/randomized across 2 populations in the study.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and randomization. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

Study Population: ***Key*** inclusion and exclusion criteria are listed below:

Inclusion Criteria – Participants must meet the following inclusion criteria, for both strata, unless otherwise specified, to be eligible for enrollment/randomization into the study:

1. Male or female 18 years or older (or the minimum age of consent in accordance with local regulations) and up to 75 years, inclusively, at the Screening Visit;

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants including requirement for pregnancy testing (Section 8.3.5);

2. For Stratum 1 ***only***:

    - Participants diagnosed with T2DM inadequately controlled with metformin at doses ≥500 mg/day with metformin dose stable for ≥8 weeks prior to Screening Visit;
    - BMI ≥23.0 kg/m^2 (≥20.0 kg/m^2 in Japan), at Screening Visit;
    - HbA1C of 7% to 10% (53-86 mmol/mol), inclusive, at Screening Visit;
    - FPG ≤270 mg/dL (15 mmol/L); at Screening Visit;

3. For Stratum 2 ***only***:

    - Participants with obesity, defined by BMI ≥30.0 kg/m^2, at Screening Visit;
    - HbA1C ≤6.4% (47 mmol/mol), at Screening Visit;
    - FPG ≤126 mg/dL (7 mmol/L), at Screening Visit;

Exclusion Criteria – Participants with any of the following characteristics/conditions, for both strata, unless otherwise specified, will be excluded:

1. Active/current, symptomatic gallbladder disease, history of pancreatitis in the 12-months prior to Screening Visit, or history of Type 1 Diabetes Mellitus, or secondary forms of diabetes (a history of gestational diabetes that has resolved is allowed), or active liver disease, or any condition affecting drug absorption;
2. Previous participation in a clinical study evaluating PF-07081532 (including exposure to placebo) **or** intolerance or hypersensitivity to a GLP-1R agonist;
3. Use of pharmacological agents with approved indication for weight loss (eg, orlistat, sibutramine), over-the-counter appetite- stimulant ***or*** appetite- suppressant, as advertised, within 12 weeks of Screening Visit; ***or*** weight loss of >5% in the 12 weeks prior to Screening Visit;
4. For Stratum 1 ***only***:

    - Use of any pharmacological agent with an approved indication for T2DM (other than metformin), or herbal medications, for the explicit purpose of glycemic control within 12 weeks of Screening Visit;
    - History of diabetic ketoacidosis;
    - Proliferative retinopathy or maculopathy requiring acute treatment;

5. For Stratum 2 ***only***:

    - Previous or planned (during the study) weight reduction surgery or device use, with selected preidentified ***exceptions***;

    - Diagnosis of Type 2 diabetes mellitus;

    - Use of pharmacological agent(s) with approved indication for glycemic control;

    - Major depressive disorder **or** other severe psychiatric disorders (eg, schizophrenia or bipolar disorder) ***within 2 years*** prior to Screening Visit or any lifetime history of a suicide attempt; **or** PHQ-9 score ≥15; **or** response of "yes" to Question 4 or 5, **or** on any suicidal behavioral question on the C-SSRS;

6. Clinically significant cardiovascular conditions;

7. Uncontrolled BP defined as ≥160 mmHg (systolic) or ≥100 mmHg (diastolic) –

    - Participants on an anti-hypertensive medication(s) to treat hypertension should be on stable dose(s) for ≥4 weeks prior to Screening Visit;

8. Personal or within first-degree relative family history of MTC or MEN2;

9. Following results reported by sponsor-identified central laboratory, at Screening Visit –

    - Fasting C-peptide <0.8 ng/mL;

    - ALT **or** AST ≥ 2.5x ULN;

    - Direct bilirubin >ULN **or** T bili >1.5x ULN ***except*** when participants have a history of Gilbert syndrome where T bili >1.5x ULN would be eligible provided direct bilirubin level is ≤ULN;

    - TSH >1.5x ULN **or** <LLN;

    - Serum calcitonin >ULN;

    - Serum amylase **or** lipase >ULN;

    - eGFR <45 mL/min/1.73 m^2;

    - Active Hepatitis B, or Hepatitis C;

    - A positive urine drug test for illicit drugs;

10. Participants requiring concomitant medications excluded based on (potential for) PK-based DDI.

Study Arms and Duration:

- In **Stratum 1**, three interventions, PF-07081532, its matching placebo, and open-label Rybelsus, will be evaluated across 7 arms in participants with T2DM on a background of metformin.

- In **Stratum 2**, two interventions, PF-07081532 and its matching placebo, will be evaluated across 6 arms in participants with obesity.

- Across all 12 treatment arms of PF-07081532/ placebo each dose will consist of 3 tablets. The treatment duration in this study will be 32 weeks for most participants; though in the first set of up to 25% randomized participants, treatment interval will extend for an additional up to 12 weeks (for a total duration of up to 44 weeks).

Study Interventions			
Intervention Name	Placebo	PF-07081532	Rybelsus
Arm Name (group of participants receiving a specific treatment or no treatment)	Placebo [Stratum 1] Placebo [Stratum 2]	20 mg QD [Stratum 1] 40 mg QD [Stratum 1] 80 mg QD [Stratum 1 and 2] 140 mg QD [Stratum 2] 160 mg QD [Stratum 1] 200 mg QD [5 steps; Stratum 2] 200 mg QD [4 steps; Stratum 2] 260 mg QD [Stratum 1 and 2]	14 mg QD [Stratum 1]
Unit Dose Strength(s)	Not applicable	20 mg; 60 mg; 100 mg	3 mg; 7 mg; 14 mg
Route of Administration	Oral	Oral	Oral
Use	Placebo	Experimental	Internal reference standard [Stratum 1]
IMP or NIMP/AxMP	IMP	IMP	IMP

Study Arms			
Arm Title	**Arm Type**	**Arm Description**	**Associated Intervention Labels**
Placebo [Stratum 1 and 2]	Placebo	Participants will receive placebo for up to 44 weeks	PF-07081532 / placebo
PF-07081532 20 mg QD [Stratum 1]	Experimental	Participants will receive PF-07081532 20 mg QD for up to 44 weeks	
PF-07081532 40 mg QD [Stratum 1]		Participants will receive PF-07081532 20 mg QD (for 4 weeks) followed by 40 mg QD (for up to 40 weeks)	
PF-07081532 80 mg QD [Stratum 1 and 2]		Participants will receive PF-07081532 20 mg QD, 40 mg QD, 60 mg QD – sequentially, each for 4 weeks followed by 80 mg QD (for up to 32 weeks)	
PF-07081532 140 mg QD [Stratum 2]		Participants will receive PF-07081532 20 mg QD, 40 mg QD, 60 mg QD, 80 mg QD, 120 mg QD – sequentially, each for 4 weeks followed by 140 mg QD (for up to 24 weeks)	
PF-07081532 160 mg QD [Stratum 1]		Participants will receive PF-07081532 20 mg QD, 40 mg QD, 60 mg QD, 80 mg QD, 120 mg QD – sequentially, each for 4 weeks followed by 160 mg QD (for up to 24 weeks)	
PF-07081532 200 mg QD [5 steps; Stratum 2]		Participants will receive PF-07081532 20 mg QD, 40 mg QD, 60 mg QD, 100 mg QD, 160 mg QD – sequentially, each for 4 weeks followed by 200 mg QD (for up to 24 weeks)	

Study Arms			
Arm Title	**Arm Type**	**Arm Description**	**Associated Intervention Labels**
PF-07081532 200 mg QD [4 steps; Stratum 2]		Participants will receive PF-07081532 20 mg QD, 40 mg QD, 80 mg QD, 140 mg QD – sequentially, each for 4 weeks followed by 200 mg QD (for up to 28 weeks)	
PF-07081532 260 mg QD [Stratum 1 and 2]		Participants will receive PF-07081532 20 mg QD, 40 mg QD, 80 mg QD, 140 mg QD, 200 mg QD – sequentially, each for 4 weeks followed by 260 mg QD (for up to 24 weeks)	
Rybelsus 14 mg QD [Stratum 1]	Internal reference standard	Participants will receive Rybelsus 3 mg QD, 7 mg QD –sequentially, each for 4 weeks followed by 14 mg QD (for up to 36 weeks)	Rybelsus

Statistical Methods:

Primary estimands:	**For the primary estimand in each stratum,** the analysis method is an MMRM analysis • The MMRM will include treatment and time as fixed effects, and baseline measure (HbA1C for Stratum 1, body weight for Stratum 2) as a covariate with time fitted as a repeated effect and participant as a random effect • An unstructured correlation matrix will be used, and the Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters • The MMRM model will be fitted to change from baseline to Weeks 4, 8, 12, 16, 20, 24, 28, and 32 • Missing values will be imputed as part of the MMRM model assumptions
Secondary Estimands:	**For the estimands containing continuous endpoints**, the analysis method is an MMRM analysis • The MMRM will include treatment and time as fixed effects, and baseline measure as a covariate with time fitted as a repeated effect and participant as a random effect • An unstructured correlation matrix will be used, and the Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters • The MMRM model will be fitted to change from baseline to Weeks 4, 8, 12, 16, 20, 24, 28, and 32 • Missing values will be imputed as part of the MMRM model assumptions
	For the estimands containing categorical endpoints, the analysis method is a logistic regression analysis • The logistic regression model will include a term for treatment and will include baseline as a covariate • No values will be imputed for missing data and missing values will not be included in the model.

No adjustments will be made for multiplicity

Ethical Considerations: The results of 2 completed Phase 1 studies, along with available nonclinical data, support the further investigation of PF-07081532 as an adjunct to diet and exercise to improve glycemic control in T2DM and for chronic weight management in a population that is overweight with co-morbidities or who have obesity. Taking into account the measures to minimize risk to participants, the potential risks associated with study intervention are justified by the anticipated benefits that may be afforded to participants in this study which include –

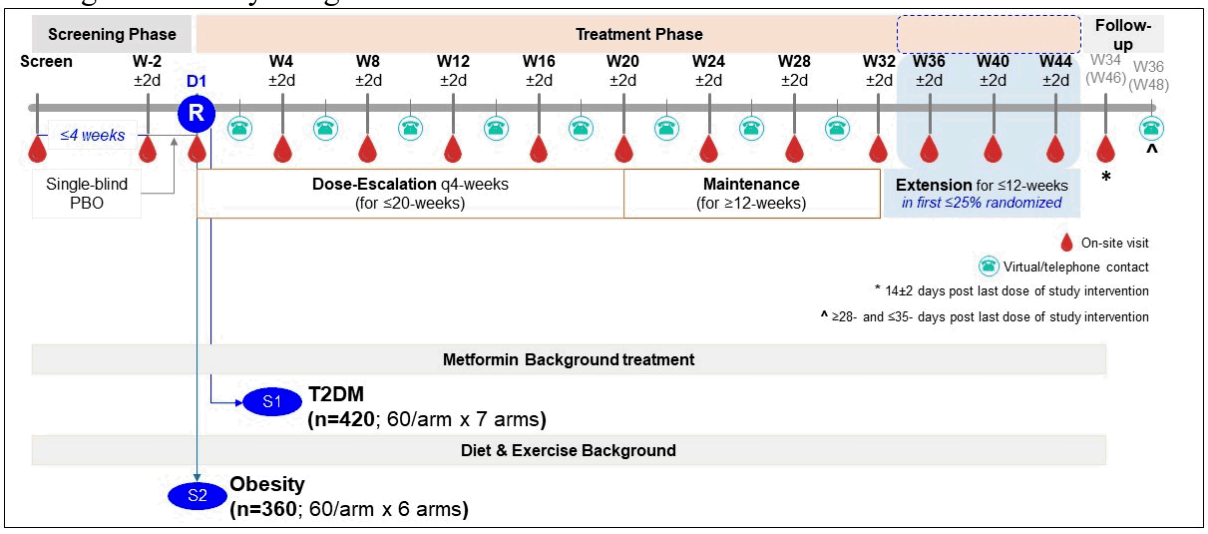
- Participants may experience improvements in glycemic control (Stratum 1) and weight management (both strata) during the study and will benefit from more intense monitoring and more frequent assessments compared to usual standard of care;

- Participants may benefit from contributing to the scientific understanding of the potential for efficacy of PF-07081532 in the context of improving glycemic control in adults with T2DM, as well as those with obesity without T2DM;

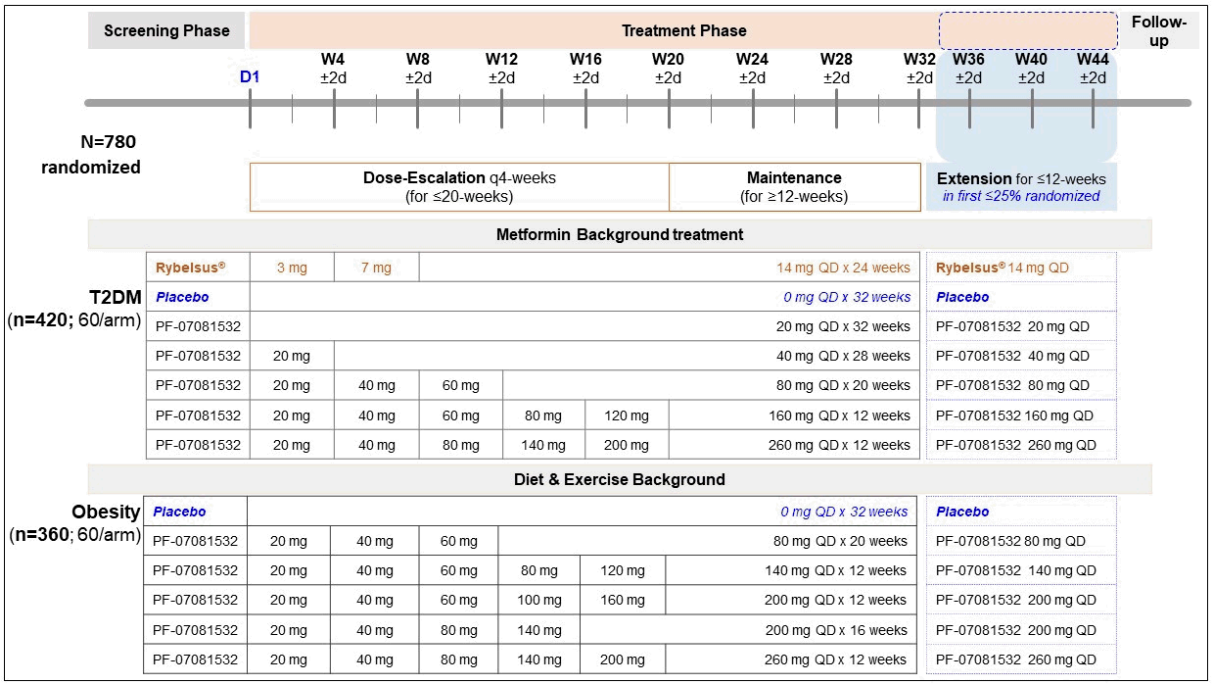
- Based on the experience with marketed peptidic GLP-1R agonists, including Rybelsus, as well as previously completed clinical and nonclinical/toxicity studies with PF-07081532, the important potential risks with the study interventions include –
    - Gastrointestinal adverse reactions;
    - Hypoglycemia;
    - Increased heart rate;
    - Other potential risks associated with long-term use of marketed GLP-1R agonists including thyroid C-cell tumors, pancreatitis, impairment of renal function, diabetic retinopathy complications, and acute gallbladder disease; and suicidal ideation/behavior in participants with Obesity.
- Participants will be expected to commit time and may experience some discomfort while undergoing study assessments
    - Female participants of childbearing potential must agree to use appropriate contraception methods;
    - Diet and lifestyle habits suggested, as part of study-related counseling, to aide management of body weight are expected to be consistently followed throughout the study.

1.2. Schema

The high-level study design is summarized below –



The dose-escalation scheme to be employed is outlined below –



1.3. Schedule of Activities

The SoA-Table 1 and SoA-Table 2 provides an overview of the protocol visits and procedures. Refer to STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA-Table 1 and SoA-Table 2, in order to conduct evaluations or assessments required to protect the well-being of the participant.

SoA-Table 1. Study-Related Procedures in Study C3991004 – for both strata unless otherwise specified

Visit Identifier	Screen	Run-In	Treatment Phase [all procedures *before* morning dose of (blinded) study intervention ± conmeds]																	In first ≤25% randomized, only			Follow-up		ET
Weeks[a] Relative to Dosing on Day 1	≤-6	-2	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	36	40	44	34/46[b]	36/48[c]	
Visit to Site[d] *or telephone contact [T]*	1	2	3	4-T	5	6-T	7	8-T	9	10-T	11	12-T	13	14-T	15	16-T	17	18-T	19	20	21	22	20/23	21/24-T	
Informed consent, demography, and dispensation of ECC	x																								
(Update) Medical & Medication history	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Exam[e]	x																								
C-SSRS *(Stratum 2)*	x		x[f]		x		x		x		x		x		x		x		x	x	x	x			x
PHQ-9 *(Stratum 2)*	x		x[f]																						
In females, assess contraception use		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Counseling on diet/exercise guidelines		x			x		x		x		x		x		x		x		x	x	x	x			
Dispense glucometer/supplies *(Stratum 1)*		x																							
Review glucose monitoring log *(Stratum 1)*			x		x		x		x		x		x		x		x		x	x	x	x	x		x
Open-ended inquiry for adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Triplicate[g] supine 12-lead ECG	x	x	x[h]		x		x[h]		x		x[h]		x		x[h]		x		x[h]			x[h]	x		x
Triplicate[g] seated vitals (BP & pulse rate)	x	x	x[h]		x		x[h]		x		x[h]		x		x[h]		x		x[h]			x[h]	x		x
Duplicate body weight	x	x	x		x		x		x		x		x		x		x		x			x			x
Triplicate waist and hip circumference		x	x						x						x				x			x			x
Registration of visit in study (via IRT)	x	x	x		x		x		x		x		x		x		x		x[i]	x	x				x
Randomization in study (via IRT)			x																						
Dispensing[i] (via IRT) of study intervention		x	x		x		x		x		x		x		x		x		x[i]	x	x				
Witnessed on site dosing of study intervention		x	x		x		x		x		x		x		x		x		x	x	x	x			
Compliance[j] of *returned* study intervention via tablet count			x[f]		x		x		x		x		x		x		x		x	x	x	x			
Continued administration of study intervention		x	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x	→	→	x			
CCI																									

SoA-Table 1. Study-Related Procedures in Study C3991004 – for both strata unless otherwise specified

Visit Identifier	Screen	Run-In	Treatment Phase [all procedures *before* morning dose of (blinded) study intervention ± conmeds]																		In first ≤25% randomized, only			Follow-up		ET
Weeks[a] Relative to Dosing on Day 1	≤-6	-2	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	36	40	44	34/46[b]	36/48[c]	
Visit to Site[d] *or telephone contact [T]*	1	2	3	4-T	5	6-T	7	8-T	9	10-T	11	12-T	13	14-T	15	16-T	17	18-T	19	20	21	22	20/23	21/24-T	

a. Defined at start of given week with ±2-day window permitted for *each* visit; *for example*: Week -2 = 14 ±2 days *before*, and Week 4 = Day 28 ±2 days *post*, Day 1/Visit 3
b. Defined as 14 ±2 days post last dose at Week 32 (or Week 44 for the first up to 25% randomized)
c. Telephone contact at ≥28- and ≤35- days post last dose for follow-up of open AEs and/or abnormal laboratory tests, *only*; **if** local regulations dictate this to be an on-site visit, selected procedures to be completed.
d. Visit to be performed in the morning following an overnight fast (except water) of ≥8 hours
e. Full PE at Screen including arm circumference, and height; otherwise, brief PE for open AEs/abnormal laboratory tests, *only*
f. C-SSRS & PHQ-9 questionnaire responses must be deemed acceptable, **plus** ≥80% and ≤ 120% compliance (with single blind placebo tablets), required to dose on Day 1
g. In those randomized to open-label Rybelsus in Stratum 1, limited to single (not triplicate) and pre-dose only (not pre- and post-dose)
h. Pre-dose assessment **plus** 1 assessment to occur immediately (⩽10-min) prior to **post dose** PK blood draw in PF-07081532/placebo arms in ***both*** Strata
i. At V2/Week -2, reflects single-blind placebo matching PF-07081532 to be dosed for 14 ± 2 days; ***starting V3/Day 1*** reflects randomized regimen (either double-blind PF-07081532/placebo) or open-label Rybelsus ***dispensed*** every 4-weeks; ***at Week 32***, IRT registration and dispensing ***only*** in those continuing dosing up to Week 44 as determined by IRT on Day 1
j. Performed at visits when study intervention is returned, *only*; participants will *not* be offered study intervention post last dose in this study

CCI [redacted]

SoA-Table 2. Study-Related Blood and Urine Collections in Study C3991004 – for both strata unless otherwise specified

Visit Identifier	Screen	Run-In	Treatment Phase [most procedures *before* morning dose of (blinded) study intervention ± conmeds, *unless otherwise specified*]																	In first ≤25% randomized, only				Follow-up		ET
Weeks[a] Relative to Dosing on Day 1	≤-6	-2	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	36	40	44	34/46[b]	36/48[c]	
Visit to Site[d] *or telephone contact [T]*	1	2	3	4-T	5	6-T	7	8-T	9	10-T	11	12-T	13	14-T	15	16-T	17	18-T	19	20	21	22	20/23	21/24-T	
Blood collection *(after overnight fast [except water] of ≥ 8-hours) –*																									
Serum FSH & pregnancy test (females only), TSH, HepB, HepC, C-peptide	x																								
Hematology, chemistry including eGFR	x	x	x		x		x		x		x		x		x		x		x	x	x	x	x	x[c]	x
HbA1C, Plasma Glucose	x	x[e]	x		x		x		x		x		x		x		x		x	x	x	x	x	x[c]	x
Serum Lipase and Amylase	x	x	x		x		x		x		x		x		x		x		x	x	x	x	x	x[c]	x
Calcitonin	x	x	x								x								x			x	x		x
CCI Serum Lipid panel, hs-CRP, Free T4, total bile acids		x	x								x								x			x	x		x
CCI																									
Predose PF-07081532/Rybelsus PK[f]			x		x		x		x		x		x		x		x		x			x			x
Post dose PF-07081532/Rybelsus PK[f]			x				x				x				x				x			x			
CCI																									
Spot urine collection –																									
Urine drug test	x																								
Urinary Albumin:Creatinine Ratio		x	x				x				x				x				x			x			x
Urinalysis (+microscopy and culture, *when appropriate*)	x	x	x		x		x		x		x		x				x		x			x	x	x[c]	x
On-site pregnancy test (WOCBP *only*)			x[e]		x[g]		x[g]		x[g]		x[g]		x[g]		x[g]		x[g]		x[g]	x[g]	x[g]	x[g]	x	x[c]	x

a. Defined at start of given week with ±2-day window permitted for *each* visit; *for example*: Week -2 = 14 ±2 days *before*, and Week 4 = Day 28 ±2 days *post,* Day 1/Visit 3.
b. Defined as 14 ±2 days post last dose at Week 32 (or Week 44 for the first up to 25% randomized).
c. Telephone contact at ≥28- and ≤35- days post last dose for follow-up of open AEs and/or abnormal laboratory tests, *only*; **if** local regulations dictate this to be an on-site visit, selected procedures to be completed.
d. Visit to be performed in the morning following an overnight fast (except water) of ≥8 hours.
e. Test results must be reviewed by medically qualified individual and deemed acceptable *before* progression to randomization and first dose of double-blinded study intervention on Day 1.
f. Predose/trough blood sample collection to occur at selected visits; *in addition*, *single* blood sample collection between 2 to 6 hours, inclusive, post dose at subset of visits.
g. *At each of these visits*, the test results must be reviewed by a medically qualified site staff and deemed acceptable to continue participation in study.

2. INTRODUCTION

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

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

2.1. Study Rationale

The current study is the first study in the clinical program with PF-07081532 powered to evaluate the efficacy of a range of PF-07081532 doses compared to matching placebo in adults with T2DM inadequately controlled on metformin and separately adults with obesity but without T2DM via outpatient dosing, employing 4-week dose-escalation intervals for up to 20 weeks (and up to 5 steps), and evaluating once-daily doses up to 260 mg. The study includes open-label administration of Rybelsus, an orally administered peptidic GLP-1R agonist, as an internal reference standard evaluated in the population with T2DM. The population enrolled will be stratified as follows:

- **Stratum 1:** participants with T2DM inadequately controlled on metformin
- **Stratum 2:** participants with obesity (defined as BMI ≥30 kg/m^2) without T2DM

Additionally, randomization will be further stratified with the aim of randomizing ≥30% male (and hence ≤70% female) participants, in ***each*** of stratum 1 (T2DM) and stratum 2 (obesity).

2.2. Background

2.2.1. Type 2 Diabetes Mellitus

The increase in the global prevalence of T2DM is largely attributed to rising rates of excess body weight and obesity[5]. T2DM is estimated to affect more than 424 million people worldwide[6], and the prevalence of T2DM within the US is estimated to range from 12% to 14%[7]. The lifetime risk of diabetes may be approximately 40% in both sexes, and above 50% in some minority populations[8]. T2DM is characterized initially 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[9]. Patients with poorly controlled T2DM have an increased risk of developing complications associated with both microvascular and macrovascular disease, including nephropathy, neuropathy, retinopathy, CV disease, and stroke, and are at 2 to 4 times increased risk of mortality than adults who do not have diabetes[10] which is associated with years of life lost[8]. While existing pharmacological options for the treatment of diabetes may provide satisfactory glycemic control for some patients, there remains a large number of patients who

do not achieve targeted HbA1C levels, suggesting a need for additional therapeutic options which minimize patient burden such as oral therapies.

Currently available GLP-1R agonists have demonstrated robust glycemic efficacy, weight loss, and CV safety, with several agents having shown a benefit in CV outcomes[11]. Most available GLP-1R agonist treatment options are injected once weekly subcutaneously[12,13]. Injectable therapies are often underutilized due to patient hesitancy, whereas oral options are preferred by many patients. Only one GLP-1R agonist (Rybelsus) is currently commercially available for oral administration. However, oral semaglutide has strict administration requirements (food and water restrictions) and has limitations due to its low bioavailability,[14] making it less convenient than an agent without such restrictions. A novel oral small molecule GLP-1R agonist that may further improve glucose control, reduce HbA1C levels, and decrease food intake and body weight compared to existing oral GLP-1R agonist, without any administration restrictions, is expected to be a preferred therapeutic option for patients with T2DM and/or obesity and their physicians.

2.2.2. Obesity

Obesity is a chronic disease that is associated with serious comorbidities, including T2DM, dyslipidemia, hypertension, atherosclerosis, obstructive sleep apnea, and certain cancers,[15] and is also associated with increased all-cause mortality[16]. The global burden of obesity is high with more than 600 million adults estimated to have obesity worldwide. In addition, the prevalence of obesity has doubled in more than 70 countries since 1980 and poses a major public health challenge[17,18]. First line treatment for obesity is lifestyle intervention including diet, exercise, and behavioral therapy. While effective in many patients, lifestyle intervention is often not sustainable, and many patients regain weight after initial weight loss[19]. Pharmacotherapy has been approved for the long-term treatment of obesity and can be a useful adjunct to lifestyle intervention to augment and maintain weight loss. However, traditional oral anti-obesity agents demonstrate modest clinical weight reduction and can be associated with significant safety and tolerability concerns.

GLP-1R agonists, injectable semaglutide and liraglutide have, more recently, been authorized in several global regions for chronic weight management in persons with obesity or overweight with one or more obesity related comorbidities and at doses higher than those approved for glycemic control in T2DM.[20,21] Based on this existing clinical history of injectable GLP-1R agonists and on Phase 1 data with PF-07081532 in participants with T2DM or obesity, oral, small molecule GLP-1R agonists are expected to decrease appetite and food intake, resulting in weight loss in patients with obesity and with or without T2DM, while avoiding the subcutaneous injection required by currently available peptidic GLP-1R agonists.

2.2.3. Nonclinical Overview of PF-07081532

PF-07081532 has been evaluated in a comprehensive nonclinical safety package that includes toxicity studies up to 6 months (in rats) and 9 months (in monkeys), as well as reproductive and developmental toxicology studies in rats and rabbits.

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[redacted]

[redacted]

[redacted]

2.2.4. Clinical Overview of PF-07081532

As of issuance of this protocol, two Phase 1 studies evaluating PF-07081532 have been completed. In total, 88 participants have been randomized including 22 healthy adult participants, 51 adult participants with T2DM, and 15 adult participants with obesity. A total of 74 unique participants have been exposed to at least 1 dose of PF-07081532. The safety profile of PF-07081532 was assessed in these 2 completed clinical studies and, to date, administration of PF-07081532 at single doses up to 200 mg and multiple doses up to 180 mg QD has been considered safe, with majority of TEAEs being mild in intensity.

One Phase 1 study, C3991003, recently concluded. This inpatient study enrolled participants with T2DM inadequately controlled on metformin, and participants with obesity, to receive PF-07081532 or placebo QD for 42 days. The starting dose for the first cohort of this study was 20 mg QD of PF-07081532, with subsequent dose levels determined based on emerging data; the maximum dose administered was 80 mg QD. While final clinical data from this study are not yet available, as of issuance of this protocol, there have been no deaths, SAEs or AEs of severe intensity reported.

2.2.5. Rybelsus, Internal Reference Standard, Approved in T2DM

In this study, Rybelsus is being used as an internal reference standard in Stratum 1. Rybelsus, semaglutide, is the only orally administered GLP-1R agonist, approved for the treatment of T2DM.[14] Semaglutide is a peptide and is co-administered with salcaprozate sodium, a gastric permeation enhancer which promotes the absorption of semaglutide from the gastrointestinal tract. Semaglutide acts in a mechanistically similar way to PF-07081532 to promote glucose-dependent insulin secretion and reduce glucagon secretion. In this study, Rybelsus, oral semaglutide, will be administered according to its approved product label. Semaglutide was developed by Novo Nordisk first as an injectable formulation under the trade name Ozempic,[12] followed by the oral formulation under the trade name Rybelsus.[14]

For more information on the safety and efficacy of oral semaglutide, see the current approved product label for Rybelsus.[14]

2.3. Benefit/Risk Assessment

While the primary pharmacology (GLP-1R agonism) is well-understood with clinical experience of peptidic GLP-1R agonists[12,13,14,20,21] given the limited prior clinical experience with PF-07081532, a small molecule (not peptidic) GLP-1R agonist, close monitoring of randomized participants is envisioned in this first study in the clinical program with PF-07081532 powered to assess efficacy. Participants in this study may benefit from contributing to the scientific understanding of the potential for efficacy of PF-07081532 in the context of improving glycemic control in adults with T2DM, as well as those with obesity without T2DM.

A high level summary of the potential risks and well as benefits are offered in Section 2.3.1 and Section 2.3.2.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07081532 may be found in the IB[22], which is the SRSD for this study. The SRSD for Rybelsus is the USPI[14].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-07081532 and Rybelsus		
Thyroid C-cell tumors	• Potential risks are based on product labeling for injectable and oral GLP-1R agonists[12,13,14,20,21] due to dose-dependent and treatment duration-dependent thyroid C-cell tumors in nonclinical studies in rats and mice at clinically relevant exposures • Of note, similar tumors were not seen in rodent studies with PF-07081532 likely as PF-07081532 does not stimulate rodent GLP-1 receptors	• Participants with a personal or within first-degree relative family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 are excluded – refer to Section 5.2 • Participants with serum calcitonin >ULN excluded (Section 5.2) ***plus*** serum calcitonin assessment included to monitor for this potential effect
Pancreatitis	• Potential risks are based on product labeling for injectable and oral GLP-1R agonists[12,13,14,20,21]	• Participants with a history of pancreatitis in the 12-months prior to Screening Visit are not eligible (Section 5.2) • Participants with serum lipase or serum amylase >ULN excluded (Section 5.2) • Participants will be monitored for clinical signs of pancreatitis (eg, severe abdominal pain), and serum amylase and lipase will be monitored

Hypoglycemia	• Clinical trials with injectable GLP-1R agonists have not demonstrated an increased risk for hypoglycemia
	• However, when administered in combination with anti-diabetic agents that are known to have an increased risk of hypoglycemia (such as insulin or sulfonylureas), an increased risk for hypoglycemia was observed
	• Hypoglycemia is listed under "Warning and Precautions" for oral semaglutide[14] when used in combination with an insulin secretagogue or insulin therapy
	• A low overall frequency of generally mild hypoglycemia has been reported in the PF-07081532 clinical development program to date
		• Only metformin will be permitted as background anti-hyperglycemic treatment - Section 6.9.1
		• For glycemic rescue, study does –
		  ○ Not permit use of insulin – refer to Section 10.10
		  ○ Plan to offer additional guidance to the participant (and site staff) regarding potential for hypoglycemia, if sulfonylurea is used - Section 6.9.1
		• Blood glucose will be monitored by finger-stick home monitoring, using supplies provided by the Sponsor, and via central lab assessments at ***every*** onsite visit in this study – refer to Section 6.9.1 and Table 5
		• Participants will be informed about the signs and symptoms of hypoglycemia, and sites will monitor for these symptoms at clinical study visits - Section 6.9.1

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Impairment in renal function	• Potential risks are based on product labeling for injectable GLP-1R agonists[12,13,20,21], and predominantly occur in patients with significant nausea, vomiting, and dehydration	• Participants with significant renal impairment (<45 mL/min/1.73 m^2) are not eligible (Section 5.2) • Renal function will be monitored at each study visit by the central lab assessments of serum BUN, Scr, eGFR, and urinary albumin:creatinine ratio - Table 5 • Hydration will be encouraged as part of diet/exercise counseling – refer to Section 10.11
Gastrointestinal adverse reactions	• Potential risks are based on product labeling for injectable and oral GLP-1R agonists[12,13,14,20,21] (ie, liraglutide, exenatide, semaglutide, and dulaglutide) • Gastrointestinal AEs, the majority of which were mild in severity, have been observed in the clinical program with PF-07081532	• Participants will be monitored during the clinical study visits, via body weight, vital signs, and laboratory assessments (SoA-Table 1), to prevent potential sequelae of any severe gastrointestinal reactions, eg, dehydration • Dose escalation is limited to once every 4 weeks to improve tolerability - refer to Schema in Section 1.2
Diabetic retinopathy complications	• Potential risk is based on the product labeling for the injectable GLP-1R agonist, semaglutide[12,14,21] (including oral semaglutide) in patients with T2DM • Participants with history of diabetic retinopathy who are taking these agents should be monitored for progression of diabetic retinopathy, as rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy	• Potential participants with known proliferative retinopathy and macular edema requiring acute treatment are excluded (Section 5.2) • Glycemic parameters will be monitored closely, in Stratum 1 (T2DM) during study (Section 6.9.1) with rescue permitted when FPG thresholds are met (Section 10.12) • FPG, CCI HbA1C monitoring in the entire study population at onsite visits - SoA-Table 2
Increase in HR	• Potential risk is based on the product labeling for the injectable GLP-1R agonists[12,21] for T2DM and obesity • Modest increases in HR have been noted in the early clinical studies with PF-07081532 with most values within the normal range.	Vital signs, including pulse rate and BP, and 12-lead ECGs assessed at on-site visits in all participants (SoA-Table 1) – • Prior to on-site dosing of study intervention • And post dose at interval coinciding with T_{max} at selected visits in those randomized to PF-07081532/placebo
Acute gallbladder disease	• Potential risk is based on the product labeling for the injectable and oral GLP-1R agonists[12,14,21]	• Participants with active/current symptomatic gallbladder disease are excluded (Section 5.2) • Participants will be closely monitored for AEs and laboratory tests that may suggest development of acute gallbladder disease with appropriate clinical follow-up undertaken • Limiting caloric-rich diet will be encouraged as part of diet/exercise counseling - refer to Section 10.11

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Suicidal ideation/behavior	• Potential risk is based on the product labeling for the injectable GLP-1R agonists, liraglutide and semaglutide for obesity • Suicidal ideation has not been observed in the PF-07081532 clinical studies to date	**In Stratum 2**, participants with major depressive disorder or other severe psychiatric disorders, any lifetime history of a suicide attempt, and/or clinically significant responses on PHQ-9 or C-SSRS are excluded (Section 5.2) • With post randomization of C-SSRS undertaken for close monitoring of participants – refer to Section 8.3.6
Study Procedures		
Use of a placebo arm	**Stratum 1:** Participants randomized to placebo may not experience sufficient glycemic efficacy and/or body weight loss **Stratum 2:** Participants randomized to placebo may not experience sufficient body weight loss	**Stratum 1 –** • A majority of the randomized study population will receive PF-07081532, or Rybelsus, and all participants will receive metformin and lifestyle counseling – Section 5.3.3.1 • All participants will be eligible for glycemic rescue medication if meeting criteria for rescue and deemed necessary by the investigator – Section 6.9.1.3 **Stratum 2 –** • A majority of the randomized study population will receive PF-07081532, and all participants will receive lifestyle counseling and support from study staff throughout the study – Section 5.3.3.2 **All** participants encouraged to adhere to protocol instructions and maintain study participation to maximize potential for weight reduction

2.3.2. Benefit Assessment

The current study is the first time that PF-07081532 is being administered in an outpatient setting to participants with T2DM inadequately controlled on metformin and separately adults with obesity without T2DM. For the participants of this study, close monitoring of their medical condition and safety will occur as outlined in this protocol –

- **In Stratum 1** (participants with T2DM inadequately controlled on metformin), for every 7 participants randomized, 5 will receive PF-07081532, 1 will receive Rybelsus, and 1 will receive PF-07081532 matching placebo;

- **In Stratum 2** (participants with obesity without T2DM), for every 6 participants randomized, 5 will receive PF-07081532, and 1 will receive PF-07081532-matching placebo.

Those randomized to active arm (PF-07081532 or Rybelsus) *may* potentially derive benefit from the desired pharmacology, namely, improvement in glycemic control (Stratum 1) and weight loss (both Strata). Those randomized to placebo are not expected to obtain any specific benefit, beyond close monitoring of their medical condition and safety. All participants will receive general, standard-of-care guidance/counseling regarding the overall benefits of diet/exercise.

2.3.3. Overall Benefit/Risk Conclusion

In line with the clinical profile of marketed GLP-1R agonists, including Rybelsus, the most frequently reported AEs in the 2 completed studies with PF-07081532 administration have been in the Gastrointestinal Disorders SOC. In addition, as has been reported for marketed GLP-1R agonists, modest increases in heart rate have been observed with PF-07081532 administration, with most heart rate values within the normal range. Based on available clinical data (Section 2.2.4 and current IB[22]), the dose-range planned for evaluation in this study is expected to be safe and well tolerated especially with the planned dose-escalation interval of 4 weeks and up to 5 steps to reach the target dose.

Based on the profile of PF-07081532 observed in nonclinical and clinical studies to date and taking into account the measures to minimize risk to study participants, the potential risks identified in association with study intervention are justified by the anticipated benefits that may be afforded to participants in this study.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To evaluate the efficacy of a range of PF-07081532 doses compared to placebo, ***in participants with T2DM inadequately controlled on metformin***	Placebo-adjusted, change from baseline in ***HbA1C*** at Week 32	The population average treatment effect on the change from baseline in HbA1C at Week 32 of PF-07081532 compared to placebo in the absence of glycemic rescue medication while on treatment • Measurements after initiation of glycemic rescue medication or discontinuation of study intervention will be censored and treated as missing data • Missing data due to censoring, study withdrawal or other reasons (eg, laboratory failure) will have data imputed based on a MAR assumption • Participants with inadequate compliance will have their HbA1C values used as-is in the analysis • The population-based treatment effect will be the difference in the mean change from baseline in each PF-07081532 arm compared to placebo
To evaluate the efficacy of a range of PF-07081532 doses compared to placebo, ***in participants with obesity but without T2DM***	Placebo-adjusted, percent change from baseline in ***body weight*** at Week 32	The population average treatment effect on the percent change from baseline in body weight at Week 32 of PF-07081532 compared to placebo while on treatment • Measurements after discontinuation of study intervention will be censored and treated as missing data • Missing data due to censoring, study withdrawal or other reasons (eg, equipment failure) will have data imputed based on a MAR assumption • Participants with inadequate compliance will have their body weight values used as-is in the analysis • The population-based treatment effect will be the difference in the mean percent change from baseline in each PF-07081532 arm compared to placebo
Secondary:	**Secondary:**	**Secondary:**
To assess the effect of a range of PF-07081532 doses compared to placebo on various parameters, ***in participants with T2DM inadequately controlled on metformin***	Proportion of participants who achieve ***HbA1C*** <7% (<53 mmol/mol) at Week 32	The odds ratio (PF-07081532 relative to placebo) of achieving HbA1C <7% (<53 mmol/mol) at Week 32 in the absence of glycemic rescue medication while on treatment • Measurements after initiation of glycemic rescue medication or discontinuation of study intervention will be censored and treated as missing data • Missing data will not be imputed. • Participants with inadequate compliance will have their HbA1C values used as-is in the analysis

Objectives	Endpoints	Estimands
		• The population-based treatment effect will be the odds ratio of PF-07081532 arm relative to placebo
	Placebo-adjusted, change from baseline in ***FPG*** at Week 32	The estimand for placebo-adjusted, change from baseline in ***FPG*** at Week 32 endpoint will be constructed in a similar manner as Placebo-adjusted, change from baseline in ***HbA1C*** at Week 32
	Placebo-adjusted, percent change from baseline in ***body weight*** at Week 32	The estimand for the placebo-adjusted, percent change from baseline in ***body weight*** at Week 32 endpoint will be constructed in a similar manner as Placebo-adjusted, change from baseline in ***HbA1C*** at Week 32
To compare the efficacy of PF-07081532 and Rybelsus relative to placebo, ***in participants with T2DM inadequately controlled on metformin***	Placebo-adjusted, change from baseline in ***HbA1C*** at Week 32	The population average treatment effect on the change from baseline in HbA1C at Week 32 of each arm of PF-07081532 and of Rybelsus compared to placebo in the absence of glycemic rescue medication while on treatment • Measurements after initiation of glycemic rescue medication or discontinuation of study intervention will be censored and treated as missing data • Missing data due to censoring, study withdrawal or other reasons (eg, laboratory failure) will have data imputed based on a MAR assumption • Participants with inadequate compliance will have their HbA1C values used as-is in the analysis • The population-based treatment effect will be the difference in the mean change from baseline in each PF-07081532 arm and Rybelsus arm compared to placebo
To assess the effect of a range of PF-07081532 doses compared to placebo on various parameters ***in participants with obesity but without T2DM***	• Proportion of participants achieving ≥5%, ≥10%, and ≥15% ***body weight loss*** at Week 32 relative to baseline • Placebo-adjusted, ***absolute*** change from baseline in ***waist circumference*** at Week 32 • Placebo-adjusted, ***absolute*** change from baseline in ***waist-to-hip ratio*** at Week 32 • Placebo-adjusted, change from baseline in ***HOMA-IR*** at Week 32 • Placebo-adjusted, change from baseline in ***HOMA-S*** at Week 32	• The ***odds ratio*** (PF-07081532 relative to placebo) of achieving HbA1C <7% (<53 mmol/mol) at Week 32 in the absence of glycemic rescue medication while on treatment ◦ Measurements after discontinuation of study intervention will be censored and treated as missing data ◦ Missing data will not be imputed ◦ Participants with inadequate compliance will have their body weight values used as-is in the analysis ◦ The population-based treatment effect will be the odds ratio of PF-07081532 arm relative to placebo • The estimand for ***each continuous endpoints*** will be constructed in a similar manner as the primary endpoint Placebo-adjusted, percent change from baseline in ***body weight*** at Week 32
To assess the safety and tolerability with a range of PF-07081532 doses compared to placebo, ***in***	In ***each*** population randomized – • Number (and percent) of participants with: ◦ TEAEs	

Objectives	Endpoints	Estimands
participants with T2DM inadequately controlled on metformin and separately *participants with obesity but without T2DM*	• SAEs • AE leading to permanent discontinuation from study intervention or study • Hypoglycemia • AESIs • Clinical laboratory abnormalities • Vital sign abnormalities • 12-lead ECG abnormalities • And TEAEs, presented in descending order of frequency	
To assess the safety and tolerability with a range of PF-07081532 doses compared to placebo, *in participants with obesity but without T2DM*	Assessment of mental health as determined by – • C-SSRS	
Tertiary:	**Tertiary:**	**Tertiary:**
CCI		
To characterize PK of – • PF-07081532, *in participants with T2DM inadequately controlled on metformin* and separately	In ***each*** population randomized, descriptive summary of trough concentrations of PF-07081532 and Rybelsus	

Objectives	Endpoints	Estimands
participants with obesity but without T2DM • Rybelsus, *in participants with T2DM inadequately controlled on metformin*		
CCI		

In all cases, baseline defined as the evaluable result closest prior to dosing on Day 1/Visit 3

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled, dose-ranging, dose-finding, parallel-group study to access efficacy and safety/tolerability of PF-07081532, and open-label Rybelsus, in adults with T2DM inadequately controlled on metformin (Stratum 1), and separately PF-07081532 compared to matching placebo in adults with obesity but without T2DM (Stratum 2) – refer to overall design schema in Section 1.2

- In **Stratum 1**, three interventions, PF-07081532, its matching placebo, and open-label Rybelsus, will be evaluated across 7 arms in participants with T2DM on a background of metformin.

- In **Stratum 2**, two interventions, PF-07081532 and its matching placebo, will be evaluated across 6 arms in participants with obesity.

- Across all 12 treatment arms of PF-07081532/ placebo each dose will consist of 3 tablets. The treatment duration in this study will be 32 weeks for most participants;

though in the first set of up to 25% randomized participants, treatment interval will extend for an additional up to 12 weeks (for a total duration of up to 44 weeks).

- Dosing across the 12 arms of placebo/PF-07081532 (including dose-escalation, maintenance, and extension (in up to first 25% randomized) – refer to dose-escalation schema in Section 1.2 – is accommodated via administration of 3 tablets per dose QD, and planned using dispensation of 3 bottles (1 tablet per bottle) – refer to Table 3.

Once confirmed to be eligible based on assessments performed at the Screening Visit, participants will transition to Run-In/Visit 2 and receive single-blind PF-07081532-matching placebo for 14 ± 2 days. On Day 1/Visit 3, participants who meet randomization criteria will be randomly assigned to receive double-blinded, double-dummy, PF-07081532 or placebo (and in Stratum 1, open-label Rybelsus).

- For the majority of participants, a total of 21 visits (from Screening to second Follow-up Visit) including 12 on-site plus 9 telephone contacts are planned – with the total duration of participation in study ranging from 40 to 44 weeks;

- For up to the first 25% of participants randomized, an additional 3 on-site visits are planned with the duration of participation extended by 12-weeks with the total duration of participation in study, hence, ranging from 52 to 56 weeks.

Approximately 780 participants (60/arm) will be enrolled (ie, randomized) in the study to ensure approximately 650 participants (51/arm) offer evaluable data for the primary endpoint. Across each of the two populations, approximately 420 participants (60/arm) with T2DM inadequately controlled on metformin plus approximately 360 (60/arm) with obesity but without T2DM, will be enrolled – refer to Section 9.5.

4.2. Scientific Rationale for Study Design

The current study is the first study with PF-07081532 powered to assess the efficacy of the agent on glycemic control and weight. A range of doses of PF-07081532 are being evaluated, via outpatient dosing and dose-escalation once every 4 weeks, in participants with T2DM inadequately controlled on metformin and separately in adults with obesity without T2DM. Duration of stable dose of metformin prior to Screening Visit set at ≥8-weeks such that by the time of baseline assessment of HbA1C, metformin would have been administered at a stable dose for ≥12-weeks. The treatment phase is proposed as at least 32 weeks (including up to 20 weeks for dose-escalation) to permit an evaluation of near nadir for glycemic effect and a clear trajectory for weight loss effect. In up to the first 25% of the total sample size randomized, an extension phase of up to 12 weeks has been added to permit sparse collection of endpoints beyond the primary timepoint (Week 32). These additional data along with model-based-meta-analysis of data from other GLP-1R agonists will permit extrapolation beyond the current study duration and better identification of doses to take forward into future clinical development.

A priori, to permit an evaluation of efficacy on glycemic control and in parallel assess effect on body weight, this study employs stratification based on population – T2DM inadequately

controlled on metformin and separately adults with obesity without T2DM. In addition, this study will enroll representative population via an additional stratification, by sex, and aim to randomize ≥30% males and hence ≤70% females, in each population stratum.

Participants with T2DM enrolled in this study (Stratum 1) will be inadequately controlled on metformin alone at doses ≥500 mg/day (and up to the highest approved dose in country). A clinical DDI study with metformin has not been conducted since based on assessment using in vitro data and a physiologically relevant static mechanistic model, PF-07081532, is not expected to impact the PK of metformin and as such the risk of a clinical interaction is deemed negligible. Given the contribution of CYP3A in the metabolism of PF-07081532 and the fact that PF-07081532 is expected to be cleared via hepatic OATP uptake, strong CYP3A inhibitors or CYP3A inducers and clinically significant OATP inhibitors will be prohibited in this study (Appendix 10). Additionally, based on the predicted DDI liabilities (using in vitro data and a physiologically relevant static mechanistic model) of PF-07081532, certain sensitive substrates for which inhibition of UGT1A1 and CYP2C19 pathways would be expected to clinically significantly alter their safety or efficacy will not be permitted in this study (Appendix 10).

The inclusion of Rybelsus will provide an internal standard for the study to better calibrate study performance and interpret findings with PF-07081532 in adults with T2DM inadequately controlled on metformin. While Rybelsus is open-label, used according to its approved dosing instructions, previous open-label studies of oral semaglutide (eg, PIONEER-4[23] and -7[24]) have yielded similar glycemic efficacy and tolerability results as those observed in double-blind study (eg, PIONEER-2[25]). In Stratum 2 (Obesity), assessment of C-SSRS (SoA-Table 1) plus PHQ9 at Screening Visit and Day 1 included given risk of mental health/suicidality in this population; but not in those with T2DM inadequately controlled on metformin (Stratum 1) – this approach is consistent with this difference in risk in the label for semaglutide in T2DM versus Obesity – refer to Section 2.3.1.

Beyond the primary assessment of HbA1C (in T2DM) and body weight (in obesity without T2DM), the current study also undertakes assessment for potential improvement on other measures of glycemia (FPG, CCI HOMA-IR, HOMA-S, as well as other continuous and categorical data), weight loss (waist circumference, waist-to-hip ratio), and fasting lipid parameters (HDL-C, direct LDL-C, TG, total cholesterol), to permit comparison to published data with peptidic GLP-1R agonists. While traditional banking of plasma/serum/whole blood is not planned, CCI [redacted]. This study includes 12-lead ECG assessments both pre- and post- PF-07081532/placebo dosing to explore any potential relationship between exposure and QT - Section 9.3.4.1. CCI [redacted]

CCI

[redacted]

While the clinical experience with PF-07081532 is limited to maximum of 6 weeks, transition to the current study of up to 44 weeks of dosing is deemed to be acceptable given: (a) precedented primary pharmacology (GLP-1R agonism) with clinical experience of peptidic GLP-1R agonists; (b) chronic toxicity studies with PF-07081532 in rats (up to 6 months) and monkeys (up to 9 months) display no evidence of off-target pharmacology with margins of 40x (C_{max}) and 29x (AUC_{24}) relative to NOAEL in 6-month rat study and 5.2x (C_{max}) and 4.6x (AUC_{24}) relative to NOAEL in 9-month monkey study; ***and*** (c) single (up to 200 mg) and repeated doses (up to 180 mg QD) up to 6 weeks were considered safe and were demonstrated to have a tolerability profile consistent with the mechanism of action. Despite this safety profile, given the transition to the proposed up to 44 weeks of dosing in this study, measures to ensure participant safety are included – **(a)** eligibility criteria and safety monitoring strategy aimed at minimizing risk – refer to Section 2.3.1; **(b)** frequent (every 2 week), visits with site staff *either* as outpatient visits *or* telephone contact, up to Week 32/Visit 19 with provisions for unplanned visits for follow-up of AEs (refer to Section 8.4.3) and clinically significant laboratory results; **(c)** *as much as practically doable*, the use of same-day shipment of safety-related blood/urine samples to sponsor-identified central laboratory with rapid turn-around of safety-related results and management of overall glycemic control (Appendix 12); **(d)** use of an IRC (refer to Section 9.4 and Section 10.1.5.1) to undertake *unblinded* review of data post randomization, at a minimum, of approximately 25%, 50%, 75% and 100% of planned total sample size; and **(e)** periodic *blinded* review of safety by the sponsors' clinical team members to assess for potential trigger for additional IRC unblinded review(s) of cumulating safety data while the study is on-going.

A comparison of exposures of PF-07081532 administered under fasted and fed conditions indicate that PF-07081532 may be administered without regard to food. The clinical PK and observed half-life of PF-07081532 (ranging between 20.7 to 26.5 hours following multiple dosing) are supportive of once daily administration. Thus, administration of PF-07081532/placebo in this study will be requested to occur with the morning meals – given the importance of regular meals to the standard-of-care diet counseling for the planned population.

For all participants deemed eligible after Screening Visit, transition to Visit 2/Run-In is mandatory for a fixed, single-blind, 2-week period (ie, Visit 2/Run-In to 1-day prior to Visit 3/Day 1). This is included with the explicit purpose of familiarizing the participants with the dosing instructions for the study intervention (refer to Table 3), and to exclude participants who are *not* compliant with the single-blind placebo prior to randomization in an attempt to minimize medications errors post randomization.

4.2.1. Diversity of Study Population

Diversity of study population in this protocol applies to sites in US ***only***. This diversity strategy will include high-performing sites with the potential to support the recruitment of diverse populations. Reasonable attempts will be made to enroll participants that are representative of the patient population that will be treated with PF-07081532 in clinical practice. The following strategies may be explored in support of diverse recruitment efforts:

- Inclusion of diversity questions into the Feasibility Survey and Pre-Trial Assessment to identify sites with access to diverse patient populations
- Selecting sites that have access to diverse participants within their locale
- Discussion with investigator sites during pre-trial assessment to assess preparedness, mitigation strategies for reaching diversity goals, and active inclusion
- Encouragement of investigator sites to complete the Investigator Site Recruitment Plan
- Have proactive discussions with investigator sites throughout the enrollment period to assess and reevaluate site specific strategies as needed to best position each site for the most diverse representation enrollment outcomes
- Collaboration with patient advocacy groups
- Monitor diverse enrollment to identify potential opportunities to include diverse populations

4.2.2. Choice of Contraception/Barrier Requirements

Both women of childbearing potential, as well as those who are of non-childbearing potential, may be enrolled given the availability of EFD nonclinical toxicity studies with PF-07081532. However, measures will be taken to limit the risk of pregnancy in the female population of childbearing potential enrolled (see SoA-Table 1, SoA-Table 2, and Appendix 4).

The potential risk of exposure to PF-07081532 in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception (condom) use in male participants is warranted. The calculated safety margin is ≥100-fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[40]

4.3. Justification for Dose

4.3.1. PF-07081532

The dose range selected (refer to dose-escalation schema in Section 1.2) for this study is based on observed safety, tolerability, PK, and PD data in completed Phase I clinical studies along with data obtained in nonclinical toxicity studies.

In Stratum 1 (T2DM inadequately controlled on metformin), this study is designed to evaluate the dose-response of PF-07081532 from low doses, predicted to have sub-maximal effects on HbA1C up to doses expected to have greater HbA1C lowering efficacy, while still having an adequate tolerability profile. Based on preliminary dose-response analysis of mean daily glucose data following repeated dose data in participants with T2DM and translation to HbA1C efficacy via semi-mechanistic modeling,[28] the proposed PF-07081532 targeted dose levels, in Stratum 1, of 20, 40, 80, 160, and 260 mg QD are expected to result in HbA1C lowering that is 26%, 40%, 56%, 71% and 80% of the maximal response, respectively.

In Stratum 2 (Obesity without T2DM), planned doses will be different than Stratum 1 with the lowest planned targeted dose in the former being 4-fold higher (80 mg QD). This acknowledges that with peptidic GLP-1R agonists, higher doses are needed to observe clinically meaningful weight loss compared to improvement in glycemic control. Based on the available Phase 1 data with PF-07081532, it is anticipated that the dose range tested in Stratum 2 (from 80 to 260 mg QD) will adequately bracket the efficacious dose needed to achieve comparable weight loss to that of approved injectable GLP-1R agonists, while still having an adequate tolerability profile. Escalation of PF-07081532 to the target dose of 200 mg QD will be assessed via different dose steps in two different arms of the study to investigate impact of the dose escalation scheme on tolerability.

Single doses up to 200 mg and multiple doses up to 180 mg QD of PF-07081532 have been shown to be safe, with no clinically relevant dose-related adverse trends and a tolerability profile consistent with the mechanism of action. The duration of repeat dosing in the completed multiple ascending dose study was limited to 6 weeks with rapid escalation over 5 weeks before reaching the top dose (180 mg QD). In the current study, PF-07081532 doses will be escalated over a period of up to 20 weeks with escalation steps of every 4 weeks, which, in line with other marketed GLP-1R agonists, is expected to further improve tolerability and mitigate the adverse MoA-based GI side effects[11,29]. The lowest dose of 20 mg QD, in Stratum 1, is expected to be well tolerated without the need for escalation and thus will be dosed at the same dose level for the entire duration. The predicted PF-07081532 exposure at the highest 260 mg QD dose is lower than the exposure observed at the NOAEL in the pivotal 9-month toxicology study in monkeys, after accounting for differences in plasma protein binding between species. Therefore, this dose level is not anticipated to pose an undue safety risk. Based on the above, PF-07081532 doses up to 260 mg QD are viewed as appropriate for assessment in this study with an expected acceptable safety and tolerability profile.

4.3.2. Rybelsus

The highest approved dose (14 mg QD) of Rybelsus, the only currently approved oral GLP-1R agonist, for the treatment of T2DM, was selected to be evaluated in this study as a

within-study benchmark of the efficacy and tolerability profiles observed with PF-07081532. The dose escalation scheme that will be employed in this study is in line with Rybelsus prescribing information[14].

4.4. End of Study Definition

The end of the study is defined as the date of the last visit in the study (ie, second Follow-up Visit shown in SoA-Table 1, SoA-Table 2) for the last participant in the study globally.

A participant is considered to have completed the study if they have completed all periods of the study, including the second Follow-up Visit shown in SoA-Table 1, SoA-Table 2.

5. STUDY POPULATION

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

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

Pfizer will review eligibility criteria verified by the investigator or qualified designee to confirm that participants meet study eligibility criteria before they are enrolled/randomized into the study. The enrollment/randomization approval process will be initiated for a participant after an informed consent document has been signed and the investigator or qualified designee has assessed the participant as eligible. The enrollment/randomization approval will be based on review of CRF/system data.

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 or female 18 years or older (or the minimum age of consent in accordance with local regulations) and up to 75 years, inclusively, at the Screening Visit.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants including requirement for pregnancy testing (Section 8.3.5);

Disease Characteristics:

2. For Stratum 1 ***only***:

   - Participants diagnosed with T2DM inadequately controlled with metformin at doses ≥500 mg/day (and up to the highest approved, in country dose) with metformin dose stable for ≥8 weeks prior to Screening Visit;

   - BMI ≥23.0 kg/m^2 (≥20.0 kg/m^2 in Japan), using the average of the duplicate body weight assessment at Screening Visit, **and** with 1 other assessment of BMI via duplicate body weight assessment permitted, ***on a different day***, to assess eligibility;

   - HbA1C of 7% to 10% (53-86 mmol/mol), inclusive, at Screening Visit, with result as assessed using a method that is NGSP certified and standardized to the DCCT assay, by the sponsor-identified central laboratory, with a single repeat permitted to assess eligibility;

   - FPG ≤270 mg/dL (15 mmol/L) at Screening Visit, with a single repeat permitted to assess eligibility;

3. For Stratum 2, ***only***:

   - Participants with obesity, defined by BMI ≥30.0 kg/m^2, using the average of the duplicate body weight assessment at Screening Visit, **and** with 1 other assessment of BMI via duplicate body weight assessment permitted, ***on a different day***, to assess eligibility;

   - HbA1C ≤6.4% (47 mmol/mol), at Screening Visit, with result as assessed using a method that is NGSP certified and standardized to the DCCT assay, by the sponsor-identified central laboratory, with a single repeat permitted to assess eligibility;

   - FPG ≤126 mg/dL (7 mmol/L) at Screening Visit, with a single repeat permitted to assess eligibility;

Other Inclusion Criteria:

4. At the Screening Visit, participants willing to adhere to dose-escalation and MoA-based GI AEs mitigation strategies – refer to Section 10.11.

5.2. Exclusion Criteria

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

Medical Conditions:

1. ***Any*** of the following clinically significant medical conditions –
    - Active/current, symptomatic gallbladder disease;
    - History of pancreatitis in the 12-months prior to Screening Visit;
    - History of Type 1 Diabetes Mellitus, or secondary forms of diabetes (*NOTE*: a history of gestational diabetes that has resolved is allowed);
    - Any condition affecting drug absorption (eg, prior bariatric surgery, gastrectomy, **or** any area of intestinal resection, active inflammatory bowel disease or pancreatic insufficiency);
    - Known medical history of active liver disease (other than non-alcoholic hepatic steatosis), including active hepatitis, primary biliary cirrhosis, ascites;
2. Use of pharmacological agents with approved indication for weight loss (eg, orlistat, sibutramine, GLP-1R agonists), over-the-counter appetite- stimulant ***or*** appetite-suppressant, as advertised, ***within 12 weeks*** of Screening Visit; ***or*** weight loss of >5% in the ***12 weeks prior*** to Screening Visit, based on participants medical records *or* as reported by the participant;
3. For Stratum 1 ***only***:
    - Use of ***any*** pharmacological agent with an approved indication for T2DM (other than metformin), **or** herbal medications, for the explicit purpose of glycemic control within 12 weeks of Screening Visit;
    - History of diabetic ketoacidosis ***unless*** this was the presentation leading to diagnosis of T2DM *without* recurrence since initial presentation;
    - Proliferative retinopathy or maculopathy requiring acute treatment;
4. For Stratum 2 ***only***:
    - Previous or planned (during the study) weight reduction surgery or device use, with the following ***exceptions so long as body weight has stabilized***
        - Liposuction and/or abdominoplasty;
        - Lap banding if band has been removed;

- Intragastric balloon if balloon removed;
- Duodenal-jejunal bypass sleeve if removed;

- Diagnosis of T2DM;
- Use of pharmacological agent(s) with approved indication for glycemic control *except* metformin when used for the *explicit **sole** purpose* of managing PCOS;
- **Any** of the following –
  - Major depressive disorder **or** other severe psychiatric disorders (eg, schizophrenia or bipolar disorder) ***within 2 years*** prior to Screening Visit;
  - Any lifetime history of a suicide attempt;
  - PHQ-9 score ≥15 – at the Screening Visit **or** Day 1/Visit 3;
  - Response of "yes" to Question 4 or 5, **or** on any suicidal behavioral question on the C-SSRS – at the Screening Visit **or** Day 1/Visit 3;

5. Clinically significant cardiovascular conditions defined by ***either*** of the following –
   - Myocardial infarction, stroke, hospitalization for unstable angina, or transient ischemic attack within **12 weeks** prior to Screening Visit;
   - Presentation of unstable angina **or** congestive heart failure (NYHA class III or IV) **or** significant edema managed with diuretics **with or without** evidence of ascites, at Screening Visit;
6. Uncontrolled blood pressure defined as ***average of triplicate*** assessment being ≥160 mmHg (systolic) or ≥100 mmHg (diastolic), at Screening Visit (Section 8.3.2.1), with 1 other assessment of average BP via triplicate assessment permitted, ***on a different day***, to assess eligibility; **or** on Day 1/Visit 3
   - Participants on anti-hypertensive medication(s) to treat hypertension should be on a stable dose ≥4 weeks prior to Screening Visit;
7. Personal or within first-degree relative family history of MTC or MEN2;
8. Other medical or psychiatric condition including recent or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study

participation or, in the investigator's judgment, make the participant inappropriate for the study including –

- Recent (within 5 years of Screening Visit) systemically administered treatments for malignancy including (but not limited to) the use of chemotherapy, radiotherapy, or immunotherapy; **or** any other active malignancy (within 3 years of Screening Visit), except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.

Prior/Concomitant Therapy:

9. Current use of any prohibited concomitant medication(s) or participants unwilling/unable to use a permitted concomitant medication(s) - refer to Section 6.9 and Section 10.10;

Prior/Concurrent Clinical Study Experience:

10. Participants noted to be non-compliant (based on tablet count and defined as compliance of <80% **or** >120%) with incorrect self-administration (ie, deviating from 1 tablet from each bottle daily) with the single-blind placebo administered from Run-In/Visit 2 to 1 day before Day 1/Visit 3, inclusive;

11. Previous administration with an investigational product (drug or vaccine) **within 30 days** (**or** as determined by the local requirement) **or** 5 half-lives preceding the first dose on Day 1/Visit 3 in this study (whichever is longer);

    - Investigational products which are strong CYP3A inducers are prohibited within 14 days plus 5 half-lives preceding the first dose of study intervention refer to Section 10.10;

12. Previous participation in a clinical study evaluating PF-07081532 (including exposure to placebo) **or** intolerance or hypersensitivity to a GLP-1R agonist;

Diagnostic Assessments:

13. Results as reported by sponsor-identified central laboratory, at Screening Visit, as below, with a single repeat permitted to assess eligibility:

    - Fasting C-peptide <0.8 ng/mL;
    - ALT **or** AST ≥2.5x ULN;
    - Direct bilirubin >ULN **or** T Bili >1.5x ULN ***except*** when participants have a history of Gilbert syndrome where total bilirubin >1.5x ULN would be eligible provided direct bilirubin level is ≤ULN;
    - TSH >1.5x ULN **or** <LLN;

- Serum calcitonin >ULN;
- Serum amylase **or** serum lipase >ULN;
- eGFR (using CKD-EPI-Scr-Scys Combined <45 ml/min/1.73 m^2 – refer to Section 10.7.2.1;
- Active Hepatitis B, or Hepatitis C;
- A positive urine drug test for illicit drugs –
  - Participants who have been medically prescribed controlled/scheduled drugs and report the use of these drugs to the investigator at Screening Visit may be allowed to participate with notification to the sponsor;
  - This one laboratory-based assessment ***not*** permitted to be repeated to confirm eligibility.

14. At Screening Visit, ***average of triplicate*** assessment of standard 12-lead ECGs (Section 8.3.3) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias) –
    - **If** the Screening Visit, ***average of triplicate*** assessment, uncorrected QT interval is >450 ms, this interval should be rate corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting;
    - **If** ***average of triplicate*** assessment of QTcF exceeds 450 ms, or QRS exceeds 120 ms, 1 other assessment of average cardiac conduction intervals (QTcF and QRS) via ***triplicate assessment*** is permitted ***on a different day***, to determine the participant's eligibility;
    - Computer-interpreted ECGs should be overread by medically qualified individual (***either*** site **or** central reader) experienced in reading ECGs before excluding a participant.

Other Exclusion Criteria:

15. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

The following sections describe guidelines for diet, physical activity, alcohol, caffeine and tobacco use and contraception requirements that are to be followed throughout the study.

5.3.1. Contraception

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

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

5.3.2. Dietary Restrictions

- Participants must abstain from all food and drink (except water) for ≥**8 hours prior** to **all** ***pre-dose*** procedures outlined in SoA-Table 1, SoA-Table 2;
- Water may be consumed as desired (ad libitum) up to 2 hours **prior** to pre-dose blood sampling;
- PF-07081532/placebo must be administered QD in the morning; ***and*** with the morning meal *as much as possible*;
- ***Stratum 1 only***: Rybelsus must be administered QD in the morning ≥30 minutes before the first meal/beverage, or other oral medications with ≤4 oz (120 mL) water;
- On scheduled on-site visits (SoA-Table 1, SoA-Table 2), participants should be instructed to arrive following an **overnight fast of ≥8 hours** (***without*** having consumed any food/beverage [except water]) and ***without*** self-administration of study intervention;
    - ***Note***: Participants, other than the Rybelsus group, may take their morning dose of their **background** medications before their visit per their usual routine, if applicable.

- On the mornings of scheduled on-site visits (SoA-Table 1, SoA-Table 2), the study intervention will be administered at the site –

  - The morning meal during site visits will be either provided by the site **or** the participant provided a voucher [or similar] by the site to purchase the meal before arriving at the site for each visit with caloric content of **approximately 300 calories** and macronutrient composition commensurate to dietary counseling (Section 5.3.3);

- Participants will be counseled on appropriate dietary (Section 5.3.3) and physical activity (Section 5.3.4) guidelines, at the times listed in SoA-Table 1, and asked to maintain these guidelines throughout participation in the study; ***of note***, initiation of participation in formal weight loss program(s) should be avoided after Day 1/Visit 3 and until the completion of the first follow-up visit.

5.3.3. Dietary Counseling

At times listed in the SoA-Table 1, participants will receive dietary counseling[29] by appropriate site staff and asked to follow these guidelines throughout the treatment phase (and up to Week 44). In addition, suggested dietary modifications are outlined in Section 10.11.

5.3.3.1. Stratum 1 (T2DM inadequately controlled with metformin)

Participants will be counseled on appropriate dietary and lifestyle guidelines for T2DM. Counseling on dietary guidelines should be in accordance with local medical standards of care for patients with T2DM.

5.3.3.2. Stratum 2 (Obesity without T2DM)

Consistent with the expected background of diet and exercise, participants in Stratum 2, as part of dietary counseling will receive instructions that encourage an energy deficit of ≥500 kcal/day[30].

Individual participants energy deficit determined based on the participant's TEE, in accordance with guidelines, using the formula below:

- TEE = REE x activity factor.

For all participants, an activity factor of 1.3 (to match a sedentary activity level) will be used. The REE for each participant will be calculated with the Harris Benedict formula[31] for men and women, using the participant's body weight, height, and age obtained at Screening Visit, as listed below:

- ***For women:*** REE (kcal/d) = 655.0955 + [9.5634 x weight (kg)] + [1.8496 x height (cm)] – [4.6756 x age (years)].

- ***For men:*** REE (kcal/d) = 66.4730 + [13.7516 x weight (kg)] + [5.0033 x height (cm)] – [6.7550 x age (years)].

5.3.4. Physical Activity Counseling

At times listed in SoA-Table 1, participants will be encouraged to maintain physical activity for ≥150 minutes per week (≥30 minutes per day most days of the week) in accordance with guidelines[30].

5.3.5. Alcohol, Caffeine, and Tobacco

- Intake of alcohol is permitted in moderation defined by alcohol consumption of up to 7 drinks/week for female participants **or** 14 drinks/week for male participants (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor);

- Caffeine containing products will be permitted during the study with the following restrictions: caffeine containing products may ***not*** be consumed within 1 hour prior to measuring **post dose** vital signs and ECGs;

- Use of nicotine-containing products is permitted in this study with the following restrictions: nicotine-containing products may not be used within 1 hour prior to measuring **post dose** vital signs and ECGs.

5.4. Screen Failures

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

For this study, rescreening may ***only*** be permitted under specific circumstances and only ***after*** contact with a Sponsor Clinical Representative –

- This may be permitted, for example, for a participant who qualified for this study but did not enroll within the protocol prescribed **interval of 6 weeks** (from Screening Visit to Day 1/Visit 3) due to logistical constraints or for administrative reasons;

- Re-screening may be appropriate, at Investigator and Sponsor discretion, following mild intercurrent illness (eg, infection) after the condition has resolved;

- Re-screening may be appropriate, at Investigator and Sponsor discretion, **after** medical decompensation has been successfully managed (eg, BP ≥160 (SBP) or ≥100 (DBP) mmHg appropriately controlled via optimization of background BP medications/diet counseling in particular related to salt intake);

Otherwise, individuals who do not meet the eligibility criteria for participation in this study (screen failure) **cannot** be re-screened.

In case of re-screening, reconsent is required and ***all*** screening procedures must be repeated. The participant will be assigned a new Screening number. It must be confirmed that participant meet ***all*** eligibility criteria under the new Screening number before progressing to randomization/Day 1.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, **study intervention** refers to –

- PF-07081532
- Placebo, matching PF-07081532
- Open-label Rybelsus (ie, oral semaglutide)

6.1. Study Intervention(s) Administered

Study Intervention(s)			
Intervention Name	Placebo	PF-07081532	Rybelsus
Arm Name (group of participants receiving a specific treatment or no treatment)	Placebo [Stratum 1] Placebo [Stratum 2]	20 mg QD [Stratum 1] 40 mg QD [Stratum 1] 80 mg QD [Stratum 1 and 2] 140 mg QD [Stratum 2] 160 mg QD [Stratum 1] 200 mg QD [5 steps; Stratum 2] 200 mg QD [4 steps; Stratum 2] 260 mg QD [Stratum 1 and 2]	14 mg QD [Stratum 1]
Type	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet
Unit Dose Strength(s)	Not Applicable	20 mg; 60 mg; 100 mg	3 mg; 7 mg; 14 mg
Dosage Level(s)	0 mg	Refer to **Arm Description** below	Refer to **Arm Description** below
Route of Administration	Oral	Oral	Oral
Storage conditions	Refrigerated (2-8°C)	Refrigerated (2-8°C)	Room temperature (15-25°C)
Use	Placebo	Experimental	Internal reference standard [Stratum 1]
IMP or NIMP/AxMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to the IPM		
Packaging and Labeling	• Study intervention will be provided in 34 count bottles • Each bottle will be labeled as required per country requirement • Blinded labels will be utilized for placebo run-in, dose-escalation, and	• Study intervention will be provided in 34 count bottles • Each bottle will be labeled as required per country requirement; • Blinded labels will be utilized for dose-escalation, and maintenance dosing bottles	• Study intervention will be provided in over-labeled 30 count commercial bottles (US Sourced) and over-labeled 30 count commercial blister packs (EU Sourced) • ***Unblinded*** labels will be utilized for dose-escalation, and

Study Intervention(s)			
	maintenance dosing bottles		maintenance bottles **or** blister packs
Current/Former Name(s) or Alias(es)	Placebo	PF-07081532	Rybelsus/oral semaglutide

Study Arms			
Arm Title	**Arm Type**	**Arm Description**	**Associated Intervention Labels**
Placebo [Stratum 1 and 2]	Placebo	Participants will receive placebo for up to 44 weeks	PF-07081532 / placebo
PF-07081532 20 mg QD [Stratum 1]	Experimental	Participants will receive PF-07081532 20 mg QD for up to 44 weeks	
PF-07081532 40 mg QD [Stratum 1]		Participants will receive PF-07081532 20 mg QD (for 4 weeks) followed by 40 mg QD (for up to 40 weeks)	
PF-07081532 80 mg QD [Stratum 1 and 2]		Participants will receive PF-07081532 20 mg QD, 40 mg QD, 60 mg QD – sequentially, each for 4 weeks followed by 80 mg QD (for up to 32 weeks)	
PF-07081532 140 mg QD [Stratum 2]		Participants will receive PF-07081532 20 mg QD, 40 mg QD, 60 mg QD, 80 mg QD, 120 mg QD – sequentially, each for 4 weeks followed by 140 mg QD (for up to 24 weeks)	
PF-07081532 160 mg QD [Stratum 1]		Participants will receive PF-07081532 20 mg QD, 40 mg QD, 60 mg QD, 80 mg QD, 120 mg QD – sequentially, each for 4 weeks followed by 160 mg QD (for up to 24 weeks)	
PF-07081532 200 mg QD [5 steps; Stratum 2]		Participants will receive PF-07081532 20 mg QD, 40 mg QD, 60 mg QD, 100 mg QD, 160 mg QD – sequentially, each for 4 weeks followed by 200 mg QD (for up to 24 weeks)	
PF-07081532 200 mg QD [4 steps; Stratum 2]		Participants will receive PF-07081532 20 mg QD, 40 mg QD, 80 mg QD, 140 mg QD – sequentially, each for 4 weeks followed by 200 mg QD (for up to 28 weeks)	
PF-07081532 260 mg QD [Stratum 1 and 2]		Participants will receive PF-07081532 20 mg QD, 40 mg QD, 80 mg QD, 140 mg QD, 200 mg QD – sequentially, each for 4 weeks followed by 260 mg QD (for up to 24 weeks)	
Rybelsus 14 mg QD [Stratum 1]	Internal reference standard	Participants will receive Rybelsus 3 mg QD, 7 mg QD –sequentially, each for 4 weeks followed by 14 mg QD (for up to 36 weeks)	Rybelsus

Across the 12 arms involving administration of varying doses of PF-07081532 or placebo, double-blind, double-dummy design will be retained as outlined in Table 3 – using 4 identical-looking tablet strengths and each dose consisting of 3 tablets.

Table 3. Double-blind, Double-dummy Regimens in Study C3991004

PF-07081532 doses	***Number of tablets***				
	Placebo	**20 mg**	**60 mg**	**100 mg**	**Total**
Placebo	3	-	-	-	3
20 mg QD	2	1	-	-	3
40 mg QD	1	2	-	-	3
80 mg QD	1	1	1	-	3
120 mg QD	1	1	-	1	3

Table 3. Double-blind, Double-dummy Regimens in Study C3991004

PF-07081532 doses	*Number of tablets*				
	Placebo	**20 mg**	**60 mg**	**100 mg**	**Total**
140 mg QD	-	2	-	1	3
160 mg QD	1	-	1	1	3
200 mg QD	1	-	-	2	3
260 mg QD	-	-	1	2	3

Open-label Rybelsus across the planned 2-step dose-escalation to target dose of 14 mg QD (ie, 3 mg QD, 7 mg QD, and 14 mg QD) consists of 1 tablet per dose.

Study intervention may be shipped courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the study intervention. Pfizer does not permit the shipment of study intervention by mail. The tracking record of shipments, including temperature monitoring data, and the chain of custody of study intervention must be kept in the participant's source documents/medical records.

6.1.1. Administration

Participants will swallow the study intervention whole and will not manipulate or chew the study intervention prior to swallowing.

- Each dose of PF-07081532/ placebo consists of 3 identical looking tablets – 1 from each of the 3 identical looking bottles dispensed;
    - **In addition**, as a means to reinforce dosing instructions, at ***each*** on-site visit, dosing of PF-07081532/ placebo with the morning meal on site should include site staff watching each participant remove 1 tablet from each bottle, and self-administering the dose of 3 tablets;
- Each dose of Rybelsus consists of 1 tablet from the single bottle or blister pack;
- Refer to Section 5.3.2 for instructions on dosing of PF-07081532/placebo and Rybelsus – while considering dietary restriction;
- Additional dosing instructions will be offered as part of the dosing diary – including management of isolated cases when dosing in the morning is missed;

6.1.2. Medical Devices

- The manufactured medical devices provided for use in this study, for participants in Stratum 1 ***only*** include glucometer and associated ancillary supplies to permit participants to undertake self-monitoring of fingerstick glucose as per local standard-of-care guidance
- Instructions for medical device use are provided as part of the instructions related to hypoglycemia.

- All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.9) and appropriately managed by the sponsor.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. Site staff will instruct participants on the proper storage requirements for take-home study intervention. See the IPM for storage conditions of the study intervention.

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. **Returned study intervention must not be re-dispensed to the participants**.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. All destruction must be adequately

documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

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

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention via an IRT system using unique container numbers on the bottles or blister packs provided, in quantities appropriate according to the SoA-Table 1. A second staff member will verify the dispensing. The participant should be instructed to maintain the product in the bottle or blister pack provided throughout the course of dosing and return the bottle or blister pack to the site at the next study visit.

6.3. Assignment to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an IRT system for –

- Single-blind placebo administered starting at Run-In/Visit 2 through 1 day prior to Day 1/Visit 3;
- Double-blind, double-dummy PF-07081532/matching placebo starting Day 1/Visit 3 and up to Week 44;
- ***and*** open-label Rybelsus starting Day 1/Visit 3 and up to Week 44;

The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number corresponding to the assigned treatment group, and DU or container number(s) when study intervention 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 stored in the site's files.

Study intervention will be dispensed at the study visits summarized in the SoA-Table 1.

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

6.4. Blinding

This is a double-blind study with administration of PF-07081532 or matching placebo in 12 of the 13 arms in this 2 strata study. One of the 13 arms includes the internal reference standard, Rybelsus, as an open-label arm in Stratum 1, only.

6.4.1. Blinding of Participants

Participants will be –

- ***blinded*** to administration of single-blind placebo during the Run-In Period (ie, Visit 2/Run-In to 1 day *prior* to Visit 3/Day 1);
- ***blinded*** to their randomized assignment of PF-07081532 **or** placebo including dose-escalation steps starting on Day 1;
- ***unblinded*** to their randomized assignment of Rybelsus including dose-escalation steps starting on Day 1.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be –

- ***unblinded*** to administration of placebo during the Run-In Period (ie, Visit 2/Run-In to 1 day *prior* to Visit 3/Day 1);
- ***blinded*** to randomized assignment of PF-07081532 **or** placebo including dose-escalation steps starting on Day 1;
- ***unblinded*** to randomized assignment of Rybelsus including dose-escalation steps starting on Day 1;
- ***blinded*** to following laboratory results as reported by sponsor-identified central laboratory –
  - HbA1C results on Day 1; and ***after*** Day 1 ***unless*** result is >10% (86 mmol/mol);
  - FPG results on Day 1; and after Day 1 ***unless*** result is –
    - >270 mg/dL (15 mmol/L) up to 1 day *prior* to Week 16/Visit 11;
    - >240 mg/dL (13.3 mmol/L) ***after*** Week 16/visit 11 and up to Week 44/Visit 22;
    - **or** <70 mg/dL (3.9 mmol/L) at any time;

CCI [redacted]

6.4.3. Blinding of the Sponsor

- Sponsor staff interfacing with the sites will maintain the same level of blinding as site personnel and outlined in Section 6.4.2;

- Additional Sponsor staff, not involved in day-to-day conduct of the study will have access to blinded information as outlined in the PK-PD unblinding plan (Section 9.4.1).

6.4.4. 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 study medical monitor 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 CRF.

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

6.5. Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit as per SoA-Table 1. Compliance will be assessed by direct questioning, counting returned tablets during the ***applicable*** on-site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of PF-07081532/placebo or Rybelsus tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or temporary pause in dosing, will also be recorded in the CRF.

Compliance with study intervention will be defined as –

- ≥80% and ≤120% of tablets in *each bottle* of study-supplied single-blind placebo consumed from Visit 2/Run-In to 1 day prior to Visit 3/Day 1 – with self-administration correctly as defined by 1 tablet from *each* of the 3 bottles dispensed each day;

    - *For example:* **If** duration of dosing was 12 days (of the permitted 14±2 days), participant can miss a maximum of 2 **doses** (*or* take a maximum of 2 extra **doses**) to remain qualified for randomization

- ≥80% (and ideally, up to 100%) of tablets in *each bottle* **or** *blister pack* of study-supplied intervention from Visit 3/Day 1 through up to Visit 22/Week 44, inclusive, are expected to be consumed

    - Investigators must closely monitor non-compliant participants in order to enhance participants adherence to the study intervention;

    - Post randomization, at ***each*** dispensation visit (refer to SoA-Table 1), participants who are <80% compliant must be re-educated on the importance of daily self-administration of study intervention;

    - ***Overall aim***: maintain ≥80% compliance over the duration of dosing with randomized study intervention.

Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

6.6. Dose Modification

6.6.1. Dose Escalation

A fixed dose escalation scheme is planned to be used for each PF-07081532 or Rybelsus study intervention dosing arm in this study as described in Section 1.2. Each dosing regimen will be provided in prefilled bottles (and blister packs in the case of Rybelsus for some region(s) as necessary based on source of this commercially available supply) –

- The protocol does ***not*** permit dose adjustment – refer to Section 10.11;

- However, participant education, expectations, and avenues to manage the temporary MoA-based GI-related AEs including permitting dosing to be temporarily paused for a ***maximum of 2 days*** is permitted – refer to Section 10.11;

- ***Whenever possible***, attempts must be made to avoid temporary pause in dosing in the 7 days immediately prior to on-site visit

6.6.2. Considerations for Pausing or Stopping Active Dose(s) Based on Observed Safety

The decision to stop dosing for 1 or more active dose(s) of PF-07081532 may be considered based on recommendations from the IRC (Section 9.4) according to their review of unblinded, study-level emerging, observed safety data, for reasons such as the following:

- More than 50% of participants develop a moderate or severe AE in the gastrointestinal SOC ***not*** responsive to symptomatic management;

- Additional details included in the IRC Charter finalized prior to initiation of randomization in this study.

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

This is the first study powered to assess efficacy of PF-07081532 with an evaluation of a range of doses to enable identification of efficacious dose(s) upon study completion (not at start of the study). Hence, no study intervention will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

For this study, any dose of PF-07081532 ***greater than 16 tablets taken from 1 bottle*** within a 24-hour time period will be considered an overdose. This reflects a dose of **1.6 g** *assuming* overdose with the bottle containing the highest strength tablets (ie, 100 mg) in any 1 bottle. A single dose of 1.6 g is projected to result in exposure that will exceed that observed at the NOAEL in the pivotal 9-month toxicology study in monkeys, after accounting for species differences in plasma protein binding.

The SRSD for Rybelsus does not identify a specific dose (mg) as overdose[14]. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of Rybelsus of approximately 1 week.

There is no specific treatment for an overdose with PF-07081532 or Rybelsus.

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

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

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

6.9. Prior and Concomitant Therapy

Details regarding prohibited concomitant medications as well as medications with timeframes for restriction prior to Screening or first dose of study intervention are provided

in Section 10.10. Sites are encouraged to contact the Sponsor should there be any questions as to whether a medication is permitted or prohibited.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants per details in Appendix 4 and in Stratum 1 (T2DM) specific restrictions are set regarding agents for glycemic control – refer to Section 6.9.1.

OTC medications are permitted during this study, unless specified as prohibited in Section 10.10. The use of herbal supplements and other natural products (including Traditional Chinese Medicine) should be discouraged. Participants should be instructed ***not*** to initiate new supplements or natural products during the study.

All concomitant treatments (both prescription and OTC) taken during the study must be recorded with indication and start and stop dates of administration. All participants will be questioned about concomitant treatment at each visit. In Stratum 1, details regarding daily dose of metformin will be captured in the CFR to permit an assessment of changes in this required background medication.

Medications **started before, or ongoing, on Day 1/Visit 3** will be documented as **prior** medications. Medications started after dosing with randomized study intervention on Day 1/Visit 3 and until the second Follow-up Visit, inclusive, will be documented as concomitant medications.

Given the duration of the dosing phase in this study (ie, up to 44 weeks), it is likely that changes in background medications will be needed as part of standard-of-care to manage concomitant medical conditions. Guidance offered herein is requested to be considered when determining how best to maintain control.

6.9.1. Management of Glycemic Control in Stratum 1

Participants are required to be on a stable dose of metformin of ≥500 mg/day and up to the highest in-country approved dose for **≥8 weeks prior to Screening Visit** and until first on-site Follow-up Visit

- Use of ***any*** other country-specific approved classes of agents for glycemic control including other biguanides, DPPIV inhibitors, SGLT2 inhibitors, thiazolidinediones/PPARγ, sulphonylureas, α-glucosidase inhibitors, meglitinide analogues, GLP-1R agonists, short or long-acting insulin – is not permitted within **12 weeks prior to Screening Visit** (Table 7);
    - Of note, short-term (ie, ≤7 days) of insulin administration is permitted if participant is hospitalized;
- In participants meeting FPG thresholds for addition of new agent (Section 10.12), any of the above mentioned classes of orally administered agents can be considered ***except*** –
    - GLP-1R agonist, DPPIV inhibitors, thiazolidinediones/PPARγ;

- Other agents with an inherent risk of HAE (*for example*: amylin analogues, sulphonylureas, and insulin) to limit added risk of hypoglycemia (Section 2.3.1).

FSBG (assessed via glucometers) and FPG (assessed by sponsor-identified central laboratory) will be routinely monitored during participation in the study. Based on this information, as well as review of the results reported by the central laboratory, an assessment of any symptomatic and asymptomatic occurrence of hypo- or hyper- glycemia must be undertaken.

6.9.1.1. Home Glucose Monitoring

- To aide in management of their T2DM, all participants in Stratum 1 will be provided home glucose monitoring supplies, including a Sponsor provided glucometer, instructions on the use of the glucometer, and accompanying supplies – SoA-Table 1.
- The Investigator will review the readings stored in the glucometer device at each on-site visit after dispensation of the device.
- Participants can use their own glucometer, provided that the daily glucose values stored in the glucometer device can be reviewed by the Investigator at each on-site visit.
- Home glucose monitoring logs, ***either*** via results saved on the glucometer **or** results transcribed into a hard copy glucose monitoring diary, will be maintained by participants and brought to each on-site visit to enable monitoring of compliance with the home glucose monitoring requirement by the site staff.
- Participants should be instructed to self-perform home glucose monitoring **at least 3 times weekly**, on separate, nonconsecutive days, following a fast of ≥8 hours (except water).
- In addition, home glucose monitoring should be performed upon experiencing symptoms of HAE.

6.9.1.2. Management of HAE

Any episode of HAE must be captured on the AE eCRF with details captured on the HAE details eCRF.

Participants noted to have a fasting fingerstick blood glucose value (during home glucose monitoring) meeting the definition of HAE must be instructed to repeat the measurement the next day (following a fast of ≥8 hours except water). If the second measurement also meets the definition of HAE, participants must be asked to return to the site **within 1 to 3 days** (following a fast of ≥8 hours except water) and have blood collected and sent to the central laboratory for analysis of FPG.

Based on review of the home glucose monitoring logs, ***either*** via results saved on the glucometer **or** results transcribed into a hard copy glucose monitoring diary, at ***each*** on-site visit per SoA-Table 1, as well as results reported by the central laboratory, the Investigator must assess the glucose values as well as any symptoms documented.

HAE will be defined using the classification published by the ADA as follows –

Severe HAE (all 3 required):

- Participant was unable to treat him/herself due to neurological impairment (not age) and require assistance of another person.
- **At least one** neurological symptom of memory loss, confusion, uncontrolled behavior, irrational behavior, unusual difficulty in awakening, documented or suspected seizure, or loss of consciousness.
- Either documented blood glucose ≤54 mg/dL (2.7 mmol/L) or, if blood glucose not measured, documented reversal of clinical symptoms by administration of oral carbohydrates, SC glucagon, or IV glucose.

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

Documented symptomatic HAE:

An event during which typical symptoms of an HAE are accompanied with a plasma/blood glucose value <70 mg/dL (3.9 mmol/L) using a glucometer or Sponsor-identified central laboratory and the clinical picture includes prompt resolution with oral food/carbohydrate intake, SC glucagon, or IV glucose.

Probable symptomatic HAE:

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

Asymptomatic HAE:

An event not accompanied by typical symptoms of an HAE, but a plasma/blood glucose value of <70 mg/dL (3.9 mmol/L) is reported using a glucometer or sponsor-identified central laboratory.

6.9.1.3. Management of Hyperglycemia

Hyperglycemia (refer to Section 10.12) is defined as the following:

- Fasting blood/plasma glucose >270 mg/dL (15.0 mmol/L) from Week 4 to 1 day ***prior*** to Week 16;
- Fasting blood/plasma glucose >240 mg/dL (13.3 mmol/L) from Week 16 and up to Week 44;

After randomization, participants noted to have a fasting blood glucose value (during home glucose monitoring) meeting the above definition of hyperglycemia must be instructed to repeat the measurement the next day (following a fast of ≥8 hours except water). If the second measurement also meets the above definition, participants must be asked to return to the site as soon as possible but **within 7 days** of the repeat home glucose assessment

(following a fast of ≥8 hours except water) and have blood collected for FPG (and shipped to the central laboratory for analysis).

The Investigator should determine if the participant collected the samples after an adequate fasting period and if the participant is following recommended dietary guidelines. Proper dietary and collection procedures should be reinforced with the participant.

If the results of the central laboratory confirm the glucometer readings, the participant should be offered glycemic rescue medication at the discretion of the Investigator.

- In order to ensure appropriate glycemic control, per local/in-country standard-of-care, and considering the duration of dosing with study intervention (ie, up to 44 weeks), it may be necessary to adjust the dose of metformin for glycemic control post randomization and/or add a new agent – refer to Section 6.9.1 and Section 10.12.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following –

- Criteria for a potential Hy's law case are met – refer to Section 10.6;
- Intent to become pregnant or pregnancy confirmed via β-hCG testing;
- Safety or tolerability concern arises, including MoA-based GI-related AEs, in particular if intolerable to the participant despite persistent best efforts to minimize symptoms, dosing with study intervention may be permanently stopped in an individual participant at the discretion of the investigator – refer to Section 10.11;
- Based on mental health assessment must be discontinued from dosing or from study, as outlined in Section 8.3.6.3.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for at least the primary endpoint. See SoA-Table 1 and SoA-Table 2 for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

It is ***strongly recommended*** that the investigator discuss permanent discontinuation of study intervention with the study medical monitor or sponsor clinician before progressing with discontinuation.

7.1.1. Potential Cases of Acute Kidney Injury

Increase in Scr concurrent with presence or absence of an increase in urea (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 that warrants additional assessment.

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in Scr 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 of Scr (after the first observations of ≥0.3 mg/dL [or ≥26.5 µmol/L] in Scr relative to the participant's own baseline) is ≥0.4 mg/dL (or ≥35.4 µmol/L), the participant should be discontinued from the study intervention 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 the increased 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.

7.1.2. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided. Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation of study intervention may be required.

Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19 –

- **If** management of COVID-19 infection includes use of Paxlovid (ritonavir-boosted nirmatrelvir), **and** participant is randomized to PF-07081532/placebo, switch administration of study intervention to every other day while taking Paxlovid ***and*** for up to 2 days post last dose of Paxlovid – as a means to manage the potential PK DDI (refer to Table 6 in Section 10.10) with coadministration is necessary;

- **If** management of COVID-19 infection includes use of remdesivir **or** monoclonal antibodies (eg, bebtelovimab), temporary pause (***for up to 2 days***) in dosing of PF-07081532/placebo may be medically appropriate (eg, in the setting of GI related AEs if participant is struggling to remain adequately hydrated).

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following:

- Reasons outlined in Section 7.1;
- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study termination by sponsor;
- Discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the participant to comply with protocol-required schedule of study visits or procedures at a given site.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See SoA-Table 1 and SoA-Table 2 for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

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

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

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

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in

detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures (Section 10.1.3).

Study procedures and their timing are summarized in SoA-Table 1 and SoA-Table 2. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in SoA-Table 1 and SoA-Table 2, 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 make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

Laboratory test results related to glycemic parameters (refer to Section 6.4.2) that have been collected for the purposes of this study and could unblind the study will not be reported to investigative sites or other blinded personnel (Section 6.4.3) until the study has been unblinded.

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

The total blood sampling volume for individual participants in this study is **up to approximately 285 mL**. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

8.1.1. Telehealth Visits

Telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit (see SoA-Table 1):

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 10.4.

Study participants must be reminded to promptly notify site staff about any change in their health status.

8.2. Efficacy Assessments

Assessments to evaluate efficacy (SoA-Table 1 and SoA-Table 2), include –

- HbA1C, FPG, CCI as assessed by the sponsor identified- central laboratory – Section 10.2;
    - With HOMA-IR and HOMA-S programmatically derived by the sponsor;
- Body weight – Section 8.2.1;
- Waist and hip circumference (for endpoint of waist circumference and waist-to-hip ratio) – Section 8.2.2;

CCI [redacted]

8.2.1. Body weight

Body weight will be measured in duplicate as indicated in SoA-Table 1 with the second weight measurement should be obtained ***at least 2 minutes*** after the first measurement.

- Weight will be recorded using a calibrated scale (with the same scale used as much as practically possible for the duration of the study);
- Weighing scale can report weight in either pounds (lb) or kilograms (kg), but must have an accuracy to the nearest 0.2 lb (or 0.1 kg); ie, the device must be able to distinguish a difference between 150.4 lb (68.4 kg) versus 150.2 lb (68.3 kg);
- With the weighing scale placed on a stable, flat surface, weight measurement can be taken under the following conditions:
    - Participant is in fasted state;
    - After the participant has voided urine (ie, forced void);
    - After the participant has removed shoes and bulky layers of clothing and jackets, so that only light clothing (with empty pockets) or a hospital gown, remains;
    - With the participant standing still while on the scale.

8.2.2. Waist and Hip Circumference and Waist-to-Hip Ratio

Waist and hip circumference will be measured as indicated in SoA-Table 1 and should be taken under the following conditions:

- Waist circumference should be measured at midpoint, between lower margin of last palpable rib and top of iliac crest (~1 inch [2.54 cm] above the navel);
- The hip circumference is defined as the circumference around the widest portion of the buttocks;

- Participant should be lightly clothed and in a fasted state;
- Measurements should be taken after the participant has been asked to void of urine (ie, forced void);
- Measurements should be taken with tape touching the skin (not clothing) for waist measurements, and the tape touching the skin, if possible, for hip measurements.

The measurements should be taken with the following steps:

- Step 1: Ask the participant to stand with their feet close together and arms at their side with their body weight evenly distributed
- Step 2: Ask the participant to relax and breathe normally
- Step 3: Measurements should be recorded at the end of a normal expiration

These measurements will be obtained using an anthropometric tape (stretch-resistant). The tape should be snug around the body, but not pulled so tight that it is constricting. The tape should be in the horizontal all around the body, parallel to the floor at the level at which the measurement is made and avoiding twists in the tape. The waist and hip circumference will be measured in triplicate[34], with a brief interval (at least 1-2 minutes) between successive measurements. All 3 measurements will be recorded in inches or cm, rounded to the nearest 1/16th inch or 0.1 cm.

CCI [redacted]

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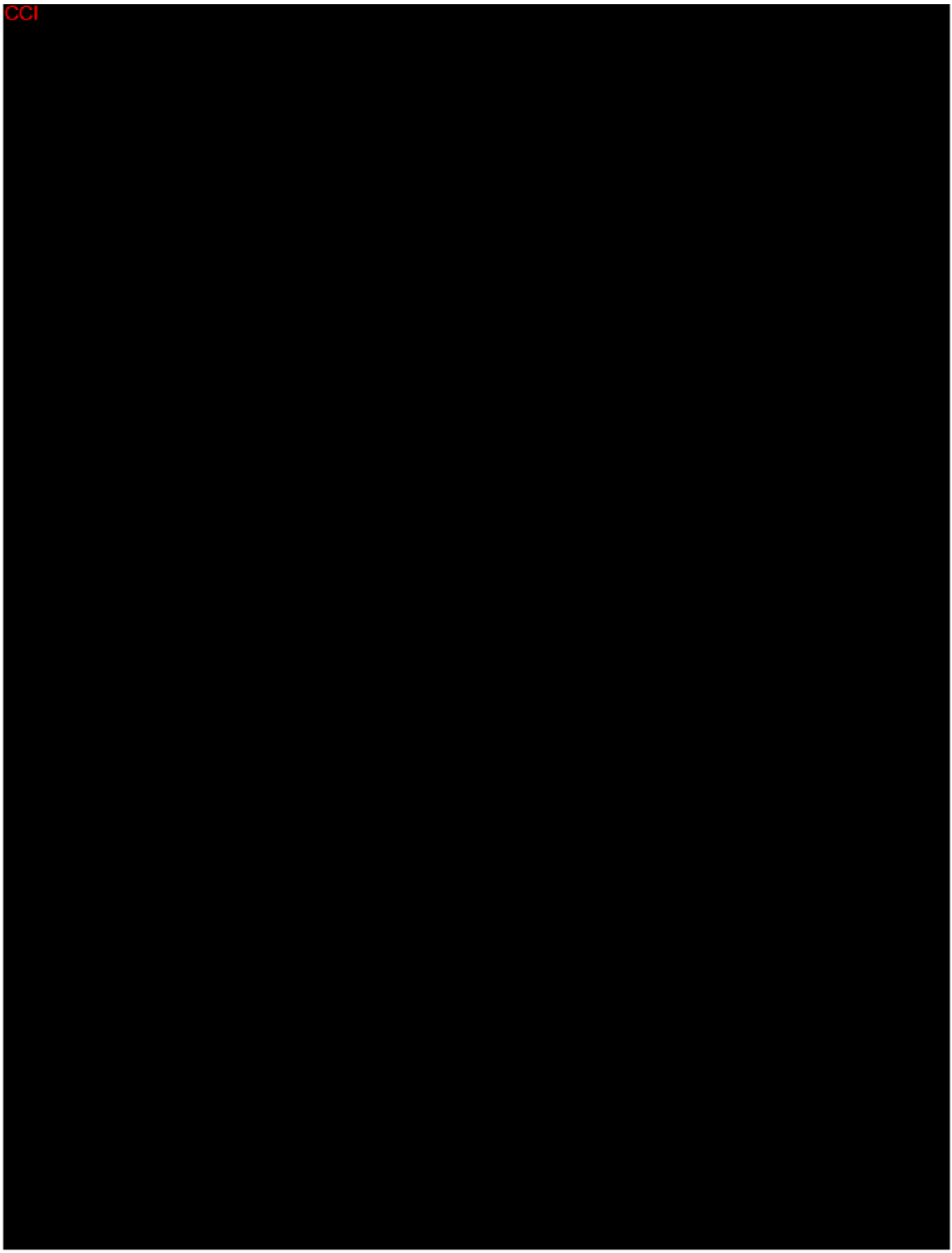

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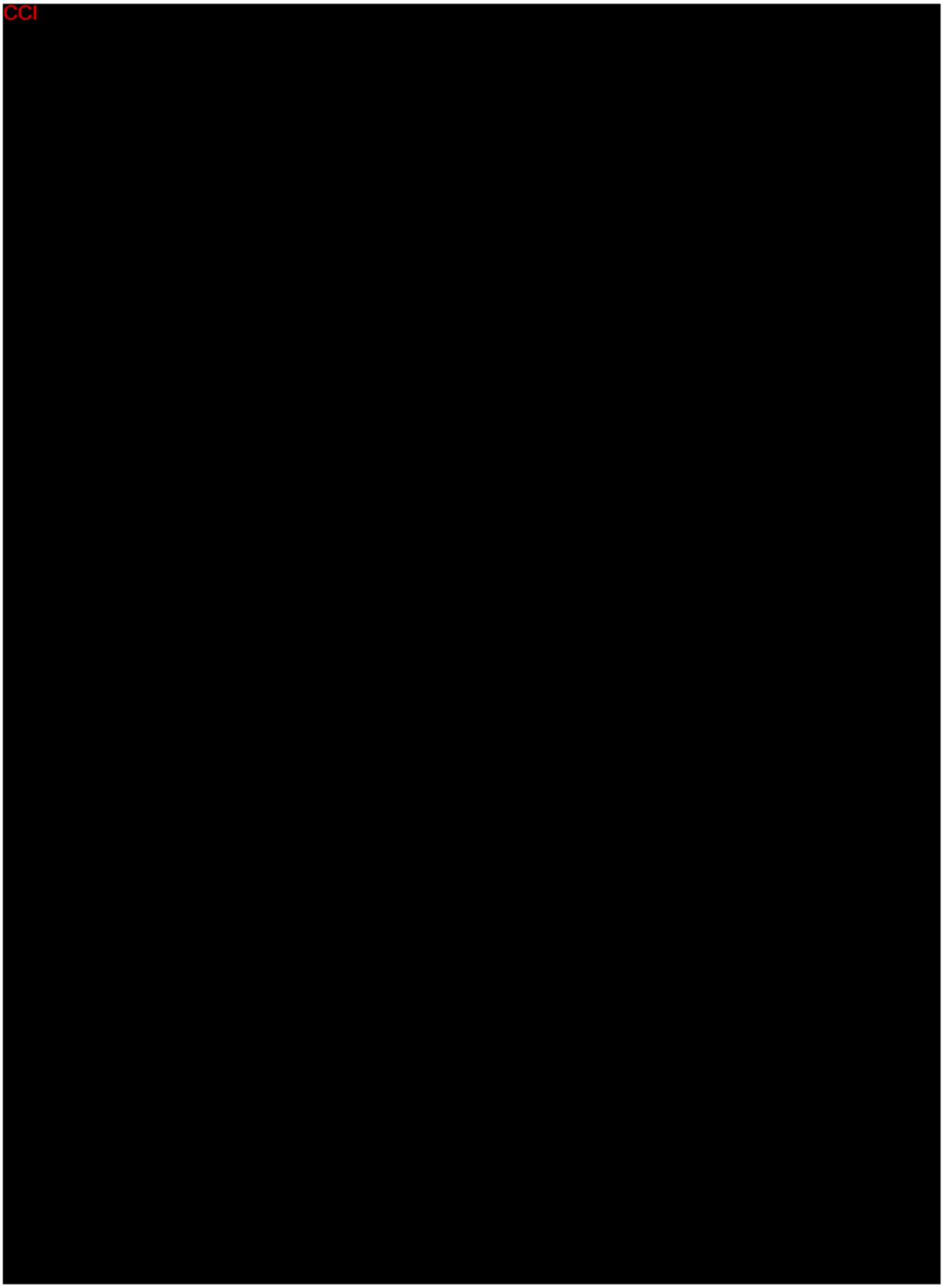

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8.3. Safety Assessments

Planned time points for all safety assessments are provided in SoA-Table 1 and SoA-Table 2. Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

8.3.1. Physical Examinations

A complete physical examination will be performed by a medically qualified or appropriately delegated site staff (eg, PAs, NPs, or similar). A complete physical examination includes, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Arm circumference, waist circumference, and height will also be measured and recorded.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

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

8.3.2. Vital Signs

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

8.3.2.1. Blood Pressure and Pulse Rate

In this study, assessment of vital signs (including seated blood pressure, and pulse rate) will occur at the nominal time points specified in the SoA-Table 1 per the following specifications:

- *At the Screening Visit,* the participants' arm circumference should be measured (using a flexible anthropometric tape) at the midpoint of the length of the upper arm and the appropriate cuff selected and used throughout the study to measure BP/PR via an automated device using an oscillometric method (not auscultation):
  - Participants with arm circumference greater than the largest cuff size available at each site are not eligible.
- **Triplicate** (in PF-07081532/placebo arms) and **single** (in Rybelsus arm) **seated BP/PR** will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg, with a rest of ≥ **5-minutes before** the first of 3 measurements is obtained with continued seated rest till third of 3 measurements is obtained; each of the 3 consecutive readings will be recorded on the CRF.
- ***As much as practically possible***, same arm (preferably the dominant arm) will be used for blood pressure/pulse rate assessment throughout the study.

8.3.3. Electrocardiograms

Standard 12-lead ECGs, as provided by the sponsor-identified central vendor, utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in SoA-Table 1 using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTc (ideally, QTcF), and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for **≥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 (in PF-07081532/placebo arms) and **single** (in Rybelsus arm) **supine** 12-lead ECGs will be obtained with a rest of ≥**10-minutes before** the first of 3 ECGs is obtained with continued supine rest till 3rd of 3 ECGs is obtained. Assessment of eligibility must be made by site-based medically qualified individual or central reader. The average of the triplicate ECG measurements collected pre-dose on Day 1/Visit 3 will serve as baseline for each participant **and** each of the 3 consecutive readings databased (via the central vendor reviewing 12-lead ECGs in ***randomized*** participants).

If a) a post dose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QTcF value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); **or** c) QTcF values get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted

if QTcF values do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

ECG tracings will be submitted to sponsor-identified central vendor for measurement. The final ECG report from the sponsor-identified central vendor should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the baseline/Day 1 ECG may potentially be AEs (Appendix 8) and should be evaluated further, as clinically warranted.

The cardiac conduction intervals as assessed by the sponsor-identified central vendor will undergo concentration-QT analysis – refer to Section 9.3.4.1.

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

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

8.3.4. Clinical Safety Laboratory Assessments

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

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

All laboratory tests with values considered clinically significant and abnormal during participation in the study or **within 14 days** after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

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

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

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

8.3.5. Pregnancy Testing

A serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in SoA-Table 2. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at Day 1/Visit 3 prior to the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

8.3.6.1. Columbia Suicide Severity Rating Scale (C-SSRS) – Stratum 2 only

The C-SSRS is an interview-based rating scale to systematically assess suicidal ideation and suicidal behavior.[32] The "baseline/screening" version of the C-SSRS will be administered at Screening Visit. The "since last visit" version of the C-SSRS will be administered at the other visits specified in SoA-Table 1. The C-SSRS will be administered by study site staff who have completed training in its administration. Participants who respond "yes" to questions 4 or 5 (indicating suicidal ideation), or to any suicidal behavioral question on the C-SSRS at Screening Visit **or** Day 1/Visit 3 will not be permitted in the study (refer to Section 5.2).

8.3.6.1.1. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate participants in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the training materials provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. The rater must become certified to perform selected study assessments before they can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written documentation will be provided by the site for each rater's certification. In return, each site will be provided written documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

8.3.6.2. Patient Health Questionnaire-9 (PHQ-9) – Stratum 2 only

The PHQ-9 is a 9 item self-report scale for the assessment of depressive symptoms[33]. The PHQ-9 will be completed by participants and reviewed by site staff at the pre-defined time points outlined in SoA-Table 1. A PHQ-9 score of ≥15 at Screening Visit **or** Day 1/Visit 3 indicates clinically significant depression and serves as an exclusion criterion for this study (refer to Section 5.2).

8.3.6.3. Referral to a Mental Health Professional – Stratum 2 only

A participant must be referred to a MHP for the following reasons:

- Response of "yes" to question 4 or 5, or on any suicidal behavioral question on the C-SSRS;
- A score of ≥15 on the PHQ-9;
- In the investigator's judgment a risk assessment or exclusion is required.

A clinically-qualified MHP is a MHP with appropriate training in the assessment of suicide risk, according to local clinical practice standards and regulations, who would normally evaluate the risk for suicidal ideation and behavior in a patient.

After Day 1/Visit 3, for any participant in study, meeting any of the above reasons, risk assessment by a clinically-qualified MHP must be performed to determine whether it is safe for a participant to continue to participate in the study.

Participants who have recurrent suicidal ideation or behavior during the study should be discontinued from the study and treated appropriately. If a study participant endorses a 4 or 5 on the ideation subscale or any suicidal behavioral item of the C-SSRS on 2 or more occasions and is confirmed to have active suicidal ideation or behavior on both occasions by a risk assessment conducted by a qualified MHP, then the participant should be discontinued from the study and treated appropriately.

Participants who meet criteria for referral to a MHP, but refuse evaluation and/or treatment by a MHP, should be discontinued from dosing or from the study.

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

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

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 9. Device deficiencies are covered in Section 8.4.9.

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

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

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

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

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

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

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

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

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in

Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

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

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

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

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

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

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

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

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

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

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

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

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

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

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

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

AESIs are examined as part of routine safety data review procedures throughout the clinical study and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.4.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.4.9. Medical Device Deficiencies

Medical devices being provided for use in this study are those listed in Section 6.1.2. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 9.

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Sections 8.4.1 through 8.4.4 and Appendix 3 of the protocol.

8.4.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 9.

8.4.9.2. Follow-Up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.4.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

When a device deficiency occurs:

1. The investigator notifies the sponsor by telephone or email within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.

2. The device deficiency must be recorded on the Medical Device Complaint form.

3. If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF.

4. If an SAE associated with the device deficiency is brought to the attention of the investigator, the investigator must immediately notify Pfizer Safety of the SAE (see Section 8.4.1.1). All relevant details related to the role of the device in the event must be included in the CT SAE Report Form as outlined in Sections 8.4.1.1 and 8.4.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.4.9.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- Administration of expired study intervention;
- Administration of an incorrect study intervention;
- Administration of an incorrect dosage (ie, not 1 tablet for each of the 3 separate bottles in the case of dosing with PF-07081532/placebo);
- Administration of study intervention that has undergone temperature excursion from the specified storage range, ***unless*** it is determined by the sponsor that the study intervention under question is acceptable for use.

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

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

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

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

8.5. Pharmacokinetics

Blood samples of approximately **3 mL** to provide a minimum of 1 mL plasma will be collected for measurement of plasma concentrations of PF-07081532 (Stratum 1 and 2) as specified in SoA-Table 2.

Blood samples of approximately **6 mL** to provide a minimum of 3 mL matrix will be collected for measurement of concentrations of Rybelsus (Stratum 1, only) as specified in SoA-Table 2.

The actual date and time of the on-site dosing with study intervention and of the blood collections related to PK (both pre- and post-dose samples) should be captured by site personnel in the eCRF. The actual date and time of the previous two doses of study intervention prior to each on-site visit that includes blood draws for PK should be noted in a dosing diary (or similar) by the participants and captured by site personnel in the eCRF.

- The PK samples must be processed and shipped as indicated in the study-specific laboratory manual provided to the site, prior to initiation of study, to maintain sample integrity:
    - Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor;
    - On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised;
    - Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation;
    - ***Any*** of the following errors in *scheduled* collection of blood samples for PK (refer to SoA-Table 2) will be captured as protocol deviations even if results are deemed to be evaluable and included in analyses
        - Predose collection (ie, C_{trough}) obtained post dose;
        - Post dose PK sample not collected within collection window following morning dose;
        - PK sample (pre- or post- dose) not collected.

Samples will be used to evaluate the PK of PF-07081532 (Stratum 1 and 2) and Rybelsus (Stratum 1, only). Each matrixed sample will be divided into 2 aliquots.

Samples collected for analyses of PF-07081532 (Stratum 1 and 2) and Rybelsus (Stratum 1, only) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will ***not*** be performed on these samples. Participant confidentiality will be maintained.

Samples collected for measurement of concentrations of PF-07081532 (Stratum 1 and 2) and Rybelsus (Stratum 1, only) will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

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

8.6. Genetics

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In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.

See Section 10.5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in laboratory manual provided by the sponsor-identified central laboratory.

8.6.2. Retained Research Samples for Genetics

Not planned.

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8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters including inpatient/outpatient/emergency department visits that take place between scheduled visits will be collected at each clinic visit.

9. STATISTICAL CONSIDERATIONS

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

Other than where expressly stated, there are no planned analyses that will combine strata. All statistical analyses will be performed separately for each stratum.

9.1. Statistical Hypotheses

9.1.1. Estimands

Estimands described below as "in the absence of glycemic rescue medication while on treatment" for Stratum 1 (T2DM inadequately controlled on metformin) and "while on treatment" for Stratum 2 (Obesity without T2DM) represent hypothetical or treatment product estimands.

9.1.1.1. Primary Estimands

For Stratum 1 (T2DM): The primary estimand will be the population average treatment effect on the change from baseline in HbA1C at Week 32 of PF-07081532 compared to placebo in the absence of glycemic rescue medication while on treatment. Measurements after initiation of glycemic rescue medication or discontinuation of study intervention will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons (eg, laboratory failure) will have data imputed based on a MAR assumption. Participants with inadequate compliance will have their HbA1C values used as-is in the analysis. The population-based treatment effect will be the difference in the mean change from baseline in each PF-07081532 arm compared to placebo.

For Stratum 2 (Obesity): The primary estimand will be the population average treatment effect on the percent change from baseline in body weight at Week 32 of PF-07081532 compared to placebo while on treatment. Measurements after discontinuation of study intervention will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons (eg, equipment failure) will have data imputed based on a MAR assumption. Participants with inadequate compliance will have their body weight values used as-is in the analysis. The population-based treatment effect will be the difference in the mean percent change from baseline in each PF-07081532 arm compared to placebo.

9.1.1.2. Secondary Estimands

For Stratum 1 (T2DM): For each of the continuous secondary endpoints evaluating PF-07081532: the population average treatment effect on the change from baseline in at each specified timepoint of PF-07081532 compared to placebo in the absence of glycemic rescue medication while on treatment. Measurements after initiation of glycemic rescue medication or discontinuation of study intervention will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons (eg, laboratory failure) will have data imputed based on a MAR assumption. Participants with inadequate compliance will have their observed values used as-is in the analysis. The population-based treatment effect will be the difference in the mean change from baseline in each PF-07081532 arm compared to placebo.

For the ***continuous secondary endpoint comparing Rybelsus to placebo:*** the population average treatment effect on the change from baseline in at each specified timepoint of Rybelsus compared to placebo in the absence of glycemic rescue medication while on treatment. Measurements after initiation of glycemic rescue medication or discontinuation of Rybelsus will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons (eg, laboratory failure) will have data imputed based on a MAR assumption. Participants with inadequate compliance will have their observed values used as-is in the analysis. The population-based treatment effect will be the difference in the mean change from baseline in the Rybelsus arm compared to placebo.

For each of the categorical secondary endpoints: The odds ratio (PF-07081532 relative to placebo) at Week 32 in the absence of glycemic rescue medication while on treatment. Measurements after initiation of glycemic rescue medication or discontinuation of study intervention will be censored and treated as missing data. Missing data will not be imputed. Participants with inadequate compliance will have their observed values used as-is in the analysis. The population-based treatment effect will be the odds ratio of PF-07081532 arm relative to placebo.

For Stratum 2 (Obesity): For each of the continuous secondary endpoints: the population average treatment effect on the change from baseline in at each specified timepoint of PF-07081532 compared to placebo while on treatment. Measurements after discontinuation of study intervention will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons (eg, equipment failure) will have data imputed based on a MAR assumption. Participants with inadequate compliance will have their observed values used as-is in the analysis. The population-based treatment effect will be the difference in the mean change from baseline in each PF-07081532 arm compared to placebo.

For each of the categorical secondary endpoints: The odds ratio (PF-07081532 relative to placebo) at Week 32 while on treatment. Measurements after discontinuation of study intervention will be censored and treated as missing data. Missing data will not be imputed. Participants with inadequate compliance will have their observed values used as-is in the analysis. The population-based treatment effect will be the odds ratio of PF-07081532 arm relative to placebo.

9.1.2. Multiplicity Adjustment

In this study, the 2 main strata (T2DM and Obesity) are defined as administrative strata and will not be adjusted for in statistical analyses. Unless expressly stated, all analyses will be performed for ***each*** stratum separately.

No adjustments will be made for multiple comparisons.

9.2. Analysis Sets

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

Defined Population for Analysis	Description
Enrolled	All participants who sign the ICD **and** are randomized • A participant will be considered enrolled if informed consent is not withdrawn prior to participating in any study activity; • Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled
Randomly assigned to investigational product	All participants randomly assigned to study intervention regardless of whether or not study intervention was administered.
Evaluable	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the randomized intervention.
Safety Analysis Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK Concentration Set	All participants randomly assigned to study intervention and who take at least 1 dose of PF-07081532 or Rybelsus and in whom at least one concentration value is reported.

9.3. Statistical Analyses

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

9.3.1 General Considerations

The primary statistical method of MMRM will apply to continuous endpoints.

Statistical efficacy comparisons will be made between each dose of PF-07081532 and placebo for primary and secondary endpoints, respectively. Placebo-adjusted LS mean difference, 95% CI and p-value will be presented.

The primary statistical method of logistic regression will apply to categorical endpoints. Statistical efficacy comparisons will be made between each dose of PF-07081532 and placebo. Odds ratios, 95% CI and p-value will be presented.

Since this study is exploratory in nature, no multiplicity adjustment of endpoints nor adjustments for multiple comparisons to placebo will be made. Sensitivity analyses and supplementary analyses are defined in the SAP.

9.3.1. Primary Estimands Analysis

For the primary estimand in each stratum, the analysis method is an MMRM analysis. The MMRM will include treatment and time as fixed effects, and baseline measure (HbA1C for Stratum 1, body weight for stratum 2) as a covariate with time fitted as a repeated effect and participant as a random effect. An unstructured correlation matrix will be used, and the Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters. The MMRM model will be fitted to change from baseline to Weeks 4, 8, 12, 16, 20, 24, 28, and 32.

Missing values will be imputed as part of the MMRM model assumptions.

A Bayesian E_{max} dose-response model will also be estimated. This model will be utilized to characterize the dose response across all PF-07081532 doses, to estimate the mean response (and 95% CI) for each dose studied, and to estimate the placebo-adjusted response for each dose (and 95% CI). If an E_{max} dose-response model cannot be fitted to the data, then other models that allow dose response to be estimated will be fitted, ie, linear, log-linear or exponential. No adjustments will be made for multiplicity.

For the estimands containing continuous endpoints, the analysis method is an MMRM analysis. The MMRM will include treatment and time as fixed effects, and baseline measure as a covariate with time fitted as a repeated effect and participant as a random effect. An unstructured correlation matrix will be used, and the Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters. The MMRM model will be fitted to change from baseline to Weeks 4, 8, 12, 16, 20, 24, 28, and 32. Missing values will be imputed as part of the MMRM model assumptions.

No adjustments will be made for multiplicity.

9.3.1.1. Sensitivity Analyses

Sensitivity analyses will be detailed in the SAP prior to database lock.

9.3.2. Secondary Estimands Analysis

For the estimands containing continuous endpoints, the analysis method is an MMRM analysis. The MMRM will include treatment and time as fixed effects, and baseline measure as a covariate with time fitted as a repeated effect and participant as a random effect. An unstructured correlation matrix will be used, and the Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters. The MMRM model will be

fitted to change from baseline to Weeks 4, 8, 12, 16, 20, 24, 28, and 32. Missing values will be imputed as part of the MMRM model assumptions.

For the estimands containing categorical endpoints, the analysis method is a logistic regression analysis. The logistic regression model will include a term for treatment and will include baseline as a covariate. No values will be imputed for missing data, and missing values will not be included in the model.

No adjustments will be made for multiplicity.

9.3.3. Tertiary/Exploratory Endpoint(s) Analysis

Pre-dose (trough) PK concentrations will be summarized descriptively by treatment group (PF-07081532 or Rybelsus), dose and visit. Post-dose PK concentrations will only be listed. Analyses CCI [redacted] levels will be specified in the SAP.

PK data may be used for population PK and/or PK/PD analyses – including both the endpoint at Week 32 and limited data acquired in those enrolled in extension to up to Week 44. The objective of such analyses, if conducted, would aim to explore the relationship between concentrations of PF-07081532 or Rybelsus and effect on endpoints of interest and also identification of potential demographic determinants (eg, age, sex, and weight) influencing the observed PK and/or PD. These analyses if conducted, will be reported separately from the main CSR.

9.3.4. Other Safety Analyses

The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive at least one dose of ***randomized*** study intervention (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulation, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study are referenced in Section 3.

9.3.4.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters HR, QTcF, PR interval, and QRS complex will be summarized by treatment and time. The frequency of uncorrected QT values above 500 ms will be tabulated. The number (%) of participants with maximum post dose QTcF values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTcF Assessment

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

CCI [redacted]

9.4. Interim Analyses

Interim analyses will be performed to ***assess safety/tolerability***, at a minimum, after approximately 25%, 50%, 75% and 100% of planned total sample size, has been randomized in the study. These analyses may include futility analysis for intolerable MoA-based GI AE profile – particularly rate of discontinuation of study intervention exceeding 50% in any given PF-07081532 arm based on unblinded review of the data. Interim analysis results may be used for internal business decisions regarding future study planning, or adapting the safety-related endpoints in the study after the interim analysis. Participants may be discontinued from the study as a result of the interim analysis, as described in Section 7.

In addition, should there be more than 12-week separation in *forecasted* PCD between Stratum 1 versus Stratum 2 (for example: 1 stratum completes enrollment/randomization of the planned sample size much faster than the other strata), an interim analysis may be performed to ***assess efficacy and safety/tolerability*** in the Stratum that achieves PCD early. In order to maintain the blind while the study is ongoing, the results of any interim analyses will be disclosed together with the PCD analyses within 1 year after end of the study as defined in Section 4.4.

Before any interim analysis is performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind (if applicable) as per Pfizer's SOPs will be documented and approved in an IRC charter. In addition, the analysis details will be documented and approved in the SAP.

9.4.1. PK/PD unblinding plan

The Sponsor staff interfacing with the site will maintain the same level of blinding as site personnel (outlined in Section 6.4.3). However, a limited number of individuals not on the study team may be unblinded according to Sponsor SOPs with the purpose of composing PK, PK/PD data sets and conducting population PK and/or PK/PD analyses that will be made available to the study team following database lock. These data may include PK, HbA1C, vitals, ECGs, body weight, and potentially other PD markers / biomarkers and AEs of interest.

9.5. Sample Size Determination

The sample size is based on the need to have an adequately sized safety database of participants on PF-07081532 following phase 2 clinical development. Approximately 780 participants will be enrolled/randomized, with the population enrolled stratified with approximately 420 with T2DM inadequately controlled on metformin and approximately 360 with Obesity but without T2DM. Within each stratum, a 1:1 allocation across treatments groups at the stratum level will be used. The Rybelsus group (existing within the T2DM stratum only) administration will be open-label. Additionally, randomization will be further

stratified with the aim of randomizing ≥30% male (and hence ≤70% female) participants, in ***each*** of stratum 1 (T2DM) and stratum 2 (obesity).

Participants who withdraw from the study or treatment after randomization will not be replaced.

The primary analysis for this study is based on the primary endpoints within each stratum, namely the CFB in HbA1C at Week 32 for the T2DM Stratum and percent CFB in body weight for the Obesity stratum.

For the T2DM stratum, the effect size was assumed to be -0.7% with an SD of 1.1. Based on these assumptions, 51 completers per treatment arm would provide at least 90% power using a 1-sided t-test at a 5% level to detect a difference between each dose of active treatment arms and placebo in CFB in HbA1C.

For the Obesity stratum, the effect size was assumed to be -4% with a SD on the log-scale of 0.08. Based on these assumptions, 51 randomized participants per treatment arm would provide at least 90% power using a 1-sided t-test at a 5% level to detect a difference between each dose of active treatment arms and placebo in percent change from baseline in body weight.

It is anticipated that up to 15% of participants may not be evaluable or discontinue prematurely before Week 32, resulting in a final randomized sample size of approximately 60 participants per treatment arm.

CCI [redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

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

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant.

10.1.4. Data Protection

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

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

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use an IRC. The IRC is independent of the study team and includes only internal members. The IRCcharter describes the role of the IRC in more detail.

The IRC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the IRC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of safety data to regulatory authorities and investigators, as appropriate.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or

www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical study results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of “bona-fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these studies available 24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not

be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk -based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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

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

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

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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

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

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

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

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

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

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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

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

10.1.10. Publication Policy

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

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

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is

submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

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

10.1.11. Sponsor's Medically Qualified Individual

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

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

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in SoA-Table 2. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 5. Protocol-Required Clinical Laboratory Assessments

Hematology	Chemistry	Urinalysis
• Hemoglobin • Hematocrit • RBC count • Platelet count • WBC count • Total neutrophils (Abs) • Eosinophils (Abs) • Monocytes (Abs) • Basophils (Abs) • Lymphocytes (Abs)	• Urea (BUN) • Scr • Serum Cystatin C • eGFR[a] • Sodium • Potassium • Phosphate/phosphorus • Calcium • AST • ALT • Total bilirubin • Direct bilirubin - Indirect bilirubin • Alkaline phosphatase • Albumin • Total protein • Fasting *plasma* glucose CCI [redacted]	• pH • Glucose (qual) • Protein (qual) • Blood (qual) • Ketones • Nitrites • Leukocyte esterase • Urinary albumin:creatinine ratio • Microscopy and culture[b]

At Screening Visit *only*	**At specific visits outlined in SoA-Table 2 –**
• Serum FSH[c] • Pregnancy test (β-hCG)[d] • Hepatitis B surface antigen • Hepatitis C antibody (and if positive, reflex HCV RNA) • Fasting C-peptide • TSH • Urine drug testing[e]	• HbA1C • Serum lipase • Serum amylase • Fasting serum lipid panel (HDL-C, direct LDL-C, TG, total cholesterol) • hsCRP • Free T4 • Total bile acids • Calcitonin CCI [redacted] • *Predose* PF-07081532/Rybelsus PK • **Post dose** PF-07081532/Rybelsus PK CCI [redacted]

a. Assess eGFR using CKD-EPI Scr-Scys combined per Section 10.7
b. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both
c. For confirmation of postmenopausal status ***only***
d. In female participants of childbearing potential, **serum** β–hCG (at Screening Visit) with **urine** β–hCG (at all other visits using kits provided by sponsor-identified central laboratory)
e. At Screening Visit with this test not permitted to be repeated and minimum requirement for urine drug screen and reflexed confirmatory testing (when done) including cocaine, opiates/opioids, benzodiazepines, and amphetamines

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.

Laboratory parameters related to efficacy (refer to Section 6.4.2) that could unblind the study and have been collected for the purpose of the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded.

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition

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

Events NOT Meeting the AE Definition

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

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

a. Results in death

a. 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.

b. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

c. Results in persistent or significant disability/incapacity

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

d. Is a congenital anomaly/birth defect

e. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic

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

f. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.

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

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

Assessment of Intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

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

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

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

10.3.4. Reporting of SAEs

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

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

A female participant is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:

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

  OR

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

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

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;

- Documented bilateral oophorectomy.

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

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

2. Postmenopausal female:

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

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

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

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

<u>Highly Effective Methods That Have Low User Dependency</u>

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

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of

contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

   - Oral + barrier*
   - Intravaginal** + barrier*
   - Transdermal** + barrier*

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - Oral** + barrier*
   - Injectable** + barrier*

8. Sexual Abstinence – Is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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

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

**Not approved in Japan.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

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

- The samples will be retained as indicated:

    - Samples for specified genetic analysis (see Section 8.6.1) will be stored for **up to 3 years** or other period as per local requirements.

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

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments and Study Intervention Rechallenge Guidelines

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: Kidney Safety Monitoring Guidelines

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

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

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

10.7.2. Adult Kidney Function Calculation Recommendations

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

2021 CKD-EPI Scr-Scys Combined[41]	Scr *(mg/dL)*	Scys *(mg/L)*	Recommended eGFR Equation
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

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

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

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

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

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

ECG Findings That Qualify as SAEs

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

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

10.9. Appendix 9: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

10.9.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 3 (Section 10.3.1). • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.9.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Appendix 3 (Section 10.3.2).
SADE Definition
• An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

USADE Definition
• A USADE (also identified as UADE in US Regulations 21 CFR 813.3) is a SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.9.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer.

10.9.4. Recording/Reporting and Follow-Up of Medical Device Deficiencies

Device Deficiency Recording
• When a device deficiency 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 device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and will also capture the required information on the Medical Device Complaint form. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the Medical Device Complaint form. • 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. • If the investigator determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. Requirements for recording and reporting an AE or SAE are provided in Appendix 3 (Section 10.3.3)

- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB for PF-07081532 and/or product information, for Rybelsus in their assessment.
- For each device deficiency, the investigator **must** document in the medical notes that they have reviewed the device deficiency and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of Medical Device Deficiency
• 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 device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form. • New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the CT SAE Report Form within 24 hours of receipt of the information, according to the requirements provided in Appendix 3.

10.9.5. Reporting of SAEs

Reporting of an SAE to Pfizer Safety must be performed according to the processes described in Appendix 3 (Section 10.3.4).

10.9.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, an SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.10. Appendix 10: Prohibited Prior / Concomitant Medications

The medications listed in Table 6 may interact (at the PK level) with PF-07081532 and thus are prohibited for the provided timeframe of restriction (Table 6) **and** until first Follow-up Visit. Additionally, the medications listed in Table 7 are also prohibited for the provided timeframe of restriction (Table 7) **and** until first Follow-up Visit.

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

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

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

Investigators should consult the SRSD for Rybelsus for information regarding medication that is prohibited for concomitant use. Rybelsus delays gastric emptying. When co-administering oral medications instruct patients to closely follow Rybelsus administration instructions. Consider increased clinical or laboratory monitoring for medications that have a narrow therapeutic index or that require clinical monitoring.

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

Table 6. Prohibited Medications that may interact [CCI] with PF-07081532

Drug Category	Drugs (Therapeutic Class)	Timeframe of Restriction
CYP3A Inhibitors (strong)	Boceprevir (Antiviral), Ceritinib (Kinase Inhibitor), Clarithromycin (Antibiotic), Cobicistat (Pharmacokinetic Enhancer), Conivaptan (Diuretic), Danoprevir and Ritonavir (Antiviral), Elvitegravir and Ritonavir (Treatment of AIDS), Grapefruit juice (Food Product), Idelalisib (Kinase Inhibitor), Indinavir (Protease Inhibitor), Indinavir and Ritonavir (Protease Inhibitor), Itraconazole (Antifungal), Josamycin (Antibiotic), Ketoconazole (Antifungal), LCL161 (Cancer Treatment), Lonafarnib (Misc agent; Rare diseases), Lopinavir and Ritonavir (Protease Inhibitor), Mibefradil (Calcium Channel Blocker),	2 weeks or 5 half-lives, whichever is longer, prior to the first dose of study intervention

Table 6. Prohibited Medications that may interact [redacted] with PF-07081532

Drug Category	Drugs (Therapeutic Class)	Timeframe of Restriction
	Mifepristone (Antiprogestin), Nefazodone (Antidepressant), Nelfinavir (Protease Inhibitor), Ombitasvir and Paritaprevir and Ritonavir and Dasabuvir (Antiviral), Posaconazole (Antifungal), Ribociclib (Kinase Inhibitor), Ritonavir (Protease Inhibitor)[a], Saquinavir (Protease Inhibitor), Saquinavir and Ritonavir (Protease Inhibitor), Telaprevir (Antiviral), Telithromycin (Antibiotic), Tipranavir and Ritonavir (Protease Inhibitor), Troleandomycin (Antibiotic), Tucatinib (Kinase Inhibitor), Voriconazole (Antifungal)	
CYP3A Inducers (strong)	Apalutamide (Antiandrogen), Avasimibe (Antilipemic), Carbamazepine (Anticonvulsant), Enzalutamide (Antiandrogen), Ivosidenib (Cancer Treatment), Lumacaftor (Cystic Fibrosis Treatment), Mitotane (Antineoplastic), Phenytoin (Anticonvulsant), Rifampin (Antibiotic), Rifapentine (Antibiotic), St. John's wort extract (Herbal Medication)	5 half-lives plus 14 days prior to the first dose of study intervention
OATP (1B1/1B3) Inhibitors	Atazanavir and Ritonavir (Protease Inhibitor), Boceprevir (Antiviral), Clarithromycin (Antibiotic), Eltrombopag (Thrombopoietin receptor agonist), Erythromycin (Antibiotic), Faldaprevir (Antiviral), Gemfibrozil (Fibric Acid Derivative), Grazoprevir (Antiviral), Itraconazole (Antifungal), Letermovir (Antiviral), Lopinavir and Ritonavir (Protease Inhibitor), Rifampin, single dose (Antibiotic), Simeprevir (Antiviral), Telaprevir (Antiviral), Velpatasvir (Antiviral)	2 weeks or 5 half-lives, whichever is longer, prior to the first dose of study intervention
CYP2C19 Substrates (Sensitive)[b]	BMS-823778 (Diabetes treatment), Clobazam (Benzodiazepine), Clopidogrel (Antiplatelet)[c], Diazepam (Benzodiazepine), Gliclazide (Sulfonylurea),	Prohibited post randomization

Table 6. Prohibited Medications that may interact [redacted] with PF-07081532

Drug Category	Drugs (Therapeutic Class)	Timeframe of Restriction
	Hexobarbital (Hypnotic – Sedative), Mephobarbital (Anticonvulsant), Proguanil (Antimalarial), S-mephenytoin (Anticonvulsant), Tilidine (Treatment of Pain & Inflammation), Valproic acid (Anticonvulsant)	
UGT1A1 Substrates (Sensitive)	Belinostat (Histone Deacetylase Inhibitor), Irinotecan (Topoisomerase Inhibitor)	Prohibited post randomization

a. Nirmatrelvir + Ritonavir (Paxlovid) is permitted; special instructions provided in Section 7.1.2
b. The PPIs dexlansoprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole, although considered sensitive CYP2C19 substrates, are not prohibited due to wide therapeutic index and no anticipated impact on their efficacy or safety
c. The PK interaction between PF-07081532 and clopidogrel has been clinically assessed (see PF-07081532 IB). Out of abundance of caution, until further clinical or model-based assessment of whether the modest changes observed in the exposure of the active metabolite of clopidogrel (H4-clopidogrel) can elicit any clinically meaningful impact on efficacy/safety, co-administration of PF-07081532 with clopidogrel is prohibited

Table 7. Other Prohibited Medications

Drug Classes and/or Drugs	Timeframe of Restriction
TZDs (ie, /PPARγ) such as pioglitazone and rosiglitazone.	• **In Stratum 1** – in 12 weeks prior to Screening Visit • **In Stratum 2** – any time
Subcutaneously administered agents for glycemic control (eg, insulin, exenatide, liraglutide, dulaglutide, semaglutide, tirzepatide, amylin analogues such as pramlintide). **Note:** Short-term (ie, ≤7 days) of insulin administration is permitted if participant is hospitalized.	• **In Stratum 1** – in 12 weeks prior to Screening Visit • **In Stratum 2** – any time
Oral anti-diabetic medications, including • Biguanides such as phenformin. **Note**: metformin, a biguanide, is a required background medication in all participants in Stratum 1 • Sulfonylureas such as acetohexamide, chlorpropamide, tolazamide, tolbutamide, glimepiride, glipizide, glyburide. • Meglitinide analogues such as repaglinide, nateglinide. • DPPIVi such as sitagliptin, saxagliptin, linagliptin, vildagliptin. • α-glucosidase inhibitors such as acarbose, miglitol. • SGLT2 inhibitors such as canagliflozin, empagliflozin, dapagliflozin, ertugliflozin. • Oral GLP-1R agonists (oral semaglutide). **Note:** Oral semaglutide is the internal reference standard arm (Rybelsus) of the study. • Anti-hyperglycemic medications, including bromocriptine and colesevelam.	• **In Stratum 1** – in 12 weeks prior to Screening Visit – though *some* of these agents (refer to Section 6.9.1.3) can be used to manage glycemic control (Appendix 12) • **In Stratum 2** – any time

Table 7. Other Prohibited Medications

Drug Classes and/or Drugs	Timeframe of Restriction
• Herbal medications for the explicit purpose of glycemic control.	
In Both Strata	
Pharmacological agents with approved indication for weight loss such as liraglutide, semaglutide, orlistat and sibutramine. Appetite or weight modifying medications, including nonprescription or herbals and medical grade marijuana.	12 weeks prior to Screening Visit
Systemic glucocorticoids such as prednisone, dexamethasone, triamcinolone, budesonide, betamethasone. **Note:** As an exception, steroid-containing inhalers, nasal sprays and topical formulations are permitted. **Note:** Intercurrent treatment with systemic corticosteroids during participation in the study may be permitted if treatment does/will not exceed 7 days.	8 weeks prior to Screening Visit
Immunosuppressants such as cyclosporine, tacrolimus, TNF-alpha inhibitors (eg, etanercept, infliximab, adalimumab), IL-6 receptor antagonists (eg, tocilizumab, sarilumab), JAK inhibitors (eg, tofacitinib).	8 weeks prior to Screening Visit
Anti-psychotic medications such as olanzapine, risperidone.	8 weeks prior to Screening Visit
Coumarin type anticoagulants or other anticoagulants (eg, dabigatran, apixaban, edoxaban, rivaroxaban, fondaparinux).	8 weeks prior to Screening Visit
Anticonvulsants if prescribed for seizure disorder.	8 weeks prior to Screening Visit (with some medications prohibited post randomization – refer to Table 6)
Antiarrhythmic medications whose primary mechanism of action is sodium or potassium channel blockade (eg, procainamide, phenytoin, quinidine, propafenone; as well as amiodarone, dofetilide, sotalol). **Note:** β-adrenergic receptor blocking agents (eg, atenolol, metoprolol) and calcium channel blockers (eg, diltiazem, amlodipine, nifedipine) are permitted.	8 weeks prior to Screening Visit
Sympathomimetic agents. **Note:** Inhaled β-adrenergic receptor agonists (e.g., albuterol) are permitted. Methylphenidate and amphetamine medications for ADHD that are at a stable dose for **at least 12 weeks** prior to Screening Visit are permitted.	8 weeks prior to Screening Visit
Systemically administered treatments for malignancy including (but not limited to) the use of chemotherapy, radiotherapy, or immunotherapy	5 years prior to Screening Visit
An investigational product (drug or vaccine)	30 days (or as determined by local requirements) or 5 half-lives prior to Day 1/Visit 3
Previous participation in a study evaluating PF-07081532 (including exposure to placebo) or intolerance/hypersensitivity to GLP-1R agonist	Any time

10.11. Appendix 11: Guidance to Investigators – Management of Individual Participants MoA-Based GI-related AEs

1 **Education and Explanation** as part of Consent at Screen/Visit 1	2 **Dose-Escalation** per protocol	3 **Effective management** of MoA-based GI-related AEs during treatment phase
1. **Counseling** participants and **setting expectations** for – • potential for GI-related AEs • their typical mild-to-moderate intensity • temporary nature • and willingness/commitment by site staff to be accessible, virtually, to participants as needed throughout study 2. **Coaching dietary modifications** – • Reducing meal size • Mindfulness to stop eating once full • Avoiding eating when not hungry • Avoiding high-fat or spicy food • Practice no more than moderate intake of alcohol-containing food/drinks 3. **Discussing** current **GI symptoms,** *relevant* **upper GI medical history** *(eg, acid reflux, GERD)* • Counsel how to manage any potential worsening after V2/Run-In	**All participants** will follow protocol-required dose-escalation ***every 4 weeks*** • Incremental *steps become smaller* as dose-escalation continues for up to 20 weeks • For example: 20 mg QD (starting dose) ↓ 40 mg QD (2-fold) ↓ 60 mg QD (1.5-fold) ↓ 80 mg QD (1.3-fold)	1. If participants complain of short-term mild AEs – not affecting food intake • Re-emphasize dietary modifications • Increase fiber and water intake to manage constipation and avoid dehydration 2. If participant has history of GERD, initiation of PPI to help manage acid reflux recommended • Use of pharmacological agents (eg, antiemetic for nausea/vomiting) is not universally recommended 3. If ≥2 attempts at dietary modification do not alleviate GI-related AEs, consider **pausing dosing** with study intervention for a **maximum of 2 days** • *Where possible*, attempts must be made to avoid temporary pause in dosing in the 7 days immediately prior to on-site visit • Depending on dose-escalation step, longer pauses in dosing with study intervention not recommended • Longer pauses may cause loss of 'toleration' of GI-related AEs such that re-initiation at given dose-level may worsen GI-related AEs 4. If despite compliance with dietary modification, and **multiple temporary pauses** in dosing with study intervention, GI-related AEs persist or become more severe → permanently stop study intervention • Reason for IP discontinuation = GI-related AE

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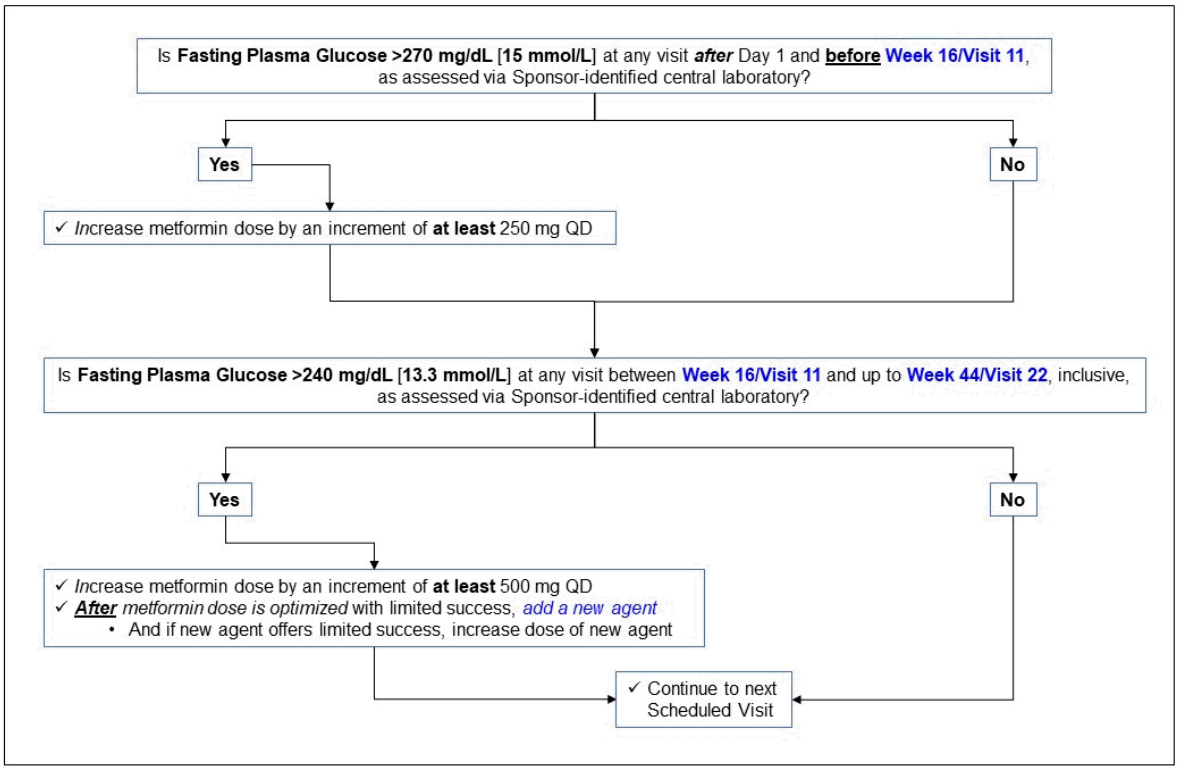
10.12. Appendix 12: Guidance to Investigators – Management of Individual Participants Glycemic Control



Sites are blinded to FPG results as reported by sponsor-identified central laboratory, starting on Day 1/Visit 3, unless above mentioned thresholds are met as outlined in Section 6.4.2; refer to Section 6.9.1.3 for guidance on agents permitted to serve as rescue.

10.13. Appendix 13: Abbreviations

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

Abbreviation	Term
A1	albuminuria (KDIGO albuminuria severity standardization)
Abs	absolute
ADA	American Diabetes Association
ADE	adverse device effect
ADHD	attention deficit hyperactivity disorder
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AV	atrioventricular
AxMP	auxiliary medicinal product
β hCG	β-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C-cell	Calcitonin-producing cells
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTIS	Clinical Trial Information System
C_{trough}	predose concentration
CV	cardiovascular
CYP	cytochrome P450
DBP	diastolic blood pressure
DBili	Direct Bilirubin
DCCT	Diabetes Control and Complications Trial
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DPPIV	dipeptidyl peptidase IV
DPPIVi	dipeptidyl peptidase IV inhibitors
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card

Abbreviation	Term
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
E_{max}	maximal effect
CCI	
eSAE	electronic serious adverse event
ET	Early Termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FPG	fasting plasma glucose
CCI	
FSBG	fingerstick blood glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
HAE	hypoglycemic adverse event
HbA1C	glycated hemoglobin
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HepB	hepatitis B
HepC	hepatitis C
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HOMA-S	Homeostatic Model Assessment for Insulin Sensitivity
HR	heart rate
HRT	hormone replacement therapy
hs-CRP	high-sensitivity C-reactive protein
Ht	height
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IRC	internal review committee
IRT	Interactive Response Technology
ISO	International Organization for Standardization
IV	intravenous(ly)
CCI	

Abbreviation	Term
CCI [redacted]	
KDIGO	Kidney Disease: Improving Global Outcomes
kg	kilogram
lb	pound
LBBB	left bundle branch block
LDL-C	low-density lipoprotein
LFT	liver function test
LLN	lower limit of normal
LS	least square
MAR	missing at random
MDR	medical device regulation
MEN2	Multiple Endocrine Neoplasia Type 2
MHP	Mental Health Professional
mIU	milli-international unit
MMRM	Mixed Model Repeated Measures
MoA	mechanism of action
MQI	medically qualified individual
ms	millisecond
MTC	Medullary Thyroid Carcinoma
n	number (subgroup or subpopulation)
N	total number
NGSP	National Glycohemoglobin Standardization Program
NIMP	non-investigational medicinal product
NOAEL	no observed adverse effect level
NP	Nurse practitioner
NYHA	New York Heart Association
OATP	organic anion transporting polypeptide
OTC	over-the-counter
PA	Physicians' assistant
PBO	placebo
PCD	primary completion date
CCI [redacted]	
PCOS	polycystic ovary syndrome
PD	pharmacodynamic(s)
PE	physical exam
CCI [redacted]	
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic(s)
PPARγ	peroxisome proliferator-activated receptor-γ
PPI	proton pump inhibitor
PR	pulse rate
CCI [redacted]	
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	Prothrombin Time
PVC	premature ventricular contraction
QD	once daily
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
QTL	quality tolerance limit

Abbreviation	Term
qual	qualitative
RBC	red blood cell
REE	resting energy expenditure
RNA	ribonucleic acid
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SC	subcutaneous(ly)
Scr	serum creatinine
Scys	serum cystatin C
SD	standard deviation
CCI [redacted]	
SGLT2	sodium glucose cotransporter 2
CCI [redacted]	
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SRSD	Single Reference Safety Document
ST-T	ST segment to T wave changes on 12-lead ECG
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	telephone contact
T2DM	type 2 diabetes mellitus
T3	total triiodothyronine
T4	total thyroxine
Tbili	total bilirubin
TEAE	treatment-emergent adverse event
TEE	total energy expenditure
TG	triglyceride
T_{max}	time to reach C_{max}
TSH	thyroid-stimulating hormone
TZD	thiazolidinedione
UADE	unanticipated adverse device effect
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
USPI	United States Prescribing Information
UTI	urinary tract infection
V	visit
W	week
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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