A PHASE 1, OPEN-LABEL, FIXED-SEQUENCE STUDY TO EVALUATE THE EFFECT OF TWO STEADY-STATE DOSE LEVELS OF PF-07081532 ON THE PHARMACOKINETICS OF SINGLE-DOSE MIDAZOLAM, OMEPRAZOLE AND AN ORAL CONTRACEPTIVE, AND THE EFFECT OF STEADY-STATE SEMAGLUTIDE ON THE PHARMACOKINETICS OF SINGLE-DOSE MIDAZOLAM, IN OBESE ADULT FEMALE PARTICIPANTS

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: A Phase 1, 2-Cohort, Fixed-Sequence Study to Evaluate the Effect of 2 Steady-State Doses of PF-07081532 on Single-Dose Midazolam, Omeprazole, and Oral Contraceptive Pharmacokinetics, and the Effect of Semaglutide on Single-Dose Midazolam Pharmacokinetics, in Obese Adult Female Participants.

Rationale

This is a Phase 1, open-label, fixed-sequence, 2-cohort study to evaluate the effect of 1) 2 steady-state dose levels of PF-07081532 on the SD pharmacokinetics of midazolam, omeprazole, and an OC (LE/EE), and 2) steady-state semaglutide on the SD pharmacokinetics of midazolam, in otherwise healthy obese adult female participants. The intent of this study is to generate safety, tolerability, and PK data for further clinical development.

Objectives and Endpoints

Objectives	Endpoints
Cohort 1	
Primary:	**Primary:**
• To evaluate the effects of PF-07081532 on the pharmacokinetics of midazolam, omeprazole, and an oral contraceptive (OC; LE/EE) in obese adult female participants.	• Midazolam plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1, 4 and 7. • Omeprazole plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1, 4 and 7. • LE plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 2, 5 and 8. • EE plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in in Periods 2, 5 and 8.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-07081532 administered separately and in combination with midazolam, omeprazole, and an OC (LE/EE) in obese adult female participants.	• Assessment of TEAEs, clinical laboratory abnormalities, and body weight. • Assessment of mental health as determined by C-SSRS and PHQ-9.
• To evaluate the pharmacokinetics of SD midazolam following the discontinuation of PF-07081532 administration in obese adult female participants.	• Midazolam plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Period 9.

• To evaluate the effects of PF-07081532 on additional pharmacokinetic parameters of midazolam, omeprazole, and an OC (LE/EE) in obese adult female participants.	• Additional plasma pharmacokinetic parameters for midazolam and omeprazole (Periods 1, 4 and 7), and LE and EE (Periods 2, 5 and 8): C_{max} and T_{max}; and CL/F, Vz/F, $t_{½}$, as data permit.
• To evaluate the effects of PF-07081532 on the metabolite/parent ratios for midazolam and omeprazole in obese adult female participants.	• MRAUC$_{inf}$ (1-hydroxymidazolam AUC$_{inf}$/midazolam AUC$_{inf}$). • MRAUC$_{inf}$ (5-hydroxyomeprazole AUC$_{inf}$/omeprazole AUC$_{inf}$).
• To evaluate the MD pharmacokinetics of PF-07081532 in obese adult female participants.	• PF-07081532 plasma pharmacokinetic parameters at Days 34 and 103: AUC_{24}, C_{max}, T_{max}.
Cohort 2	
Primary:	**Primary:**
• To evaluate the effects of semaglutide (subcutaneous semaglutide) on the SD PK of midazolam in obese adult female participants.	• Midazolam plasma pharmacokinetic parameters: AUC$_{inf}$ (if data permit* otherwise AUC$_{last}$) in Periods 1 and 3.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of semaglutide administered separately and in combination with midazolam in obese adult female participants.	• Assessment of TEAEs, clinical laboratory abnormalities, and body weight. • Assessment of mental health as determined by C-SSRS and PHQ-9.
• To evaluate the pharmacokinetics of SD midazolam following the discontinuation of semaglutide administration in obese adult female participants.	• Midazolam plasma pharmacokinetic parameters: AUC$_{inf}$ (if data permit* otherwise AUC$_{last}$) in Period 4.
• To evaluate the effects of semaglutide on additional pharmacokinetic parameters of midazolam in obese adult female participants.	• Additional plasma pharmacokinetic parameters for midazolam (in Periods 1 and 3): C_{max}, T_{max}, and CL/F, Vz/F, $t_{½}$ as data permit.
• To evaluate the effects of semaglutide on the metabolite/parent ratio for midazolam in obese adult female participants.	• MRAUC$_{inf}$ (1-hydroxymidazolam AUC$_{inf}$/midazolam AUC$_{inf}$).

*Should it be deemed that too few AUC$_{inf}$ estimates (eg, less than 12 for a single treatment) are obtained from the evaluable participants, AUC$_{last}$ may be selected as the primary endpoint for CSR reporting. This will be considered for the midazolam, 1-hydroxymidazolam, omeprazole, 5-hydroxyomeprazole, LE, and EE objectives separately.

Overall Design

Brief Summary

This study is a Phase 1, open-label study that will be conducted in 2 cohorts; both cohorts will enroll otherwise healthy, obese, adult female participants. Cohort 1 is an open-label, 9-period, fixed-sequence design to evaluate the effect of 2 steady-state dose levels of PF-07081532 on the SD pharmacokinetics of midazolam and omeprazole, administered simultaneously, and an OC (LE/EE). Cohort 2 is an open-label, 4-period, fixed-sequence design to evaluate the effect of steady-state semaglutide on the SD pharmacokinetics of

midazolam. Additionally, participants in both cohorts will be discharged from the clinical site for 2 weeks following the final PK sample collection of OC (LE/EE) in Period 8, Day 2 (Cohort 1) or midazolam in Period 3, Day 2 (Cohort 2), and discontinue all further PF-07081532 or semaglutide dosing at that time. Following the 2-week out-patient duration, participants will return to the clinical site for a final midazolam assessment (without either PF-07081532 or semaglutide coadministration).

Participants will participate in either Cohort 1 or Cohort 2 (not both), and Cohort 1 and Cohort 2 are preferred to be conducted in parallel, if possible. For participants in Cohort 1, the total duration of participation from the Screening Visit to the F/U contact will be approximately 188 days or 27 weeks. For participants in Cohort 2, the total duration of participation from the Screening Visit to the F/U contact will be approximately 228 days or 33 weeks.

Number of Participants

A sample size of approximately 16 participants in Cohort 1 and approximately 16 participants in Cohort 2 will be enrolled such that approximately 12 evaluable participants complete each cohort of the study.

Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

Intervention Groups and Duration

For the purposes of this protocol, study intervention refers to PF-07081532, midazolam, omeprazole, OC and semaglutide.

The purpose of this study is to characterize the effect of PF-07081532, administered at 2 steady-state dose levels, on the PK of single doses of midazolam (2 mg oral) and omeprazole (20 mg oral), administered simultaneously, and an OC (LE 0.15 mg/ EE 0.03 mg oral) in otherwise healthy, obese, adult female participants in Cohort 1. Additionally, Cohort 2 will characterize the effect of semaglutide (2.4 mg subcutaneous) administered to steady state on the PK of single doses of midazolam (2 mg) in otherwise healthy, obese, adult female participants. Titration of PF-07081532 and semaglutide doses will be utilized to achieve a maximum dose of 260 mg QD in Cohort 1 (Table 8) and 2.4 mg (given once weekly) in Cohort 2 (Table 9), respectively.

Additionally, participants in both cohorts will be discharged from the clinical site for 2 weeks following the final PK sample collection of OC (LE/EE) in Period 8, Day 2 (Cohort 1) or midazolam in Period 3, Day 2 (Cohort 2), and discontinue all further PF-07081532 or

semaglutide dosing at that time. Following the 2-week out-patient duration, participants will return to the clinical site for a final midazolam assessment (without either PF-07081532 or semaglutide coadministration). In Cohort 1, the drug-drug interaction effect will be assessed at PF-07081532 doses of 80 mg QD and 260 mg QD, as 80 mg QD is projected as a potential therapeutic dose for T2DM and 260 mg QD is the maximum dose being studied in Phase 2 for T2DM and obesity. In Cohort 2, the DDI effect will be assessed at a semaglutide dose of 2.4 mg as this is the maximum approved dose for weight loss. In both cohorts, the impact of discontinuation for 2 weeks of either PF-07081532 (Cohort 1) or semaglutide (Cohort 2) on the PK of midazolam will be assessed.

PF-07081532 will be provided as tablets for oral administration. Study intervention (PF-07081532), midazolam and omeprazole or the OC must be administered within approximately 10 minutes of completion of the morning meal when taken alone. PF-07081532 will be administered first and midazolam and omeprazole or the OC will be administered within 5 minutes of PF-07081532 during the DDI assessment periods.

Semaglutide (Ozempic and/or Wegovy) will be provided as pre-filled, single-dose pens/dose level for subcutaneous injection. Drug administration will follow the instructions provided in the approved Highlights of Prescribing Information as outlined in the USPI. Study intervention (semaglutide) must be administered once weekly, preferably in the morning, without regard to timing of the breakfast meal during outpatient visits to the CRU for dose administration. During the DDI assessment inpatient visit (Period 3), semaglutide and midazolam must be administered within approximately 10 minutes of completion of the morning meal. Semaglutide will be administered first and midazolam will be administered within 5 minutes of semaglutide.

Cohort 1: 112 days will be in-patient as follows: Period 1 (SD midazolam and omeprazole): 1 day; Period 2 (SD OC): 5 days; Period 3 (PF-07081532 titrated to 80 mg QD): 28 days; Period 4 (80 mg PF-07081532 + SD midazolam and omeprazole): 1 day; Period 5 (80 mg PF-07081532 + SD OC): 5 days; Period 6 (PF-07081532 titrated to 260 mg QD): 63 days; Period 7 (260 mg PF-07081532 + SD midazolam and omeprazole): 1 day; Period 8 (260 mg PF-07081532 + SD OC): 6 days; Period 9 (SD midazolam only): 2 days.

Cohort 2: 6 days will be in-patient as follows: Period 1 (SD midazolam): 1 day; Period 2 (final day of semaglutide titrated to 2.4 mg once weekly): 1 day; Period 3 (2.4 mg semaglutide once weekly + SD midazolam) 2 days; Period 4 (SD midazolam): 2 days. Participants will also be required to return to the clinic during out-patient visits, preferably in the morning, to receive their once weekly semaglutide injections (Period 2).

The F/U visit will occur 7-10 days from the last dose of study intervention and a telephone F/U contact will occur 28-35 days from the last dose of study intervention.

Data Monitoring Committee or Other Independent Oversight Committee:

This study will not use a DMC.

Statistical Methods

The PK data for PF-07081532, midazolam, 1-hyroxymidazolam, omeprazole, 5-hydroxyomeprazole, LE, and EE will be analyzed and reported separately.

Cohort 1

Natural $\log_e$ transformed AUC_{inf} (as data permit), C_{max} and AUC_{last} of omeprazole administered without PF-07081532 or coadministered with PF-07081532 will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the models. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. The 2 test treatments will be 'omeprazole and PF-07081532 80 mg QD' (Period 4) and 'omeprazole and PF-07081532 260 mg QD' (Period 7), which will be reported separately in comparison to the reference treatment of 'omeprazole without PF-07081532' (Period 1).

Natural $\log_e$-transformed AUC_{inf} (as data permit), C_{max} and AUC_{last} of midazolam administered without PF-07081532 or coadministered with PF-07081532 will be analyzed and reported separately using the same mixed effect model as described above for omeprazole. The 2 test treatments will be 'midazolam and PF-07081532 80 mg QD' (Period 4)' and 'midazolam and PF-07081532 260 mg QD' (Period 7), which will be reported separately in comparison to the reference treatment of 'midazolam without PF-07081532' (Period 1).

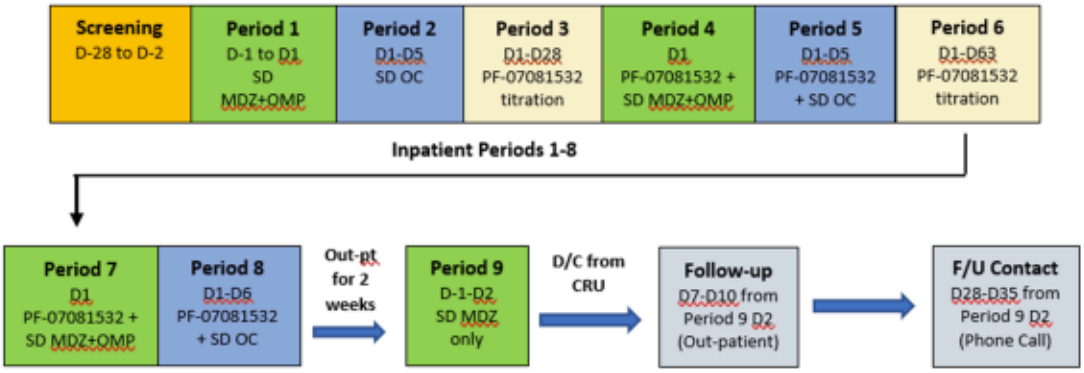
Natural $\log_e$-transformed AUC_{inf} (as data permit), C_{max} and AUC_{last} of LE and EE administered alone or coadministered with PF-07081532 will be analyzed and reported separately using the same mixed effect model as described above for omeprazole. For LE, the 2 test treatments will be 'LE and PF-07081532 80 mg QD' (Period 5) and 'LE and PF-07081532 260 mg QD' (Period 8), which will be reported separately in comparison to the reference treatment of 'LE alone' (Period 2). Similarly for EE, the 2 test treatments will be 'EE and PF-07081532 80 mg QD' (Period 5) and 'EE and PF-07081532 260 mg QD' (Period 8), which will be reported separately in comparison to the reference treatment of 'EE alone' (Period 2).

Cohort 2

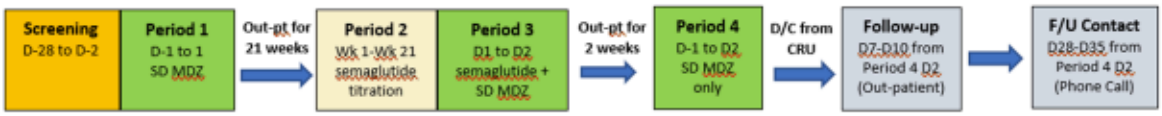
Natural $\log_e$-transformed AUC_{inf} (as data permit), C_{max} and AUC_{last} of midazolam administered alone or coadministered with semaglutide in Cohort 2 will be analyzed and reported separately using the same mixed effect model as described above for omeprazole. The test treatment will be 'midazolam and semaglutide 2.4 mg weekly' (Period 3) which will be reported separately in comparison to the reference treatment of 'midazolam alone' (Period 1).

1.2. Schema

Cohort 1 – PF-07081532 and Midazolam, Omeprazole, and an OC (LE/EE)



Cohort 2 – Semaglutide and Midazolam



Note: for Cohort 2, participants will be discharged from the study site following administration of the first 0.25 mg semaglutide injection on Day 1 of Period 2. Period 2 will be conducted out-patient until the final day when participants will be readmitted to the study site the day prior to the Period 3 DDI assessment. For both Cohorts 1 and 2, participants will be readmitted to the study site following a 2-week out-patient duration with no study intervention at Period 9 and Period 4, respectively.

1.3. Schedule of Activities

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

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

Cohort 1: Schedule of Activities

Table 1. Cohort 1 - Overall Schedule of Activities Screening to Period 5

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Screening	Period 1 (MDZ + OMP only)		Period 2 (OC only)			Period 3 (PF-07081532 only)									Period 4 (PF-07081532 + MDZ + OMP)	Period 5 (PF-07081532 + OC)		
Day in Study Period[a]	-28 to -2	-1	1	1	2-4	5	1	2-7	8	9-14	15	16-21	22	23-27	28	1	1	2-4	5
Days in Study[b]	-28 to -2	-1	1	2	3-5	6	7	8-13	14	15-20	21	22-27	28	29-33	34	35	36	37-39	40
Informed consent and demography	x																		
Outpatient visit (after ≥10 h fast)	x																		
Medical history	x																		
Eligibility criteria	x	x																	
Physical exam[c] (height at Screen only)	x																		
Review contraception use - WOCBP Only (Section 5.3.4)	x	x																	
Review drug, alcohol/tobacco use	x	x																	
COVID-19 pre-screening[d]		x																	
SARS-CoV-2 testing[d]		x																	
Temperature check[d]		x																	
C-SSRS and PHQ-9	x	x					x				x					x			
Review prior or concomitant treatments	x	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
AE monitoring	x	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Inpatient stay at CRU		x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Standardized meals/snacks[e]		x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Body weight	x		Table 3	Table 4			x		x		x		x		Table 5	Table 3	Table 4		
Supine 12-lead ECG	x																		
Single, supine vital signs assessment[f]	x																		
Midazolam administration																			
Omeprazole administration																			
OC administration																			
PF-07081532 administration[g]							x	x	x	x	x	x	x	x		x	x	x	x
Blood Sampling for:[h]																			
- Chemistry	x	x							x				x						

Table 1. Cohort 1 - Overall Schedule of Activities Screening to Period 5

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Screening	Period 1 (MDZ + OMP only)		Period 2 (OC only)			Period 3 (PF-07081532 only)									Period 4 (PF-07081532 + MDZ + OMP)		Period 5 (PF-07081532 + OC)		
Day in Study Period[a]	-28 to -2	-1	1	1	2-4	5	1	2-7	8	9-14	15	16-21	22	23-27	28	1		1	2-4	5
Days in Study[b]	-28 to -2	-1	1	2	3-5	6	7	8-13	14	15-20	21	22-27	28	29-33	34	35		36	37-39	40
- Calcitonin, amylase, lipase	x	x							x				x							
- Free T4, TSH, lipid panel, total bile acids	x	x																		
- Hematology/ HbA1c	x	x											x							
- FSH,[i] HIV, HBsAg, HCVAb, HCV RNA, C-peptide	x																			
- Serum pregnancy test[i]	x	x																		
- MDZ and 1-hydroxy-MDZ PK				x[j]														x[j]		
- OMP & 5-hydroxy-OMP PK				x[j]														x[j]		
- OC (LE and EE) PK					x[k]	x[k]	x[k]												x[k]	x[k]
- PF-07081532 PK																x[l]		x		
- 4β-hydroxycholesterol, cholesterol, [CCI]																				
[CCI]																				
Urine Sampling for:																				
- Urine drug test[a]	x	x																		
- Urinalysis (and microscopy, as appropriate)	x																			

Table 1. Cohort 1 - Overall Schedule of Activities Screening to Period 5

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Screening	Period 1 (MDZ + OMP only)		Period 2 (OC only)			Period 3 (PF-07081532 only)									Period 4 (PF-07081532 + MDZ + OMP)	Period 5 (PF-07081532 + OC)		
Day in Study Period[a]	-28 to -2	-1	1	1	2-4	5	1	2-7	8	9-14	15	16-21	22	23-27	28	1	1	2-4	5
Days in Study[b]	-28 to -2	-1	1	2	3-5	6	7	8-13	14	15-20	21	22-27	28	29-33	34	35	36	37-39	40

a. Day relative to start of dosing Day 1 of that Period.

b. Day relative to first dose of investigational product (midazolam/omeprazole) on Day 1 of Period 1.

c. Complete physical exam at Screening; otherwise, brief exam if findings during previous exam or new/open AEs, if appropriate, at investigator discretion.

d. Participants will be tested for SARS-COVID-19 infection by PCR. Test must be negative prior to admission on Day -1, Period 1. A subsequent test will be done according to local procedure if participants develop COVID-19 like symptoms. Prior to SARS-CoV-2 test, temperature check and COVID-19 pre-screening for COVID-19 related signs and symptoms will be done. See also Section 8.3.5 (COVID-19 Specific Assessments). If participants test positive for SARS-CoV-2 infection, they will be discharged from the study.

e. Meals to be provided at approximately 0h, 4h, and 10h post AM dose; plus, snacks provided according to Section 5.3.1.

f. Includes BP and PR predose.

g. Dosing to occur QD with breakfast as specified in Section 5.3.1.

h. Collection following fasting duration specified in Section 5.3.1.

i. FSH for female participants to confirm PM status only. Serum β-hCG for all WOCBP; test result should confirm no pregnancy prior to dosing.

j. Following midazolam and omeprazole dosing on Day 1 in both Periods 1 and 4, midazolam, omeprazole, 1-OH-midazolam, and 5-hydroxyomeprazole PK should be obtained at approximately 24h post midazolam and omeprazole dose.

k. Following OC dosing on Day 1 in both Periods 2 and 5, LE and EE PK should be obtained at 24h, 48h, 72h, 96h and 120h post OC dose on Day 1 of the same period.

l. The PF-07081532 PK sample should be obtained at 24 hours following the dose in P3D28, which is the same as the 0 hour PK sample in P4D1.

CCI [redacted]

n. Participants may undergo random urine drug testing at the discretion of the investigator.

Table 2. Cohort 1 - Overall Schedule of Activities Period 6 to ET

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Period 6 (PF-07081532 only)									Period 7 (PF-07081532 + MDZ + OMP)	Period 8 (PF-07081532 + OC)			Period 9 (MDZ only)			F/U Visit	F/U Contact Telephone	ET
Day in Study Period[a]	1-7	8-14	15-21	22-28	29-35	36-42	43-49	50-56	57-63	1	1	2-5	6	-1	1	2	7-10	28-35	-
Days in Study[b]	41-47	48-54	55-61	62-68	69-75	76-82	83-89	90-96	97-103	104	105	106-109	110	124	125	126	132-135	153-160	-
Informed consent and demography																			
Outpatient visit (after ≥10-h fast)																	x		
Medical history														x					
Eligibility criteria																			
Physical exam (height at Screen only)																			X[c]
Review contraception use - WOCBP Only (Section 5.3.4)														x			x	x	
Review drug, alcohol/tobacco use														x	→	→	x		
COVID-19 pre-screening[d]														x					
SARS-CoV-2 testing[d]														x					
Temperature check[d]														x					
C-SSRS and PHQ-9[e]		x		x		x		x	x				x				x		
Review prior or concomitant treatments	→	→	→	→	→	→	→	→	→	→	→	→	x	x	→	→	x	x	
AE monitoring	→	→	→	→	→	→	→	→	→	→	→	→	x	x	→	→	x	x	
Inpatient stay at Clinical Research Unit	→	→	→	→	→	→	→	→	→	→	→	→	x[f]	x[g]	→	x[f]			
Standardized meals/snacks[h]	→	→	→	→	→	→	→	→	→	→	→	→	→	x	→	→			
Body weight[i]	x	x	x	x	x	x	x	x	x	Table 5	Table 3		x		Table 3		x		x
Supine 12-lead ECG													x			x			x
Single, supine vital signs assessment[j]													x			x			x
PF-07081532 administration[k]	x	x	x	x	x	x	x	x	x		x	x	x						
Omeprazole administration																			
Midazolam administration																			
OC administration																			
Blood Sampling for:[l]																			
- Chemistry[m]	x		x		x		x		x				x			x	x		x
- Calcitonin, amylase, lipase[m]	x		x		x		x		x				x			x	x		x
- Free T4, TSH, lipid panel, total bile acids													x			x			x

Table 2. Cohort 1 - Overall Schedule of Activities Period 6 to ET

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Period 6 (PF-07081532 only)									Period 7 (PF-07081532 + MDZ + OMP)		Period 8 (PF-07081532 + OC)				Period 9 (MDZ only)			F/U Visit	F/U Contact Telephone	ET
Day in Study Period[a]	1-7	8-14	15-21	22-28	29-35	36-42	43-49	50-56	57-63	1		1	2-5	6		-1	1	2	7-10	28-35	-
Days in Study[b]	41-47	48-54	55-61	62-68	69-75	76-82	83-89	90-96	97-103	104		105	106-109	110		124	125	126	132-135	153-160	-
- Hematology/HbA1c[n]			x				x							x				x	x		x
- FSH,[o] HIV, HBsAg, HCV RNA, HCVAb, C-peptide																					
- Serum pregnancy test[o]																x					
- OMP and 5-hydroxy-OMP PK												x[p]									x
- MDZ and 1-hydroxy-MDZ PK												x[p]						x[p]			x
- OC (LE/EE) PK	x[q]												x[q]	x[q]							x
- PF-07081532 PK										x[r]		x									x
- 4-β-hydroxycholesterol, cholesterol, CCI																					
CCI [redacted]																					
Urine Sampling for:																					
- Urine drug test[s]																					
- Urinalysis (and microscopy, as appropriate)																x					x

a. Day relative to start of dosing Day 1 of that Period.

b. Day relative to first dose of investigational product (midazolam/omeprazole) on Day 1 of Period 1.

c. Brief exam if findings during previous exam or new/open AEs, if appropriate, at investigator discretion.

d. Participants will be tested for SARS-COVID-19 infection by PCR. Test must be negative prior to readmission on Day -1, Period 9. A subsequent test will be done according to local procedure if participants develop COVID-19 like symptoms. Prior to SARS-CoV-2 test, temperature check and COVID-19 pre-screening for COVID-19 related signs and symptoms will be done. See also Section 8.3.5 (COVID-19 Specific Assessments). If participants test positive for SARS-CoV-2 infection, they will be discharged from the study.

e. C-SSRS and PHQ will be administered in Period 6 on Days 14, 28, 42, 56, and 63.

f. Discharge from CRU.

g. Readmit to CRU.

h. Meals to be provided at approximately 0h, 4h, and 10h post AM dose.

i. Body weight to be obtained once weekly in Period 6 on Days 1, 8, 15, 22, 29, 36, 43, 50, and 57.

Table 2. Cohort 1 - Overall Schedule of Activities Period 6 to ET

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Period 6 (PF-07081532 only)									Period 7 (PF-07081532 + MDZ + OMP)	Period 8 (PF-07081532 + OC)			Period 9 (MDZ only)			F/U Visit	F/U Contact Telephone	ET
Day in Study Period[a]	1-7	8-14	15-21	22-28	29-35	36-42	43-49	50-56	57-63	1	1	2-5	6	-1	1	2	7-10	28-35	-
Days in Study[b]	41-47	48-54	55-61	62-68	69-75	76-82	83-89	90-96	97-103	104	105	106-109	110	124	125	126	132-135	153-160	-

j. Includes BP and PR predose.

k. Dosing to occur QD with breakfast. Note that there is no PF-07081532 administration on Day 110 or anytime thereafter.

l. Collection following fasting duration specified in. Section 5.3.1.

m. To be obtained on Days 1, 15, 29, 43, and 57 in Period 6.

n. To be obtained on Days 15 and 43 in Period 6.

o. FSH for female participants to confirm PM status only. Serum β-hCG for all WOCBP; test result should confirm no pregnancy prior to dosing.

p. Following midazolam and omeprazole dosing on Day 1 in Period 7, midazolam, omeprazole, 1-OH-midazolam, and 5-hydroxyomeprazole PK should be obtained at approximately 24h post midazolam and omeprazole doses. Following the midazolam dose on Day 1 in Period 9, midazolam and 1-OH-midazolam PK should be obtained at approximately 24h post-dose.

q. Following OC dosing in Period 5, LE and EE PK should be obtained at 120h post dose on Day 1 of the same period. Following OC dosing in Period 8, LE and EE PK should be obtained at 24h, 48h, 72h, 96h, and 120h post OC dose on Day 1 of the same period.

r. The PF-07081532 PK sample should be obtained at 24 hours following the dose in P6D63, which is the same as the 0 hr PK sample in P7D1.

s. Participants may undergo random urine drug testing at the discretion of the investigator.

Table 3. Schedule of Activities – Day 1 of Period 1 (Midazolam + Omeprazole ONLY), Period 4 (Midazolam + Omeprazole + PF-07081532 80 mg QD), Period 7 (Midazolam + Omeprazole + PF-07081532 260 mg QD), and Period 9 (Midazolam ONLY)

Hours Relative to Dosing at 0h	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**14**
Body Weight	X									
Midazolam administration	X[a]									
Omeprazole administration *(Periods 1,4, and 7 only)*	X[a]									
PF-07081532 administration *(Periods 4 and 7 only)*	X[a]									
Blood sampling for:[b]										
- Chemistry *(Period 9 only)*	x									
- Calcitonin, amylase, lipase *(Period 9 only)*	x									
- Free T4, TSH, lipid panel, total bile acids *(Period 9 only)*	x									
- Hematology/HbA1c *(Period 9 only)*	x									
CCI										
- Midazolam and 1-hydroxy-MDZ PK	x	x	x	x	x	x	x	x	x	x
- Omeprazole and 5-hydroxy-OMP PK *(Periods 1, 4, and 7 only)*	x	x	x	x	x	x	x	x	x	x
- 4-β-hydroxycholesterol/cholesterol, CCI	x									
- PF-07081532 PK *(Periods 4 and 7 only)*[d]	x									
Urine sampling for:										
- Urinalysis and microscopy, as appropriate *(Period 1 only)*	x									

a. Dosing to occur with breakfast as specified in Section 5.3.1.

b. Collection following fasting duration according to dosing frequency as specified in Section 5.3.1.

CCI

d. For Periods 4 and 7 only, PF-07081532 PK sample to be drawn at 0h, approximately 24h after the PF-07081532 morning dose on the previous day (Period 3 Day 28 and Period 6 Day 63, respectively).

Table 4. Schedule of Activities – Day 1 of Period 2 (OC ONLY), Period 5 (OC + PF-07081532 80 mg QD) and Period 8 (OC + PF-07081532 260 mg QD)

Hours Relative to Dosing at 0h	0	0.75	2	4	8	12
OC administration	X[a]					
PF-07081532 administration *(Periods 5 and 8 only)*	X[a]					
Blood sampling for:[b]						
- OC PK	x	x	x	x	x	x
- Midazolam, 1-hydroxy-MDZ, omeprazole, 5-hydroxy-OMP PK	X[c]					
- PF-07081532 PK *(Periods 5 and 8 only)*	x					

a. Dosing to occur with breakfast as specified in Section 5.3.1.

b. Collection following fasting duration according to dosing frequency as specified in Section 5.3.1.

c. Midazolam, 1-hydroxy-MDZ, omeprazole, and 5-hydroxy-OMP PK samples to be drawn at 0h, approximately 24h after the midazolam/omeprazole morning dose on the previous day (Day 1 of Period 1, Period 4, and Period 7.

Table 5. Schedule of Activities – Day 28 of Period 3 and Day 63 of Period 6 (PF-07081532 only)

Hours Relative to Dosing at 0h	0	0.5	1	2	4	6	8	10	14
PF-07081532 administration	X[a]								
Blood sampling for:[b]									
- PF-07081532 PK	x	x	x	x	x	x	x	x	x
Urine sampling for:									
- Urinalysis and microscopy, as appropriate	x								

a. Dosing to occur with breakfast as specified in Section 5.3.1.

b. Collection following fasting duration according to dosing frequency as specified in Section 5.3.1.

Table 6. Cohort 2: Schedule of Activities

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Screening	Period 1 (MDZ only)		Period 2 (Out-patient: Semaglutide only)																						Period 3 (Semaglutide + MDZ)		Period 4 (MDZ Only)			F/U Visit	F/U Contact Tele-phone	ET
Day in Study Period[a]	-28 to -2	-1	1	1-7	8-14	15-21	22-28	29-35	36-42	43-49	50-56	57-63	64-70	71-77	78-84	85-91	92-98	99-105	106-112	113-119	120-126	127-133	134-140	141-146	147	1	2	-1	1	2	7-10	28-35	
Week in Study Period[a]	-	-	-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	21	-	-	-	-	-	-	-	-
Days in Study[b]	-28 to -2	-1	1	2-8	9-15	16-22	23-29	30-36	37-43	44-50	51-57	58-64	65-71	72-78	79-85	86-92	93-99	100-106	107-113	114-120	121-127	128-134	135-141	142-147	148	149	150	164	165	166	172-175	193-200	
Informed consent and demography	x																																
Outpatient visit (after ≥10 h fast)	x				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x									
Medical history	x																								x			x					
Eligibility criteria	x	x																															
Physical exam[c] (height at Screen only)	x																																x
Review contraception use (Section 5.3.4)[d]	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	x
COVID-19 pre-screening[e]		x																							x			x					
SARS-CoV-2 testing[e]		x																							x			x					x
Temperature check[e]		x																							x			x					x
C-SSRS and PHQ-9[f]	x	x						x				x				x				x							x				x		
Review drug, alcohol/tobacco use[g]	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x	→	→			
Review prior or concomitant treatments[g]	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	→	→	x	x	x
AE monitoring[g]	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	→	→	x	→	→	x	x	x
Inpatient stay at CRU		x	x	x[h]																					x[i]	x	x[h]	x[i]	→	x[h]			

Table 6. Cohort 2: Schedule of Activities

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Screening	Period 1 (MDZ only)		Period 2 (Out-patient: Semaglutide only)																						Period 3 (Semaglutide + MDZ)		Period 4 (MDZ Only)			F/U Visit	F/U Contact Tele-phone	ET
Day in Study Period[a]	-28 to -2	-1	1	1-7	8-14	15-21	22-28	29-35	36-42	43-49	50-56	57-63	64-70	71-77	78-84	85-91	92-98	99-105	106-112	113-119	120-126	127-133	134-140	141-146	147	1	2	-1	1	2	7-10	28-35	
Week in Study Period[a]	-	-	-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	21	-	-	-	-	-	-	-	-
Days in Study[b]	-28 to -2	-1	1	2-8	9-15	16-22	23-29	30-36	37-43	44-50	51-57	58-64	65-71	72-78	79-85	86-92	93-99	100-106	107-113	114-120	121-127	128-134	135-141	142-147	148	149	150	164	165	166	172-175	193-200	
Standardized meals/snacks[j]		x	→																						x	→	→	→	→	→			
Body weight[k]	x		Table 7	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		Table 7	x		Table 7		x		x
Supine 12-lead ECG	x																										x			x			x
Single, supine vital signs assessment[l]	x																										x			x			x
Semaglutide dosing[m]				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x									
Midazolam dosing																																	
Blood Sampling for:[n]																																	
-Chemistry[o]	x						x				x				x				x				x				x			x	x		x
- Calcitonin, amylase, lipase[o]	x						x				x				x				x				x				x			x	x		
- Hematology/HbA1c[o]	x						x				x				x				x				x				x			x	x		x
- Free T4, TSH, lipid panel, total bile acids	x																										x			x	x		
- FSH[p], HIV, HBsAg, HCVAb, HCV RNA, C-peptide	x																																
- Serum pregnancy test[p]	x	x																							x			x			x		x
- Urine pregnancy test[s]					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x									

Table 6. Cohort 2: Schedule of Activities

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Screening	Period 1 (MDZ only)		Period 2 (Out-patient: Semaglutide only)																						Period 3 (Semaglutide + MDZ)		Period 4 (MDZ Only)			F/U Visit	F/U Contact Tele-phone	ET
Day in Study Period[a]	-28 to -2	-1	1	1-7	8-14	15-21	22-28	29-35	36-42	43-49	50-56	57-63	64-70	71-77	78-84	85-91	92-98	99-105	106-112	113-119	120-126	127-133	134-140	141-146	147	1	2	-1	1	2	7-10	28-35	
Week in Study Period[a]	-	-	-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	21	-	-	-	-	-	-	-	-
Days in Study[b]	-28 to -2	-1	1	2-8	9-15	16-22	23-29	30-36	37-43	44-50	51-57	58-64	65-71	72-78	79-85	86-92	93-99	100-106	107-113	114-120	121-127	128-134	135-141	142-147	148	149	150	164	165	166	172-175	193-200	
- MDZ, 1-hydroxy-MDZ PK				x[q]																							x[q]				x[q]			x
- Semaglutide PK[r]								x				x				x				x													x
- 4-β-hydroxycholesterol, cholesterol,[CCI]																																	
[CCI]																																	
Urine Sampling for:																																	
- Urine drug test[t]	x	x																							x			x					
- Urinalysis (and microscopy, as appropriate)	x																																

Table 6. Cohort 2: Schedule of Activities

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Screening	Period 1 (MDZ only)		Period 2 (Out-patient: Semaglutide only)																						Period 3 (Semaglutide + MDZ)		Period 4 (MDZ Only)			F/U Visit	F/U Contact Tele-phone	ET
Day in Study Period[a]	-28 to -2	-1	1	1-7	8-14	15-21	22-28	29-35	36-42	43-49	50-56	57-63	64-70	71-77	78-84	85-91	92-98	99-105	106-112	113-119	120-126	127-133	134-140	141-146	147	1	2	-1	1	2	7-10	28-35	
Week in Study Period[a]	-	-	-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	21	-	-	-	-	-	-	-	-
Days in Study[b]	-28 to -2	-1	1	2-8	9-15	16-22	23-29	30-36	37-43	44-50	51-57	58-64	65-71	72-78	79-85	86-92	93-99	100-106	107-113	114-120	121-127	128-134	135-141	142-147	148	149	150	164	165	166	172-175	193-200	

a. Day or Week relative to start of dosing Day 1 of that Period.
b. Day relative to first dose of midazolam on Day 1 of Period 1.
c. Complete physical exam at Screening, otherwise, brief exam if findings during previous exam or new/open AEs, if appropriate, at investigator discretion.
d. For WOCBP, contraceptive use will be reviewed and a urine pregnancy test conducted at weekly out-patient visits. If the urine pregnancy test is positive or inconclusive, a serum pregnancy test will be conducted.
e. Participants will be tested for SARS-COVID-19 infection by PCR prior to admission on Day -1 in Periods 1, 3 and 4. A subsequent test will be done according to local procedure if participants develop COVID-19 like symptoms or signs. Prior to SARS-CoV-2 test, a temperature check and COVID-19 pre-screening for COVID-19 related signs and symptoms will be done. See also Section 8.3.5 (COVID-19 Specific Assessments). If participants test positive for SARS-CoV-2 infection, they will be discharged from the study.
f. C-SSRS and PHQ-9 will be administered in Period 2 at the Week 5, 9, 13, and 17 visits.
g. To be monitored at weekly out-patient visits in Period 2.
h. Discharge from CRU on Day 1 in Period 2 and on Days 2 in Periods 3 and 4.
i. Readmit to CRU.
j. Meals to be provided at approximately 0h, 4h, and 10h post AM dose.
k. Body weight to be obtained once weekly in Period 2 when participants return to the CRU for their weekly semaglutide injections.
l. Includes BP and PR.
m. Dosing to occur weekly, preferably in the morning, as specified in Section 5.3.1.
n. Collection following fasting duration specified in Section 5.3.1.
o. To be collected on Days 22, 50, 78, and 106, and 134 of Period 2.
p. FSH for female participants to confirm PM status only. Serum b-hCG for all WOCBP; test result should confirm no pregnancy prior to dosing.
q. Following midazolam dosing on Day 1 in Periods 1, 3, and 4, midazolam and 1-hydroxymidazolam PK should be obtained at approximately 24h postdose.
r. Semaglutide PK samples to be collected prior to the first 0.5, 1.0, 1.7, and 2.4 mg semaglutide doses at the in-patient visits at Weeks 5, 9, 13, and 17, respectively, during Period 2, and prior to dosing in Period 3, Day 1.
CCI [redacted]
t. Participants may undergo random urine drug testing at the discretion of the investigator.

Table 7. Schedule of Activities – Day 1 of Period 1 (Midazolam ONLY), Period 3 (Midazolam + Semaglutide 2.4 mg), and Period 4 (Midazolam ONLY)

Hours Relative to Dosing at 0h	0	0.5	1	2	3	4	6	8	10	14
Body weight	x									
Midazolam administration	x[a]									
Semaglutide administration *(Period 3 only)*	x[a]									
Blood sampling for:[b]										
- Chemistry	x									
- Calcitonin, amylase, lipase	x									
- Free T4, TSH, lipid panel, total bile acids	x									
- Hematology/HbA1c	x									
- Midazolam and 1-hydroxy-MDZ PK	x	x	x	x	x	x	x	x	x	x
- Semaglutide PK *(Period 3 only)*	x									
- 4-β-hydroxycholesterol/cholesterol, CCI	x									
CCI [redacted]										

a. Dosing to occur with breakfast as specified in Section 5.3.1.
b. Collection following fasting duration according to dosing frequency as specified in Section 5.3.1.

CCI [redacted]

2. INTRODUCTION

GLP-1 is a neuroendocrine hormone that is predominantly released from the small intestine in response to food intake.[1] GLP-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 purpose of this Phase 1, open-label, fixed-sequence study is to evaluate the effect of 2 dose levels of PF-07081532 administered to steady state on the SD pharmacokinetics of midazolam, omeprazole, and an OC (LE/EE) (Cohort 1), and to evaluate the effect of steady-state semaglutide on the SD pharmacokinetics of midazolam (Cohort 2), in otherwise healthy, obese, adult female participants. The intent of this study is to generate safety, tolerability, and PK data for further clinical development.

2.2. Background

T2DM is estimated to affect more than 424 million people worldwide,[5] and the prevalence of T2DM within the US is estimated to range from 12 to 14%.[6] Patients with poorly controlled T2DM have an increased risk of developing complications associated with both microvascular and macrovascular disease, including nephropathy, neuropathy, retinopathy, cardiovascular disease and stroke; and are at 2 to 4 times increased risk of mortality than adults who do not have diabetes.[7] 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 target glycated HbA1c levels, suggesting a need for additional therapeutic options.

Obesity is a chronic disease that is associated with serious co-morbidities, including T2DM, dyslipidemia, hypertension, atherosclerosis, obstructive sleep apnea and certain cancers,[8] and is also associated with increased all-cause mortality.[9] 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.[10] 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.[11] 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.

Marketed injectable GLP-1R agonists have demonstrated robust glycemic efficacy, weight loss, and cardiovascular safety, with more than one marketed agent demonstrating cardiovascular benefit.[12] Based on the clinical history of injectable GLP-1R agonists, an oral, small molecule GLP-1R agonist is expected to improve glucose control and reduce HbA1c levels in patients with T2DM, while decreasing appetite and body weight, resulting in weight loss in patients with T2DM and obesity, while avoiding the subcutaneous injection required by currently available peptidic GLP-1R agonists.

2.2.1. Nonclinical Pharmacology

Refer to the IB for details on the nonclinical pharmacology of PF-07081532.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

In rats and monkeys following single IV and oral dosing, PF-07081532 exhibited low CL_p (13 and 0.6 mL/min/kg, respectively), with low to moderate steady-state V_{ss} (0.76 and 0.21 L/kg, respectively), leading to a $t_{½}$ of 1.6 hours in rats and 8.8 hours in monkeys. Renal excretion was negligible in both species, and biliary excretion was minimal in rats. The systemic exposure (assessed by AUC and C_{max}) of PF-07081532 following oral repeat dose pivotal toxicity studies in rats, rabbits and monkeys generally increased in a dose-proportional manner.

In vitro, PF-07081532 was a substrate for the hepatic uptake transporter, OATP1B3, but not for OATP1B1. Coadministration of an OATP inhibitor with PF-07081532 in monkeys resulted in a notable increase in the plasma AUC exposure of PF-07081532 and corresponding decrease in CL, suggesting a potential role for OATP transport in the uptake-limited CL in monkeys.

Preliminary evaluation of the in vitro metabolism of PF-07081532 showed similar metabolic profiles across species with no evidence of human specific metabolites. PF-07081532 was extensively metabolized via oxidative CYP and conjugation UGT pathways. CYP-mediated metabolism accounted for 67% of the hepatic metabolism, with CYP3A (31%) being the predominant CYP isoform. The contribution of non-CYP metabolism was estimated to be 33% of the hepatic metabolism, which was due to glucuronidation (24%) and chemical hydrolysis (9%). UGT1A1 and UGT1A3 were primarily responsible for the glucuronidation of PF-07081532, with possible minor contributions by the non-hepatic UGT isoforms, UGT1A7 and UGT1A8.

Using a physiologically relevant static mechanistic model, PF-07081532 was shown to have the potential to be a reversible inhibitor of UGT1A1 and a moderate time-dependent inhibitor of CYP2C19 activity at a clinical dose of 260 mg.

After evaluating the ability to induce CYP enzymes, PF-07081532 elicited a weak induction of CYP3A4 and CYP2B6 mRNA in a single lot of hepatocytes, and did not elicit a >2-fold induction of CYP1A2 mRNA or enzyme activity. Although PF-07081532 demonstrated >2-fold CYP3A4 and CYP2B6 mRNA induction, the responses lacked concentration dependency, therefore, PF-07081532 was not an in vitro inducer of CYPs 3A4, 2B6, or 1A2.

Refer to the IB for more details on the nonclinical PK and metabolism of PF-07081532.

2.2.3. Nonclinical Safety

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Refer to the IB for more details on the nonclinical safety of PF-07081532.

2.2.4. Clinical Overview and Safety

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 the majority of the 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.

Refer to the IB for more details on the clinical safety of PF-07081532.

2.2.4.1. Clinical Pharmacokinetics

The clinical PK of PF-07081532 in adult participants have been evaluated to date in 2 completed studies (C3991001 and C3991002). The results of these completed studies are summarized in the PF-07081532 IB.

In Study C3991001 following administration of single oral doses of PF-07081532 under fasted conditions to healthy participants, PF-07081532 was absorbed relatively rapidly with a median T_{max} of 1.00 to 4.02 hours (individual T_{max} values ranged between 0.5 and 6 hours). Based on the individual plasma concentration-time profiles, the absorption phase exhibited multiple peaks, especially at the higher dose levels. Mean $t_{½}$ ranged from 18.03 to 20.90 hours across all doses. Plasma C_{max} increased less than proportionally across the entire investigated dose range (from 10 mg to 200 mg), while plasma AUC_{inf} increased less than proportionally from 10 mg to 30 mg and approximately proportionally from 30 mg to 200 mg. Inter-participant variability for PF-07081532 exposure was low to moderate and ranged from 9% to 36% CV for C_{max} and 15% to 44% CV for AUC_{inf} across all doses. Overall, the results indicate that PF-07081532 may be administered without regard to food.

In Study C3991002 following administration of PF-07081532, C_{max} was observed at 1 to 2 hours on Day 1, and 2 to 8 hours following the last dose on Day 28 or 42. Across all dose groups, the mean $t_{½}$ ranged from 20.70 to 26.50 hours. PF-07081532 exposure generally increased in an approximately dose proportional manner across the dose range studied, and accumulation of less than 2.1-fold was observed. Urinary recovery of unchanged PF-07081532 was low, with less than 0.2% of the dose recovered in the 24-hour dosing interval following last dose administration. Inter-participant variability for PF-07081532 exposure ranged from 17% to 51% CV for C_{max} and 15% to 62% CV for AUC_{tau} across all doses. No substantial differences in PF-07081532 exposure (C_{max} and AUC_{tau}) were observed between participants with T2DM and obesity either after single dose (Day 1, 10 mg) or multiple dose (Day 28, 120 mg and Day 42, 180 mg) administration.

Refer to the IB for more details on the clinical PK of PF-07081532.

2.3. Benefit/Risk Assessment

PF-07081532 is not expected to provide any long-term clinical benefit to the healthy adult female participants in this study. This study is designed primarily to generate safety, tolerability, and PK data for further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07081532 may be found in the IB, which is the SRSD for this study. The SRSD for the site sourced midazolam (midazolam hydrochloride syrup), omeprazole, and OC (0.15 mg LE/0.03 mg EE) products are the corresponding USPIs.[13,14,15] The SRSD for the semaglutide (prefilled, single-use pens, doses 0.25 to 2.4 mg) product(s) are the corresponding USPIs.[16,17]

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention PF-07081532 and semaglutide		
Thyroid C-cell tumors	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, dulaglutide, semaglutide, and exenatide) 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.	Potential participants with a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 are excluded from the clinical development program. Thyroid function tests are included in the clinical trial protocols to monitor participants' thyroid function.
Pancreatitis	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, exenatide, semaglutide and dulaglutide). One SAE of obstructive pancreatitis has been observed in the PF-07081532 clinical trial program, which was considered to be treatment-related by the investigator, but unrelated by the Sponsor.	Per exclusion criteria, potential participants with acute pancreatitis or a history of chronic pancreatitis are not eligible for study entry. Serum amylase and lipase are monitored during clinical studies.
Hypoglycemia	Clinical trials with injectable GLP-1R agonists have not demonstrated an increased risk for hypoglycemia. But 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. Participants with obesity who do not have co-existing T2DM would not be taking anti-diabetic agents and therefore would not be expected to have an increased risk for hypoglycemia. A low overall frequency of generally mild hypoglycemia has been reported in	Anti-diabetic medications are prohibited in this study, and blood glucose is monitored as a part of the lab assessments during the study. Participants are informed about the signs and symptoms of hypoglycemia and are monitored for these symptoms during the study.

	the PF-07081532 clinical development program to date.	
Impairment in renal function	Potential risks are based on product labeling for injectable GLP-1R agonists, and predominantly occur in patients with significant nausea, vomiting, and dehydration. In the clinical trial program only one mild adverse event (Preferred Term Blood creatinine increased) has been observed.	Per exclusion criteria, potential participants with significant renal impairment are not eligible for study entry. Renal function is monitored by lab assessments of serum BUN, creatinine and eGFR. Hydration will be encouraged, and reduced fluid intake and evidence of dehydration, if detected, will be treated by close clinical follow-up.
Gastrointestinal adverse reactions	The potential risks are based on product labeling for injectable GLP-1R agonists (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. In nonclinical studies with PF-07081532, gastrointestinal adverse effects were observed in rats and monkeys.	Participants are monitored during the clinical studies to prevent potential sequelae of any severe gastrointestinal reactions, eg, dehydration. Hydration will be encouraged and concomitant medication for nausea is permitted in the study. PF-07081532 will be titrated from a 20 mg QD dose to 80 mg QD over 28 days, then from 100 mg QD to 260 mg QD over 63 days in the study in an attempt to minimize gastrointestinal adverse reactions.
Diabetic retinopathy complications	The potential risk is based on the product labeling for the injectable GLP-1R agonist semaglutide and dulaglutide in patients with T2DM. There are no nonclinical or clinical data involving PF-07081532 to suggest an increased risk of diabetic retinopathy complications.	Potential participants with diabetes mellitus are excluded from this clinical study.
Suicidal ideation and behavior	The potential risk is based on the product labeling for the injectable GLP-1R agonists liraglutide and semaglutide for obesity based on long-term studies. Suicidal ideation has not been observed in the PF-07081532 clinical studies to date.	Suicidal ideation and behavior, along with symptoms of depression, will be monitored at specified intervals during the study using the C-SSRS and PHQ-9 questionnaires, with referral to a MHP for further evaluation if needed.
Changes in heart rate	Potential risk is based on the product labeling for the injectable GLP-1R agonists, liraglutide and semaglutide, for T2DM and obesity. Modest increases in HR have been noted in the early clinical studies with PF-07081532, with most values remaining within the normal range.	HR is monitored during the clinical study.

Declines in body weight	Decreased appetite and body weight loss have been reported for marketed GLP-1R agonists, and declines in body weight have been noted at higher doses of PF-07081532.	Weight is collected at multiple timepoints and will be monitored throughout the trial.
Acute gallbladder disease	Potential risk is based on the product labeling for the injectable GLP-1R agonists, semaglutide and liraglutide, for T2DM and obesity. Acute gallbladder disease has not been observed in the PF-07081532 clinical trial program to date.	Participants with symptomatic gallbladder disease are excluded from this clinical study. Participants are monitored for AEs and laboratory tests that may suggest development of acute gallbladder disease.
Study Intervention: Omeprazole		
Headache, abdominal pain, nausea, diarrhea, vomiting, and flatulence	Risk based on product labeling.	A single oral dose of 20 mg is administered in this study and poses minimal risk. Participants will be monitored in an inpatient clinical research unit.
Study Intervention: Midazolam		
Respiratory depression	Risk based on product labeling.	A single oral dose of 2 mg is administered in the study and poses minimal risk. Participants will be monitored in an inpatient clinical research unit.
Study Intervention: OC (LE/EE)		
Increased BP	Risk based on product labeling.	A single dose of 0.15 mg LE/0.03 mg EE is administered in this study and poses minimal risk. Participants will be monitored in an inpatient clinical research unit.
Other		
Risk of COVID-19 exposure during study	During the pandemic, study participants could be infected with the SARS-CoV-2 virus during study participation. This could lead to increased health risk for this participant and others in the study.	Participants undergo COVID-19 specific assessments prior to admission to study site and according to the SoA.

2.3.2. Benefit Assessment

While PF-07081532 is not expected to provide any significant long-term clinical benefit to the healthy obese participants in this relatively short-term study, potential benefits may include weight loss, receiving medical evaluations/ assessments associated with clinical study visits (eg, physical examinations, ECGs, labs), and contributing to the process of developing a potential new therapy for T2DM and obesity.

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

2.3.3. Overall Benefit/Risk Conclusion

The Sponsor considers that the available information from the nonclinical studies and the clinical studies completed to date with PF-07081532 comprises a benefit-risk profile that supports the continued clinical investigation of the compound as a potential option for the treatment of T2DM and obesity. Considering the measures to minimize risk to study participants, the potential risks identified in association with PF-07081532 are justified by the anticipated benefits that may be afforded to participants with obesity.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Cohort 1	
Primary:	**Primary:**
• To evaluate the effects of PF-07081532 on the pharmacokinetics of midazolam, omeprazole, and an oral contraceptive (OC; levonorgestrel [LE]/ethinyl estradiol [EE]) in obese adult female participants.	• Midazolam plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1, 4 and 7. • Omeprazole plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1, 4 and 7. • LE plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 2, 5 and 8. • EE plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in in Periods 2, 5 and 8.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-07081532 administered separately and in combination with midazolam, omeprazole, and an OC (LE/EE) in obese adult female participants.	• Assessment of TEAEs, clinical laboratory abnormalities, and body weight. • Assessment of mental health as determined by C-SSRS and PHQ-9.
• To evaluate the pharmacokinetics of SD midazolam following the discontinuation of PF-07081532 administration in obese adult female participants.	• Midazolam plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Period 9.
• To evaluate the effects of PF-07081532 on additional pharmacokinetic parameters of midazolam, omeprazole, and an OC (LE/EE) in obese adult female participants.	• Additional plasma pharmacokinetic parameters for midazolam and omeprazole (Periods 1, 4 and 7), and LE and EE (Periods 2, 5 and 8): C_{max} and T_{max}; and CL/F, Vz/F, $t_{½}$, as data permit.
• To evaluate the effects of PF-07081532 on the metabolite/parent ratios for midazolam and omeprazole in obese adult female participants.	• $MRAUC_{inf}$ (1-hydroxymidazolam AUC_{inf}/midazolam AUC_{inf}). • $MRAUC_{inf}$ (5-hydroxyomeprazole AUC_{inf}/omeprazole AUC_{inf}).

• To evaluate the MD pharmacokinetics of PF-07081532 in obese adult female participants.	• PF-07081532 plasma pharmacokinetic parameters at Days 34 and 103: AUC_{24}, C_{max}, T_{max}.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To evaluate the effects of PF-07081532 on the pharmacokinetics of 1-hydroxymidazolam in obese adult female participants.	• 1-hydroxymidazolam plasma pharmacokinetic parameters: AUC_{last}, C_{max}, T_{max}; and AUC_{inf} and $t_{½}$ as data permit in Periods 1, 4 and 7. • Metabolite/parent (1-hydroxymidazolam/midazolam) ratios for AUC_{inf} (as data permit), AUC_{last}, and C_{max} will also be calculated.
• To evaluate the effects of PF-07081532 on the pharmacokinetics of 5-hydroxyomeprazole in obese adult female participants.	• 5-hydroxyomeprazole plasma pharmacokinetic parameters: AUC_{last}, C_{max}, T_{max}; and AUC_{inf} and $t_{½}$ as data permit in Periods 1, 4 and 7. • Metabolite/parent (5-hydroxyomeprazole /omeprazole) ratios for AUC_{inf} (as data permit), AUC_{last}, and C_{max} will also be calculated.
• To evaluate the effects of PF-07081532 on biomarkers of CYP3A induction. [Optional].	• Morning predose 4β-hydroxycholesterol/cholesterol plasma ratio on Day 1 in Periods 1, 4, and 7. CCI [redacted]
Cohort 2	
Primary:	**Primary:**
• To evaluate the effects of semaglutide (subcutaneous semaglutide) on the SD PK of midazolam in obese adult female participants.	• Midazolam plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1 and 3.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of semaglutide administered separately and in combination with midazolam in obese adult female participants.	• Assessment of TEAEs, clinical laboratory abnormalities, and body weight. • Assessment of mental health as determined by C-SSRS and PHQ-9.
• To evaluate the pharmacokinetics of SD midazolam following the discontinuation of semaglutide administration in obese adult female participants.	• Midazolam plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Period 4.
• To evaluate the effects of semaglutide on additional pharmacokinetic parameters of midazolam in obese adult female participants.	• Additional plasma pharmacokinetic parameters for midazolam (in Periods 1 and 3): C_{max}, T_{max}, and CL/F, Vz/F, $t_{½}$ as data permit.
• To evaluate the effects of semaglutide on the metabolite/parent ratio for midazolam in obese adult female participants.	• $MRAUC_{inf}$ (1-hydroxymidazolam AUC_{inf}/midazolam AUC_{inf}).

Tertiary/Exploratory:	Tertiary/Exploratory:
• To evaluate the effects of semaglutide on the pharmacokinetics of 1-hydroxymidazolam in obese adult female participants.	• 1-hydroxymidazolam plasma pharmacokinetic parameters: AUC_{last}, C_{max}, T_{max}; and AUC_{inf} and $t_{½}$ as data permit in Periods 1 and 3. • Metabolite/parent (1-hydroxymidazolam/midazolam) ratios for AUC_{inf} (as data permit), AUC_{last}, and C_{max} will also be calculated.
• To evaluate the effects of semaglutide on biomarkers of CYP3A induction. [Optional]	• Morning predose 4β-hydroxycholesterol/cholesterol plasma ratio on Day 1 in Periods 1 and 3. CCI [redacted]

* Should it be deemed that too few AUC_{inf} estimates (eg, less than 12 for a single treatment) are obtained from the evaluable participants, AUC_{last} may be selected as the primary endpoint for CSR reporting. This will be considered for the midazolam, 1-hydroxymidazolam, omeprazole, 5-hydroxyomeprazole, LE, and EE objectives separately.

4. STUDY DESIGN

4.1. Overall Design

This study will be conducted with 2 cohorts. Cohort 1 will evaluate the effect of 2 steady-state dose levels of PF-07081532 on the SD pharmacokinetics of midazolam, omeprazole, and an OC (LE/EE). Cohort 2 will evaluate the effect of steady-state semaglutide on the SD pharmacokinetics of midazolam. Titration will be implemented in both cohorts in order to enhance gastrointestinal tolerability similarly to the approach implemented for marketed GLP-1R agonists. Participants will participate in either Cohort 1 or Cohort 2 (not both), and Cohort 1 and Cohort 2 are preferred to be conducted in parallel, if possible.

All participants will provide informed consent and undergo Screening evaluations to determine their eligibility. Screening will occur within 28 days of the first dose of study intervention on Day 1 of Period 1 for both Cohorts 1 and 2. Participants who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and Sponsor.

PF-07081532 will be provided as tablets for oral administration. PF-07081532 must be administered within approximately 10 minutes of completion of the morning meal. PF-07081532 will be administered first and midazolam and omeprazole or the OC will be administered within 5 minutes of PF-07081532 during the DDI assessment periods.

Semaglutide will be provided as pre-filled, single-dose pens for subcutaneous injection. Drug administration will follow the instructions provided in the approved Highlights of Prescribing Information as outlined in the USPI.[16,17] Semaglutide must be administered once weekly, preferably in the morning, without regard to timing of the breakfast meal during outpatient visits to the CRU for dose administration. During the DDI assessment inpatient

visit (Period 3), semaglutide and midazolam must be administered within approximately 10 minutes of completion of the morning meal. Semaglutide will be administered first, and midazolam will be administered within 5 minutes of semaglutide.

4.1.1. Cohort 1

Cohort 1 is an open-label, 9-period, fixed-sequence design to evaluate the effect of 2 steady-state dose levels of PF-07081532 on the SD pharmacokinetics of midazolam and omeprazole, administered simultaneously, and an OC (LE/EE) in otherwise healthy obese adult female participants with a BMI $\geq$30 kg/m^2.

Approximately 16 participants will be enrolled in Cohort 1.

The total duration of participation from the Screening Visit to the F/U telephone contact will be approximately 27 weeks; ie, 188 days, of which 112 days will be in-patient as follows:

Period 1 (SD midazolam and omeprazole): 1 day; Period 2 (SD OC): 5 days; Period 3 (PF-07081532 titrated to 80 mg QD): 28 days; Period 4 (80 mg PF-07081532 + SD midazolam and omeprazole): 1 day; Period 5 (80 mg PF-07081532 + SD OC): 5 days; Period 6 (PF-07081532 titrated to 260 mg QD): 63 days; Period 7 (260 mg PF-07081532 + SD midazolam and omeprazole): 1 day; Period 8 (260 mg PF-07081532 + SD OC): 6 days; Period 9 (SD midazolam only): 2 days.

The F/U out-patient visit will occur 7-10 days from the last dose of study intervention and a telephone F/U contact will occur 28-35 days from the last dose of study intervention.

4.1.2. Cohort 2

Cohort 2 is an open-label, 4-period, fixed-sequence design to evaluate the effect of steady-state semaglutide on the SD PK of midazolam in obese adult female participants with a BMI $\geq$30 kg/m^2.

Approximately 16 participants will be enrolled in Cohort 2.

The total duration of participation from the Screening Visit to the F/U telephone contact will be approximately 33 weeks; i.e., 228 days, of which 6 days will be in-patient as follows:

Period 1 (SD midazolam): 1 day; Period 2 (final day of semaglutide treatment (2.4 mg): 1 day; Period 3 (2.4 mg semaglutide once weekly + SD midazolam) 2 days; Period 4 (SD midazolam): 2 days. Participants will also be required to return to the clinic during out-patient visits, preferably in the morning, to receive their once weekly semaglutide injections (Period 2).

The out-patient F/U visit will occur 7-10 days from the last dose of study intervention and a telephone F/U contact will occur 28-35 days from the last dose of study intervention.

4.2. Scientific Rationale for Study Design

The purpose of this study is to characterize the effect of PF-07081532, administered at 2 steady-state dose levels, on the PK of single doses of midazolam (2 mg oral) and omeprazole (20 mg oral), administered simultaneously, and an OC (LE 0.15 mg/EE 0.03 mg oral) in otherwise healthy obese adult female participants in Cohort 1. Midazolam and omeprazole will be administered simultaneously to allow for evaluation of 2 DDIs within one study period. Simultaneous administration of these 2 probe substrates has been validated; ie, no DDI and shown to be safe.[18,19] The impact of steady-state subcutaneous semaglutide on the PK of single-dose midazolam (2 mg oral) will also be assessed in otherwise healthy obese adult female participants in Cohort 2. Otherwise healthy obese adult females will be enrolled in this study as they are one of the target populations for PF-07081532.

In Cohort 1, titration of PF-07081532 doses will be utilized to achieve 80 mg QD and 260 mg QD. The DDI effect will be initially assessed at the PF-07081532 80 mg QD dose as this is expected to be a potential therapeutic dose for treatment of T2DM. The DDI effect will also be assessed at the 260 mg QD dose as this is the maximum dose in the Phase 2 study for both T2DM and obesity. PF-07081532 will be administered for a duration of 7 days at each of the 80 mg QD and 260 mg QD dosing regimens prior to administration of the SD midazolam and omeprazole, or OC treatments (Table 8) to ensure that clinically relevant steady-state PF-07081532 exposures are achieved.

Titration of semaglutide doses will be utilized to achieve 2.4 mg in Cohort 2, which is the maximum approved dose for weight loss. The DDI effect will be assessed at the 2.4 mg dose following weekly titrations for 4 weeks each at the 0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg, and 2.4 mg doses as instructed in the USPI.[16,17] Semaglutide will be administered for one additional week (half-life approximately 1 week) at the 2.4 mg dose to ensure that clinically relevant steady-state exposures are achieved prior to administration of SD midazolam in Period 3 (Table 9).

Additionally, participants in both cohorts will be discharged from the clinical site for 2 weeks following the final PK sample collection of OC (LE/EE) in Period 8, Day 2 (Cohort 1) or midazolam in Period 3, Day 2 (Cohort 2), and discontinue all PF-07081532 or semaglutide dosing at that time. Following the 2-week out-patient duration, participants will return to the clinical site for a final midazolam assessment, without either PF-07081532 or semaglutide coadministration.

4.2.1. Cohort 1

4.2.1.1. Midazolam Administration

Preliminary 4-β-hydroxycholesterol/cholesterol (biomarker for CYP3A activity) results from Study C3991003 with PF-07081532 suggest a potential perturbation of CYP3A activity. Therefore, midazolam will be used as a "sensitive substrate" of CYP3A in this study to assess the impact of PF-07081532 administration on both midazolam and its 1-hydroxy metabolite, which is formed via CYP3A. To further investigate the mechanism of this interaction, plasma 4-β-hydroxycholesterol/cholesterol and CCI samples, used as endogenous

probes for CYP3A induction, will be collected in this study. If there are no observed changes in midazolam exposures during concomitant administration of either PF-07081532 or semaglutide, neither plasma 4-β-hydroxycholesterol/cholesterol nor [redacted] samples will be analyzed.

Following assessment of the DDI between PF-07081532 and midazolam, the administration of PF-07081532 will be discontinued for a 2-week period, after which an additional single dose of midazolam will be administered to assess the impact of discontinuation of PF-07081532 administration on midazolam pharmacokinetics. If induction of CYP3A activity is observed (as determined by midazolam PK during coadministration of PF-07081532), a 2-week period of time without PF-07081532 dosing is expected to be sufficient to allow CYP3A activity to return to baseline.[20]

Midazolam is rapidly absorbed after oral administration and is subject to substantial intestinal and hepatic first-pass metabolism. Food effect has not been tested using midazolam HCl syrup; but when a 15 mg oral tablet of midazolam was administered with food to adults, the absorption and disposition of midazolam was not affected. The extent of plasma protein binding of midazolam is moderately high and concentration independent. In adults and pediatric patients older than 1 year, midazolam is approximately 97% bound to plasma protein, principally albumin. In healthy volunteers, 1-hydroxymidazolam is bound to the extent of 89%.[13]

Midazolam is primarily metabolized in the liver and gut by human CYP3A4 to its pharmacologic active metabolite, 1-hydroxymidazolam, followed by glucuronidation of the 1-hydroxyl metabolite which is present in unconjugated and conjugated forms in human plasma. The 1-hydroxymidazolam glucuronide is then excreted in urine. Midazolam is also metabolized to 2 other minor metabolites: 4-hydroxy metabolite (about 3% of the dose) and 1,4-dihydroxy metabolite (about 1% of the dose) are excreted in small amounts in the urine as conjugates.[13]

Six single-dose pharmacokinetic studies involving healthy adults yielded pharmacokinetic parameters for midazolam in the following ranges: volume of distribution, 1 to 3.1 L/kg; elimination half-life, 1.8 to 6.4 hours (mean approximately 3 hours); and total clearance, 0.25 to 0.54 L/hr/kg. In a study comparing normal (n=20) and obese patients (n=20) the mean half-life was greater in the obese group (5.9 hours vs. 2.3 hours), which was attributed to an increase of approximately 50% in the volume of distribution corrected for total body weight.[13,21,22] Plasma samples for midazolam and 1-hydroxy-midazolam will be collected in this study for up to 24 hours after dosing, which is expected to be adequate even with the longer elimination half-life in obese subjects.

Single oral doses of midazolam ranging from 2 to 7.5 mg have been safely administered to healthy participants in previous internal Pfizer drug-drug interaction studies (A5351012, B3291023, B7451022, C1061016).

4.2.1.2. Omeprazole Administration

Adults with T2DM and obesity often require treatment for GERD, therefore, it is likely that PF-07081532 will be coadministered with omeprazole in clinical practice. Additionally, PF-07081532 was shown to be a moderate in vitro time-dependent inhibitor of CYP2C19 at a clinical dose of 260 mg. Therefore, omeprazole will be used as a "sensitive substrate" of CYP2C19 in this study to assess the impact of PF-07081532 administration on the PK of both omeprazole and its 5-hydroxy metabolite, which is formed via CYP2C19.

Omeprazole absorption is rapid, with peak plasma levels occurring within 0.5 to 3.5 hours. Peak plasma concentrations of omeprazole and AUC are approximately dose proportional up to 40 mg. Absolute bioavailability is about 30-40% at doses of 20-40 mg, due in large part to presystemic metabolism. In healthy subjects the plasma half-life is 0.5 to 1 hour, and the total body clearance is 500-600 mL/min. Protein binding is approximately 95%.[14]

Omeprazole is extensively metabolized by CYP450, with CYP2C19 being the primary pathway resulting in formation of 5-hydroxyomeprazole. CYP3A4 is a minor metabolic pathway resulting in the formation of the omeprazole sulphone. Approximately 2-3% of Caucasian, 2% of African Americans, and 11–23% of Asian populations are CYP2C19 poor metabolizers (PM), therefore, CYP3A is the predominant metabolic route in these individuals.[23] In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately 4-fold was noted in Asian subjects compared with Caucasians.[14]

Following single-dose oral administration of a buffered solution of omeprazole, little if any unchanged drug was excreted in urine. Most of the dose (about 77%) was eliminated in urine as at least 6 metabolites. Two were identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma; the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.[14]

Because the elimination half-lives of omeprazole and its 5-hydroxy metabolite range from 0.5 to 1 hour following single doses,[24] plasma will be collected for 24 hours after dosing for determination of PK parameters.

Omeprazole is generally well-tolerated by healthy individuals following single, oral, doses of 10 mg[25] and 20 mg.[26] In addition, the safety of omeprazole for the treatment of gastric ulcer disease has been established at doses as high as 40 mg once daily for 4 to 8 weeks. Adverse reactions have usually been mild and transient. For more complete information, please refer to the USPI for omeprazole.[14]

4.2.1.3. Oral Contraceptive Administration

The estrogens and progestins contained in oral contraceptives are substrates for CYP3A4/5 and other inducible metabolic enzymes. Because the anticipated target population for PF-07081532 will include females of childbearing potential who may use an OC, a third

objective of this study is to estimate the effect of administration of 80 mg QD and 260 mg QD PF-07081532 on the SD PK of an OC containing 0.15 mg LE and 0.03 mg EE.

The mean (SD) half-lives of LE and EE are 29.8 (8.3) and 15.4 (3.2) hours,[15] respectively; therefore, plasma will be collected for up to 120 hours after dosing for determination of PK parameters. The effect of food on the rate and the extent of LE and EE absorption following oral administration of LE and EE tablets has not been evaluated.[15]

Oral contraceptive use has been shown to cause an increase in BP that is reversible when the oral contraceptive is discontinued. The use of an OC agent containing 30 µg EE and 150 ug LE was associated with a small increase in both systolic and diastolic BP.[27] Although the risk of increased BP is expected to be small following SD administration of the OC in this study, BP effects resulting from coadministration of PF-07081532 with the OC will be monitored as described below. For more complete information, please refer to the USPI for the OC.[15]

4.2.1.4. PF-07081532 Administration

A dense PK profile will be collected for PF-07081532 after reaching the target doses of PF-07081532 for each DDI assessment; ie, 80 mg in Period 3, Day 28 and 260 mg in Period 6, Day 63, to better understand the PK in obese female participants.

PF-07081532 will be administered via 7-day (1-week) titration increments up to the 80 mg QD regimen in Period 3 prior to the administration of midazolam and omeprazole in Period 4, and the OC in Period 5. Likewise, PF-07081532 will be administered via 1-week titration increments up to the 260 mg QD regimen in Period 6 prior to administration of midazolam and omeprazole in Period 7, and the OC in Period 8 (Section 6.1.1, Table 8). The PF-07081532 dosing regimen is designed to achieve and maintain PK steady-state for approximately 7 days prior to assessment of the interaction with the 3 substrates. This will enable any interaction that is present to be assessed under conditions that are expected to increase the potential for maximal CYP3A induction and/or CYP2C19 inhibition at the PF-07081532 doses being studied should this occur. Based on emerging data from other clinical studies that may become available during the conduct of this study, the titration rate, incremental increases in dose, and/or the PF-07081532 doses at which the midazolam and omeprazole, or OC PK interactions are evaluated may be adjusted.

Dosing of PF-07081532 (with or without midazolam, omeprazole, or the OC) is planned to occur in the fed state with a standard breakfast, as this is the anticipated mode of administration in clinical use.

4.2.2. Cohort 2

4.2.2.1. Semaglutide and Midazolam Administration

Obesity has long been associated with a state of chronic, low-level inflammation,[28,29,30] with adipose tissue being one of the main sources of inflammatory mediators, including IL-6.[31] Adipose tissue has been described as an active endocrine organ that secretes signaling molecules involved in the regulation of insulin sensitivity, food intake and inflammation. To

that end, decreases in IL-6 and other inflammatory mediators have been observed following weight loss in obese individuals, whether it be a result of caloric deficit or bariatric surgery.[32,33,34]

Inflammatory cytokines, such as IL-6, IL-1β, and TNFα have been shown to inhibit CYP3A activity. Indeed, IL-6 is the target for drugs such as sarilumab and tocilizumab used to treat RA, a disease known to have a high inflammatory burden. The exposure of simvastatin, a CYP3A substrate, was decreased by 45% and 57%, respectively, during administration of sarilumab or tocilizumab. This observation was likely due to the attenuation of the inhibitory impact of IL-6 on CYP3A activity, thus, resulting in a return to baseline or a "normalization" of enzyme activity.[35,36]

Prior publications have demonstrated lower clearance of CYP3A substrates, including midazolam, in participants with obesity.[21,37] Furthermore, a number of clinical studies have demonstrated increased clearance of CYP3A substrates following weight loss.[38,39,40] For example, one year after bariatric surgery, systemic clearance of midazolam was 1.7 times higher [0.65 (7%) vs 0.39 (11%) L/min, mean±RSE ($p<0.01$), respectively] in 18 morbidly obese individuals who lost a mean of 44.5±10.2 kg body weight.[41] The authors suggested that the observed increase in midazolam clearance was potentially due to increased CYP3A activity following weight loss.

To that end, in vitro CYP enzyme activity down-regulation for a novel GLP-1Ra/glucagon co-agonist did not translate to clinical DDIs.[42] Based on in vitro data and PBPK modeling, a 2.4-fold increase in midazolam AUC and a 1.6-fold increase in midazolam C_{max} was expected, while in the clinic no change was observed in AUC and C_{max} was decreased by 21%. Subjects also lost a considerable amount of body weight (~10%) over the course of the study. These data highlight the uncertainty for translation of in vitro data to clinical DDI for this mechanism, and provide additional support that the increases in CYP3A activity observed clinically with the GLP-1Ra/glucagon co-agonist and the apparent increased CYP3A activity following weight loss may be mechanism-related; ie, due to weight loss itself, alterations in inflammatory status, GLP-1R pharmacology, etc.

The objective of Cohort 2 is to test the hypothesis that decreases in body weight lessen the inflammatory burden of obesity, and therefore, attenuate some of the inhibitory impact of obesity on CYP3A activity. This results in "normalization" of CYP3A activity, which manifests as enzyme induction as evidenced by the aforementioned decreases in midazolam exposure.

Once weekly semaglutide administration up to the maximum approved dose of 2.4 mg is expected to result in considerable weight loss. As semaglutide is a peptide intended for subcutaneous injection, CYP-mediated DDIs are not expected; in vitro studies have shown very low potential for semaglutide to inhibit or induce CYP enzymes.[16,17] Therefore, any decrease observed for midazolam sytstemic exposures in Cohort 2 would likely be mechanism based; ie, due to weight loss, alterations in inflammatory status, GLP-1Ra pharmacology, etc. Based on historical weight loss data for PF-07081532 in the

multiple-ascending dose study (C3991002), PF-07081532 is expected to result in weight loss in the current study, thus, allowing for a comparison of the impact of weight loss on midazolam PK between Cohorts 1 and 2.

Following assessment of the DDI between semaglutide and midazolam, the administration of semaglutide will be discontinued for a 2-week period, after which an additional single dose of midazolam will be administered to assess any impact of discontinuation of semaglutide administration on midazolam pharmacokinetics. If induction of CYP3A activity is observed (as determined by midazolam PK during coadministration of semaglutide), the discontinuation of semaglutide is not expected to have an impact on subsequent midazolam PK, and would most likely be attributed to weight loss and the attenuation of circulating inflammatory markers that impact CYP3A activity.

Midazolam will be used as a "sensitive substrate" of CYP3A in Cohort 2 to assess the impact of multiple-dose semaglutide administration on the PK of both midazolam and its 1-hydroxy metabolite. To further investigate the mechanism of this interaction, plasma 4-β-hydroxycholesterol/cholesterol and CCI samples, used as endogenous probes for CYP3A induction, will be collected and analyzed if changes are observed in midazolam exposures.

Semaglutide will be administered as instructed in the respective approved USPIs; ie, once weekly subcutaneous injections at the 0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg doses, each for 4 weeks.[16,17] One additional 2.4 mg dose of semaglutide will be administered to ensure attainment of PK steady-state (terminal half-life is approximately 1 week) prior to administration of the second midazolam dose in Period 3 (Section 6.1.1). This will enable any interaction that is present to be assessed under conditions that are expected to increase the potential for maximal CYP3A induction at the 2.4 mg semaglutide dose, should this occur.

4.2.3. Safety Assessments (Cohorts 1 and 2)

Clinical laboratory tests, assessments of vital signs, body weight, 12-lead ECGs, physical examinations, and AE monitoring will provide data to evaluate the safety and tolerability of PF-07081532. Vital signs and 12-lead ECGs will be monitored at the Screening and study discharge visits, and as necessary at the discretion of the investigator. Body weight will be measured at timepoints in the SoA, as GLP-1R agonists have been shown to decrease food intake and body weight. COVID-19 specific assessments have been incorporated to minimize the risks of COVID-19 related complications to participants and the study site personnel.

As part of the clinical safety laboratory tests, fasting blood glucose and HbA1c will be used to assess changes in glycemic parameters in this study population. In addition, calcitonin, amylase, and lipase will be assessed, as these laboratory parameters have been shown to increase with marketed GLP-1R agonists.[16,17,43,44,45,46] TSH, free T4, lipids, and TBA will also be assessed, based on nonadverse findings in the nonclinical studies with PF-07081532. Assessment of SIB by C-SSRS [47] and PHQ-9 [48] will also be performed based on the potential

risk related to the product labeling for the injectable GLP-1R agonists liraglutide and semaglutide in long-term studies of patients with BMI ≥30 kg/m^2.[16,17,44,45]

While GLP-1R agonists typically are not associated with hypoglycemia unless coadministered with anti-diabetic agents that can cause hypoglycemia (such as insulin or sulfonylureas), blood glucose concentrations will be monitored throughout the study via laboratory assessments, and monitoring of symptomatic HAEs will be performed. In addition, all participants will be instructed regarding the symptoms associated with, and management of, hypoglycemia, which will permit the monitoring of symptomatic HAEs.

WOCBP may be enrolled given the availability of embryo fetal developmental toxicity studies with PF-07081532. However, as marketed GLP-1R agonists are listed as contraindicated in pregnancy, the use of a highly effective method of nonhormonal contraception is required and measures will be taken to limit the risk of pregnancy in the WOCBP population enrolled (see SoA and Appendix 4).

4.2.4. Diversity of Study Population

Not applicable.

4.2.5. Choice of Contraception/Barrier Requirements

Human reproductive safety data are limited for PF-07081532, but there is no suspicion of human teratogenicity based on the completed nonclinical embryo-fetal developmental studies. However, the use of a highly effective method of nonhormonal contraception is required for both cohorts in this study (see Appendix 4).

4.2.6. Collection of Retained Research Samples

CCI [redacted]

4.3. Justification for Dose

PF-07081532:

The DDI will be assessed at 2 pharmacokinetic steady-state PF-07081532 dose levels, 80 mg QD and 260 mg QD. These doses represent a potential therapeutic dose for T2DM, and the highest dose being assessed in the Phase 2 study (C3991004) for T2DM and obesity, respectively. Exposure margins for PF-07081532 260 mg QD are given in Section 2.2.3.

The titration to PF-07081532 80 mg QD is planned to occur over an approximately 28-day period in increments of 20 mg QD every 7 days, and from 80 mg QD to 260 mg QD over 9 weeks, in increments of 20 mg every 7 days (Section 6.1.1, Table 8 and Table 9). Titration increments as short as 1-2 days have been administered previously in Study C3991002 and were sufficiently tolerated. Based on emerging data from other clinical studies that may become available during the conduct of this study, the titration rate, incremental increases in

dose, and/or the PF-07081532 doses at which midazolam, omeprazole or the OC PK interactions are evaluated may be adjusted.

Midazolam:

Midazolam has been administered at doses of 2-15 mg to assess CYP3A4/5 DDIs and was generally well tolerated. The single, oral 2 mg dose of midazolam in this study should allow for adequate quantification of midazolam and its 1-hydroxymetabolite in plasma for 24 hours and is expected to be well-tolerated. Additionally, as midazolam and omeprazole are to be administered simultaneously (Cohort 1 only), midazolam doses greater than 2 mg have not been validated for coadministration with omeprazole.[18,19]

Omeprazole:

The safety data described in the USPI[14] for omeprazole monotherapy reflects exposure to PRILOSEC Delayed-Release Capsules in 3096 patients from worldwide clinical trials (465 patients from US studies and 2,631 patients from international studies). Indications clinically studied in US trials included duodenal ulcer, resistant ulcer, and Zollinger-Ellison syndrome. The most common adverse reactions reported (ie, with an incidence rate ≥2%) from PRILOSEC-treated patients enrolled in these studies included headache (6.9%), abdominal pain (5.2%), nausea (4.0%), diarrhea (3.7%), vomiting (3.2%), and flatulence (2.7%).

The dose range and recommended starting doses for omeprazole in clinical practice is 20 to 60 mg once daily for up to 8 weeks in adults depending on the condition being treated.[14] In patients with Zollinger-Ellison syndrome, doses of up to 240 mg/day may be required.

Based on in vitro data, PF-07081532 is a moderate time-dependent inhibitor of CYP2C19 and could potentially increase omeprazole exposure 2.2- to 3.4-fold at a 260 mg dose. Therefore, a 20 mg single dose of omeprazole was selected for this study. Given the established safety and tolerability for omeprazole with multiple-dose administration up to 240 mg/day, a 20 mg single dose is expected to be well tolerated even if systemic exposures increase up to 5-fold as a result of coadministration with PF-07081532. Additionally, as midazolam and omeprazole are to be administered simultaneously (Cohort 1 only), omeprazole doses greater than 20 mg have not been validated for coadministration with midazolam.[18,19]

LE/EE:

The OC selected for this study contains a fixed dose of 0.15 mg LE and 0.03 mg EE. The amounts of estrogen and progestin in this preparation are comparable to those found in many of the commonly prescribed OCs and have been used in a number of published OC DDI studies.[49,50]

Semaglutide:

Subcutaneous semaglutide will be titrated up to 2.4 mg weekly as this is the maximum approved dose for weight loss and was shown to be safe and well-tolerated in clinical trials.[16,17]

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the F/U contact visit, approximately 28 to 35 days post last dose of study intervention.

The end of the study is defined as the date of the last visit (F/U contact) of the last participant in the study.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Otherwise healthy female participants must be at least 18 years of age at the time of signing the ICD (healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, physical examination, including blood pressure and pulse rate measurement, standard 12-lead ECG and clinical laboratory tests).

    - Women can be of child-bearing potential, but cannot be pregnant, breastfeeding, or planning to become pregnant while participating in the study and may not be taking either oral contraceptives or non-oral hormonal contraceptives.

    - Refer to Appendix 4 for reproductive criteria for female participants (Section 10.4.2).

Type of Participant and Disease Characteristics:

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

Weight:

3. BMI: ≥30.0 kg/m^2 and not more than 45.4 kg/m^2 at Screening

4. Stable body weight, defined as <5 kg change (per participant report) for 90 days before Screening.

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

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

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

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

4. Known intolerance or hypersensitivity to GLP-1R agonists.

5. Known hypersensitivity to midazolam, omeprazole, LE, EE, or semaglutide.

6. Diagnosis of type 1 or type 2 diabetes mellitus or secondary forms of diabetes at screening. **Note:** women with prior diagnoses of gestational diabetes *during pregnancy only* are eligible if they meet the other eligibility criteria.

7. History of myocardial infarction, unstable angina, arterial revascularization, stroke, New York Association Functional Class II-IV heart failure, or transient ischemic attack within 6 months of Screening.

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

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

10. Acute pancreatitis or history of chronic pancreatitis. Symptomatic gallbladder disease.

11. Medical history or characteristics suggestive of genetic or syndromic obesity or obesity induced by other endocrinological disorders (eg, Cushing Syndrome).

12. History of major depressive disorder or history of other severe psychiatric disorders (eg, schizophrenia or bipolar disorder) within the last 2 years from screening.

13. Known medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic active hepatitis B or C, primary biliary cirrhosis, alcoholic liver disease, primary sclerosing cholangitis, autoimmune hepatitis, overlap syndrome, or prior known drug-induced liver injury.

14. History of HIV infection.

15. Any lifetime history of a suicide attempt.

Prior/Concomitant Therapy:

16. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.9 Concomitant Therapy for additional details).

17. Use of any the medications that are moderate or strong CYP3A4/5 and/or CYP2C19 inhibitors within 28 days or 5 half-lives (whichever is longer) or moderate or strong CYP3A and/or CYP2C19 inducers within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention (Refer to Section 6.9 for additional details).

18. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.9 Concomitant Therapy.

Prior/Concurrent Clinical Study Experience:

19. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

20. Previous administration with a GLP-1R agonist within 90 days preceding the first dose of study intervention used in this study.

21. Known prior participation in a trial involving PF-07081532 unless placebo treatment was received.

Diagnostic Assessments (at Screening unless indicated):

22. A PHQ-9 score ≥15 obtained at Screening or Day -1 in Study.

23. Response of "yes" to question 4 or 5, or on any suicidal behavioral question on the C-SSRS at Screening or Day -1 in Study.

24. A positive urine drug test.

25. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. BP should be measured in triplicate and the average of the 3 BP values should be used to determine the participant's eligibility. Note: At Screening, the participant's arm circumference should be measured (eg, 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.

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

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

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

    - HbA1c ≥6.5%.
    - AST or ALT level ≥1.5x ULN.
    - Total bilirubin level ≥1.5x ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.
    - TSH >1.5x ULN or <LLN.

- Serum calcitonin > ULN.
- Amylase or lipase > ULN.
- Fasting blood glucose ≥126 mg/dL.
- Fasting C-peptide <0.8 ng/mL.
- eGFR <75 mL/min/1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
- Positive testing for HIV, HBsAg, or HCVAb. Study participants positive for HCVAb are to be excluded unless known to have been treated with a known curative therapy and negative for HCV RNA. Hepatitis B vaccination is allowed.
- A positive SARS-CoV-2 test.

Other Exclusions: at Screening unless indicated

28. Participation in a formal weight reduction program (eg, Weight Watchers) within 90 days prior to Screening.
29. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).
30. Current use of tobacco or nicotine containing products in excess of the equivalent of 5 cigarettes per day.
31. Known or suspected illicit drug use.
32. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing randomization (Day-1).
33. History of sensitivity to heparin or heparin induced thrombocytopenia if Hep lock is used for IV blood draw.
34. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.
35. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) for at least 8 hours prior to any morning predose PK evaluations (specified times in Periods 1-9 in Cohort 1 and Periods 1-4 in Cohort 2). On days without PK evaluations, participants must abstain from all food and drink (except water) for at least 4 hours prior to any safety laboratory evaluations (at least 12 hours if lipids are to be evaluated).

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

- **Cohort 1** - Participants should begin consumption of a standard breakfast (morning) approximately 30 minutes prior to dosing. The breakfast meal will be consumed over approximately a 20-minute period, with the study intervention (PF-07081532) administered within approximately 10 minutes of completion of the meal. Participants will be encouraged to consume the entire meal.

  PF-07081532 will be administered first and the single dose of midazolam and omeprazole or the OC will be administered within 5 minutes of PF-07081532 for the periods in which midazolam and omeprazole or the OC are coadministered with PF-07081532.

  Midazolam and omeprazole, or the OC, when administered alone, will be given within approximately 10 minutes of completion of the morning meal.

  Cohort 2 – Period 1: On the in-patient DDI assessment day, participants should begin consumption of a standard breakfast (morning) approximately 30 minutes prior to dosing. The breakfast meal will be consumed over an approximate 20-minute period, with the study intervention (semaglutide) administered within approximately 10 minutes of completion of the meal, followed within 5 minutes by the single dose of midazolam. Participants will be encouraged to consume the entire meal.

  Period 2: On out-patient days, participants may consume meals at any time.

  Period 3: On the in-patient DDI assessment day, participants should begin consumption of a standard breakfast (morning) approximately 30 minutes prior to dosing. The breakfast meal will be consumed over an approximate 20-minute period, with the study intervention (semaglutide) administered within approximately 10 minutes of completion of the meal, followed within 5 minutes by the single dose of midazolam. Participants will be encouraged to consume the entire meal.

- Noncaffeinated drinks (except red wine, grapefruit or grapefruit-related citrus fruit juices [eg, Seville oranges, pomelos]) may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after dosing with study intervention (PF-07081532 or semaglutide). This applies to midazolam, omeprazole and the OC also.

- Dinner will be provided approximately 10 hours after dosing with study intervention. This applies to midazolam, omeprazole and the OC also.

- An evening snack may be permitted.

- Cohort 1: Participants will refrain from consuming red wine, grapefruit, or grapefruit related citrus fruits and juices (eg, Seville oranges, pomelos) from 7 days prior to Period 1 Day 1 until collection of the final PK blood sample in Period 9, Day 2. Participants are also expected to refrain from consuming these products during the 2-week out-patient portion of the study following the OC DDI assessment in Period 8; ie, between Period 8, Day 6 and Period 9, Day 1.

- Cohort 2: Participants will refrain from consuming red wine, grapefruit, or grapefruit related citrus fruits and juices (eg, Seville oranges, pomelos) from 7 days prior to admission to the clinical site on Day 1 of Periods 1 and 3 and during all in-patient stays. Participants are also expected to refrain from consuming these products during the 2-week out-patient portion of the study following the midazolam DDI assessment in Period 3; ie, between Period 3, Day 2 and Period 4, Day 1.

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.2. Caffeine, Alcohol, and Tobacco

- Tobacco or nicotine use may be allowed according to CRU practices. Tobacco or nicotine use will not be permitted during frequent sampling procedures and will not be permitted within 2 hours prior to any vital sign or ECG assessments. Tobacco or nicotine use will also not be permitted 2 hours before and 2 hours following any dose of study intervention.

- 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 vital signs and ECGs.

- Participants will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample in Cohort 1, Period 9, Day 2. Participants will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final midazolam PK sample in Cohort 2; Period 2 Day 1, Period 3 Day 2, and Period 4 Day 2. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down for 4 hours after dosing in the morning on days of post-dose PK sample collections (except if required for BP, pulse rate, and ECG measurements).

5.3.4. Contraception

WOCBP Only - The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of nonhormonal contraception for the individual participant and his or her partner(s) from the permitted list of nonhormonal contraception methods (see Appendix 4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use highly effective nonhormonal 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 nonhormonal 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 nonhormonal contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently dosed in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

A participant who qualified for this protocol but did not enroll within the 28-day screening window may be re-screened. In this situation, all screening procedures must be repeated, and the participant assigned a new 8-digit SSID number. This criterion would also apply to participants who screened for this study more than 28 days prior to dosing.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to PF-07081532, midazolam, omeprazole, OC and semaglutide.

6.1. Study Intervention(s) Administered

20 mg, 60 mg, and 100 mg PF-07081532 oral tablets will be supplied by Pfizer to the CRU in bulk along with individual dosing containers, as necessary, for unit dosing.

Commercially available subcutaneous semaglutide (Wegovy) will be supplied by Pfizer to the CRU.

Commercially available midazolam oral syrup (2 mg/mL) will be supplied by the CRU.

Commercially available oral omeprazole 20 mg tablets will be supplied by the CRU.

Commercially available oral OC tablets (LE 0.15 mg/EE 0.03 mg) will be supplied by the CRU.

6.1.1. Administration

Cohort 1 - Participants will receive PF-07081532, midazolam and omeprazole, or the OC as applicable per the SoA at approximately 0800 hours (±2 hours). Details on meals and dietary requirements and activity restrictions on dosing days are given in Section 5.3.

Following an overnight fast of at least 10 hours, participants will receive study intervention with the breakfast meal at approximately 0800 hours (±2 hours). Investigator site personnel will administer PF-07081532, midazolam and omeprazole, or the OC during each period (as applicable per SoA) with ambient temperature water to a total volume of approximately 240 mL. Participants will swallow the study intervention whole and will not manipulate or chew the study intervention prior to swallowing. The study intervention will be administered according to the IP manual.

PF-07081532 must be administered within approximately 10 minutes of completion of the morning meal. PF-07081532 will be administered first and midazolam and omeprazole or the OC will be administered within 5 minutes of PF-07081532 during the DDI assessment periods.

When midazolam and omeprazole or the OC are administered alone, they must be administered within approximately 10 minutes of the completion of the morning meal.

Administration of study intervention will occur according to the following Dosing Periods and Dosing Days, also listed in the SoA and Table 8.

Modification of dosing of PF-07081532 maybe permitted upon Sponsor approval only. See Section 6.6.

Table 8. Cohort 1 Dosing

Study Period	Days in Study	Drug and Dosage
Period 1, Day 1	1	SD Midazolam (2 mg) + SD Omeprazole (20 mg)
Period 2, Days 1-5	2-6	SD OC (LE 0.15 mg/ EE 0.03 mg)
Period 3, Days 1-7	7-13	PF-07081532 20 mg QD
Period 3, Days 8-14	14-20	PF-07081532 40 mg QD
Period 3, Days 15-21	21-27	PF-07081532 60 mg QD
Period 3, Days 22-28	28-34	PF-07081532 80 mg QD
Period 4, Day 1	35	PF-07081532 80 mg QD + SD Midazolam (2 mg) + SD Omeprazole (20 mg)
Period 5, Days 1-5	36-40	PF-07081532 80 mg QD + SD OC (LE 0.15 mg/EE 0.03 mg)
Period 6, Days 1-7	41-47	PF-07081532 100 mg QD
Period 6, Days 8-14	48-54	PF-07081532 120 mg QD
Period 6, Days 15-21	55-61	PF-07081532 140 mg QD
Period 6, Days 22-28	62-68	PF-07081532 160 mg QD
Period 6, Days 29-35	69-75	PF-07081532 180 mg QD
Period 6, Days 36-42	76-82	PF-07081532 200 mg QD
Period 6, Days 43-49	83-89	PF-07081532 220 mg QD
Period 6, Days 50-56	90-96	PF-07081532 240 mg QD
Period 6, Week 57-63	97-103	PF-07081532 260 mg QD
Period 7, Day 1	104	PF-07081532 260 mg QD + SD Midazolam (2 mg) + SD Omeprazole (20 mg)
Period 8, Days 1-6	105-110*	PF-07081532 260 mg QD + SD OC (LE 0.15 mg/EE 0.03 mg)
Out-patient	111-124	No dosing
Period 9, Days 1-2	125-126	SD Midazolam (2 mg) only
* There is no PF-07081532 administration on Day 110 or thereafter.		

Cohort 2 – Participants will receive semaglutide or midazolam as applicable per the SoA at approximately 0800 hours (±2 hours). Details on meals and dietary requirements and activity restrictions on dosing days are given in Section 5.3.

Following an overnight fast of at least 10 hours, participants will receive study intervention at approximately 0800 hours (±2 hours). Investigator site personnel will administer (as applicable per SoA) semaglutide as a subcutaneous injection during each period. Midazolam will be administered with ambient temperature water to a total volume of approximately 240 mL. The study intervention will be administered according to the IP manual.

Semaglutide must be administered once weekly, preferably in the morning, without regard to timing of the breakfast meal during outpatient visits to the CRU for dose administration. During the DDI assessment inpatient visit (Period 3), semaglutide and midazolam must be administered within approximately 10 minutes of completion of the morning meal. Semaglutide will be administered first, and midazolam will be administered within 5 minutes of semaglutide.

When midazolam is administered alone, it must be administered within approximately 10 minutes of the completion of the morning meal.

Administration of study intervention will occur according to the following Dosing Periods and Dosing Days, also listed in the SoA and Table 9.

Modification of semaglutide dosing may be permitted upon Sponsor approval only. See Section 6.6.

Table 9. Cohort 2 Dosing

Study Period	Days in Study	Drug and Dosage
Period 1, Day 1	1	SD Midazolam (2 mg)
Period 2, Weeks 1-4	2-29	Semaglutide 0.25 mg once weekly
Period 2, Weeks 5-8	30-57	Semaglutide 0.5 mg once weekly
Period 2, Weeks 9-12	58-85	Semaglutide 1.0 mg once weekly
Period 2, Weeks 13-16	86-113	Semaglutide 1.7 mg once weekly
Period 2, Weeks 17-21	114-148	Semaglutide 2.4 mg once weekly
Period 3, Days 1-2	149-150*	Semaglutide 2.4 mg once weekly + SD Midazolam (2 mg)
Out-patient	151-164	No dosing
Period 4, Days 1-2	165-166	SD Midazolam (2 mg) only
* There is no semaglutide administration on Day 150 or thereafter.		

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

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

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

7. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, the sponsor must be notified within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

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

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

The commercially available products midazolam, omeprazole, and the OC provided by the CRU, and semaglutide (Ozempic or Wegovy) provided by the Pfizer, will be prepared as per the label and in accordance with the protocol by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets (omeprazole, OC and PF-07081532), syrup (midazolam), or single-dose prefilled pens (semaglutide) will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Assignment to Study Intervention

This is a non-randomized, open-label study. The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant numbers to the participants as they are screened for the study. The first four digits of the SSID will reflect the sponsor-assigned site number and the remaining four digits will reflect each participant's unique number assigned in chronological order as informed consent is obtained. In addition, on Day 1 of Period 1, each participant who is dosed with the investigational product will be assigned a separate, distinct number (as provided to the site by the Sponsor at the start of the study) to enable execution of Sponsors' standard processes for analysis of all PK-related samples.

In Cohort 1 (Periods 3 to 8) participants will receive the PF-07081532 doses as described in Table 10. In Cohort 2 (Periods 2 and 3) participants will receive the semaglutide doses as described in Table 11.

Table 10. PF-07081532 Dosing Regimens in Cohort 1

Period & PF-07081532 Dose (dosed once daily)	Number of PF-07081532 Tablets			Total Number of Tablets
	20 mg	60 mg	100 mg	
Period 3: 20 mg	1	-	-	1
Period 3: 40 mg	2	-	-	2
Period 3: 60 mg	-	1	-	1
Period 3: 80 mg	1	1	-	2
Period 4: 80 mg	1	1	-	2
Period 5: 80 mg	1	1	-	2
Period 6: 100 mg	-	-	1	1
Period 6: 120 mg	1	-	1	2
Period 6: 140 mg	2	-	1	3
Period 6: 160 mg	-	1	1	2
Period 6: 180 mg	1	1	1	3
Period 6: 200 mg	-	-	2	2
Period 6: 220 mg	1	-	2	3
Period 6: 240 mg	2	-	2	4
Period 6: 260 mg	-	1	2	3
Period 7: 260 mg	-	1	2	3
Period 8: 260 mg	-	1	2	3

Table 11. Semaglutide Dosing Regimens in Cohort 2

Period	Weekly Dose	Dose per Injection (pre-filled, disposable, single-dose pens)	Total Strength per Total Volume
Period 2: Weeks 1-4	0.25 mg	0.25 mg	0.25 mg / 0.5 mL
Period 2: Weeks 5-8	0.5 mg	0.5 mg	0.5 mg / 0.5 mL
Period 2: Weeks 9-12	1.0 mg	1.0 mg	1.0 mg / 0.5 mL
Period 2: Weeks 13-16	1.7 mg	1.7 mg	1.7 mg / 0.75 mL
Period 2: Weeks 17-21	2.4 mg	2.4 mg	2.4 mg / 0.75 mL
Period 3: Day 1	2.4 mg	2.4 mg	2.4 mg / 0.75 mL

Study intervention will be dispensed at the study visits as summarized in the SoA. Returned study intervention must not be redispensed to the participants.

6.4. Blinding

Not applicable as this is a non-randomized, open-label study.

6.5. Study Intervention Compliance

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

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

Study site personnel will examine each participant's mouth to ensure that the study intervention (except semaglutide) was ingested; this is vitally important to ensure dosing compliance in light of the potential gastrointestinal AEs. Additionally, if vomiting occurs following oral dosing and up to 4 hours post-dose (twice the median T_{max} of PF-07081532), site personnel will examine the emesis for evidence of drug product. Additionally, for Cohort 2, each weekly injection of semaglutide will be documented by study site staff.

6.6. Dose Modification

If participants are not able to tolerate titration to higher doses of PF-07081532 (eg, ≥220 mg QD) or semaglutide the dose may be temporarily down-titrated, titration to the next dose level may be delayed temporarily, or titration to a maximum tolerated dose may be permitted, with Sponsor approval only.

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

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

6.8. Treatment of Overdose

For this study, any dose of PF-07081532 greater than 1.6 g within a 24-hour time period will be considered an overdose. 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.

For this study, overdose for midazolam,[13] omeprazole,[14] the OC[15] or semaglutide[16,17] will be as per the USPI label.

There is no specific treatment for an overdose for PF-07081532. Treatment of overdose should consist of general supportive measures.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives (approximately 5 days) after the overdose of study intervention, and as medically appropriate 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 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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

6.9. Concomitant Therapy

Study participants will abstain from all concomitant treatments, except for the treatment of AEs, as described in the Exclusion Criteria sections of this protocol.

Use of prescription or nonprescription drugs and dietary and herbal supplements (eg, St. John's wort) are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Systemic therapy with any medications that are moderate or strong CYP3A4/5 and/or CYP2C19 inhibitors or moderate or strong CYP3A4/5 and/or CYP2C19 inducers within 14 days or 5 half-lives (whichever is longer) prior to the first dose of midazolam and omeprazole are prohibited.

Use of a GLP-1R agonist is prohibited within 90 days prior to the first dose of study intervention.

Hormonal contraceptives (including oral and non-oral) are not allowed to be used in participants who are WOCBP (see Appendix 4).

Females using hormonal contraceptives or taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study. Depo-Provera® must be discontinued at least 6 months prior to the first dose of study treatment.

Systemic therapy with inhibitors of OATP transporters within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention are prohibited.

Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

Anti-emetics (eg, prochlorperazine, promethazine, ondansetron) may be administered at the investigator's discretion with notification to the sponsor and entry in the CRF (See Section 6.9.1.1).

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

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment as listed in the SoA.

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

6.9.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07081532; standard medical supportive care must be provided to manage the AEs, including administration of carbohydrates to treat HAEs (see Section 8.3.6).

6.9.1.1. Management of Nausea and Vomiting

Nausea and vomiting have been reported with administration of GLP-1R agonists and also with administration of PF-07081532 (see Section 2.2.4). Study participants complaining of nausea may be managed conservatively with bed rest and/or fluid management at the discretion of the investigator. If nausea and vomiting are not amenable to conservative management, anti-emetics (eg, prochlorperazine, promethazine, ondansetron) may be administered at the investigator's discretion with notification to the sponsor and entry in the CRF.

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 (definitive discontinuation). Reasons for permanent discontinuation of study intervention include the following:

- Criteria for a potential Hy's law case are met (see Appendix 6).
- Intent to become pregnant or pregnancy confirmed by serum β-hCG testing.
- Safety or tolerability concern arises, in particular if not responsive to symptomatic management, dosing with study intervention may be stopped in an individual participant at investigator discretion.
- Based on mental health assessment as outlined in Section 8.3.8, should be discontinued from dosing at investigator discretion.
- If the criteria for permanent discontinuation are met, the site should notify the sponsor Medical Monitor or sponsor Clinician.
- Positive SARS-CoV-2 Test.

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

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

Additionally, the sponsor designee reserves the right to close the study site or terminate the study or any portion of the study (eg, Cohort 2) at any time for any reason (eg, inability to secure investigational product supplies) at the sole discretion of the sponsor. (Appendix 1, Section 10.1.9).

7.2. Participant Discontinuation/Withdrawal from the Study

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

- Refused further study procedures.

- Lost to follow-up.
- Death.
- Study terminated by sponsor.
- Safety or behavioral reasons at the discretion of the investigator, including reasons related to mental health assessments.

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

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

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

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

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

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

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

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study.

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

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

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

The total blood sampling volume for individual participants in this study is approximately 880 mL in Cohort 1 and 400 mL in Cohort 2. The total blood volume taken does not exceed 550 mL in any given 56-day consecutive period of time for either Cohort 1 or 2. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

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

8.2. Efficacy Assessments

Not applicable.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

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

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

Complete physical exam will be done at time points specified in the SoA otherwise, brief exam if findings during previous exam or new/open AEs, if appropriate, at investigator discretion.

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

Height and weight will also be measured and recorded as per the SoA. Height will be measured at screening only. Weight will be recorded using a calibrated scale (with the same scale used if possible, for the duration of the study) reporting weight in either pounds (lb) or kilograms (kg), and 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). The scale must be placed on a stable, flat surface.

Weight measurement should be taken under the following conditions:

- In the morning in a fasting state.
- After void of urine.
- After removal of shoes, bulky layers of clothing and jackets so that only light clothing remains.
- After removal of pocket contents.
- While remaining still during the measurement.

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 Section 8.4.1 to 8.4.3.

8.3.2. Vital Signs

Vital signs (systolic BP, diastolic BP and PR) will occur as specified in the SoA. Supine-BP will be measured with the participant's arm supported at the level of the heart and recorded to the nearest mm Hg after approximately 5 minutes of supine rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements. When triplicate measurements are obtained, they should be collected approximately 2 minutes apart.

At Screening, the participant's arm circumference should be measured (eg, 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. The same properly sized and calibrated BP cuff will be used to measure BP each time.

The use of an automated device for measuring BP and PR is acceptable; but when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and PR should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and PR will be permitted, as necessary, to ensure appropriate collection of safety data.

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

8.3.2.1. Temperature

Body temperature will be measured at the timepoints listed in the SoA. Temperature will be measured orally. No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement.

8.3.3. Electrocardiograms

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

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

If a) a postdose QTcF interval remains ≥30 msec from the screening **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

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

8.3.4. Clinical Safety Laboratory Assessments

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

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within [28-35 days] after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

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

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

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

8.3.4.1. Alternative Facilities for Clinical Safety Laboratory Assessment

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

8.3.5. COVID-19 Specific Assessments

Cohort 1: Participants will be tested for SARS-CoV-2 infection by PCR prior to being admitted to the clinic for confinement in Periods 1 and 9. A subsequent test will also be done according to local procedure, if participants develop symptoms suggestive of COVID-19. If participants test positive for SARS-CoV-2 infection, they will be discharged from the study.

Cohort 2: Participants will be tested for SARS-CoV-2 infection by PCR prior to being admitted to the clinic for confinement in Periods 1, 3 and 4. A subsequent test will also be done according to local procedure, if participants develop symptoms suggestive of COVID-19. If participants test positive for SARS-CoV-2 infection, they will be discharged from the study.

Additional testing may be required by local regulations or by the Principal Investigator. Results must be negative for admission to the CRU.

8.3.6. Management of Hypoglycemia

While hypoglycemia is not expected in the study participants, fasting blood glucose will be measured as part of laboratory assessment per the SoA. In addition, as a precaution, participants will be monitored for the signs and symptoms associated with hypoglycemia.

Any episode of hypoglycemia must be captured on the HAE CRF with specific details captured on the HAE Form CRF. For the definition of a hypoglycemic episode and severity categorization see Section 8.3.6.1 below.

For medical management of hypoglycemia, the investigator may administer oral carbohydrate, glucagon, or IV glucose according to his or her medical judgment.

8.3.6.1. Definition and Severity of Categorization of Hypoglycemic Adverse Event (HAE)

The investigator must assess the glucose values reported by the central/local laboratory, as well as any signs or symptoms reported by the study participant.

HAE is defined as **one** of the following:[51]

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

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

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

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

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

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

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

3. Either:

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

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

8.3.6.2. Glucometer Monitoring of Glucose

Monitoring of FSBG using glucometer measurements is not required per protocol but may be obtained if the investigator or participant notes symptoms of hypoglycemia.

If obtained, FSBG readings will be maintained at the CRU in source documents, and only the glucose results from the laboratory will be reported in the study database.

If an FSBG result is ≤70 mg/dL, a second FSBG should be obtained to confirm the glucose value, in addition to a venous sample that will be sent to the clinical laboratory for confirmation. If the value from this second FSBG is also ≤70 mg/dL, the second value will be recorded as a hypoglycemic AE. FSBG will continue to be monitored until the glucose value returns to >70 mg/dL. Samples may be taken more frequently if deemed necessary by the investigator.

8.3.7. Pregnancy Testing

A serum pregnancy test is required at screening. Pregnancy tests may be urine or serum tests but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate nonhormonal contraception must be commenced, and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention/study treatment. 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.

8.3.8. Suicidal Ideation and Behavior Risk Monitoring

8.3.8.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an interview-based rating scale to systematically assess suicidal ideation and suicidal behavior.[43] The "baseline/screening" version of the C-SSRS will be administered at Screening and Day -1 in study. Participants who respond "yes" to Question 4 or 5 (indicating suicidal ideation), or to any suicidal behavioral question on the C-SSRS at screening or Day-1 will not be permitted in the study (see Section 5.2). The "since last visit" version of the C-SSRS will be administered at the time points specified in the SoA. The C-SSRS will be administered by study site staff who have completed training in its administration.

8.3.8.1.1. 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 guidance document 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 he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the

site for each rater's certification. In return, each site will be provided with written and signed 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.

8.3.8.2. Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a 9 item self-report scale for the assessment of depressive symptoms.[48] The PHQ-9 will be completed by participants and reviewed by site staff at the pre-defined time points outlined in the SoA. A PHQ-9 score of ≥15 at Screening or Day -1 indicates clinically significant depression and serves as an exclusion criterion for this study (see Section 5.2).

8.3.8.3. Referral to a Mental Health Professional

A participant should 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 an 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.

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 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, must be assessed by the investigator to determine if the participant 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.

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

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize to 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 he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.4.1.1. 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 it 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 given 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. Environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion.

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

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

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

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

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

- Spontaneous abortion including miscarriage and missed abortion;

- 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 exposure during breastfeeding occurs if:

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

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

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

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; but a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

Not applicable.

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

8.5. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of midazolam, 1-hydroxymidazolam, omeprazole, 5-hydroxyomeprazole, LE, EE, PF-07081532, and semaglutide as specified in the SoA.

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

Samples collected for analyses of study intervention 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.

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

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

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

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.5.1. PK of Midazolam and 1-hydroxymidazolam

Samples will be used to evaluate the PK of midazolam and 1-hydroxymidazolam. For Cohort 1, blood samples of approximately 4 mL, to provide 2 aliquots of plasma volume of approximately 0.8 mL each, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of midazolam and 1-hydroxymidazolam as specified in the SoA. For Cohort 2, blood samples of approximately 5 mL, to provide 2 aliquots of plasma volume of approximately 0.8 mL each will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of midazolam and 1-hydroxymidazolam as specified in the SoA.

8.5.2. PK of Omeprazole and 5-hydroxyomeprazole

Samples will be used to evaluate the PK of omeprazole and 5-hydroxyomeprazole. Blood samples of approximately 2 mL, to provide 2 aliquots of plasma volume of approximately 0.4 mL each, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of omeprazole and 5-hydroxyomeprazole as specified in the SoA.

8.5.3. PK of Levonorgestrel

Samples will be used to evaluate the PK of LE. Blood samples of approximately 6 mL, to provide 2 aliquots of plasma volume of approximately 1.2 mL each, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of LE as specified in the SoA.

8.5.4. PK of Ethinyl Estradiol

Samples will be used to evaluate the PK of EE. Blood samples of approximately 6 mL, to provide 2 aliquots of plasma volume of approximately 1.2 mL each, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of EE as specified in the SoA.

8.5.5. PK of PF-07081532

Samples will be used to evaluate the PK of PF-07081532. Blood samples of approximately 2 mL, to provide 2 aliquots of plasma volume of approximately 0.3 mL each, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of PF-07081532 as specified in the SoA.

8.5.6. PK of Semaglutide

Samples will be used to evaluate the PK of semaglutide. Blood samples of approximately 6 mL, to provide 2 aliquots of plasma volume of approximately 1.2 mL each, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of semaglutide as specified in the SoA.

8.6. Genetics

8.6.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

CCI [redacted]

CCI [redacted]

See CCI [redacted] for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.7. Biomarkers

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA.

8.7.1. Specified Protein Research

CCI [redacted]

8.7.2. Specified Gene Expression (RNA) Research

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

8.7.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.4. Retained Research Samples for Biomarkers

CCI [redacted]

CCI

[redacted]

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

Blood samples of approximately 4 mL, to provide 2 aliquots of plasma volume of approximately 0.8 mL each, will be collected into appropriately labeled tubes containing K_2EDTA for the analysis of 4β-hydroxycholesterol and cholesterol at times specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual.

Samples collected for analyses of 4β-hydroxycholesterol/cholesterol plasma concentration may also be used to evaluate safety aspects or efficacy 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.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

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

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.
PK Concentration Set	The PK concentration population is defined as all participants who received at least 1 dose of midazolam, omeprazole, an oral contraceptive, and/or PF-07081532 and in whom at least 1 plasma concentration value is reported.
PK Parameter Set	The PK parameter analysis population is defined as all participants who received at least 1 dose of midazolam, omeprazole, an oral contraceptive, and/or PF-07081532 and have at least 1 of the PK parameters of interest calculated. Should vomiting occur after coadministration of midazolam, omeprazole, or the oral contraceptive with PF-07081532, the resulting PK parameters from that participant from the corresponding period may be excluded, where further details will be provided in the SAP.

9.3. Statistical Analyses

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

9.3.1. General Considerations

9.3.1.1. Derivation of Pharmacokinetic Parameters

The plasma PK parameters for midazolam, 1-hydroxymidazolam, omeprazole, 5-hydroxyomeprazole, LE and EE following SD administration (either alone or during coadministration with PF-07081532 or semaglutide [midazolam only]) will be derived from the concentration-time profiles as detailed in Table 12 below. The plasma PK parameters for PF-07081532 following MD administration will be derived from the concentration-time profiles as detailed in Table 13 below.

Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 12. Plasma PK Parameters for Midazolam, 1-OH-Midazolam, Omeprazole, 5-OH-Omeprazole, Levonorgestrel and Ethinyl Estradiol

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}).	Linear/Log trapezoidal method.
AUC_{inf}*	Area under the plasma concentration-time profile from time zero extrapolated to infinite time.	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	Maximum plasma concentration.	Observed directly from data.
T_{max}	Time for C_{max}.	Observed directly from data as time of first occurrence.
$t_{1/2}$*	Terminal half-life.	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F*	Apparent oral clearance.	$Dose/AUC_{inf}$.
V_z/F*	Apparent volume of distribution.	$Dose/ (AUC_{inf} * k_{el})$.
MR	Midazolam metabolite/parent ratio.	1-hydroxymidazolam/midazolam for AUC_{inf}, AUC_{last}, and C_{max} (adjusted to account for differences in molecular weight).
MR	Omeprazole metabolite/parent ratio.	5-hydroxyomeprazole/omeprazole for AUC_{inf}, AUC_{last}, and C_{max} (adjusted to account for differences in molecular weight).

* as data permit; CL/F and V_z/F will not be calculated for 1-OH-midazolam or 5-OH-omeprazole

Table 13. Plasma PK Parameters for PF-07081532

Parameter	Definition	Method of Determination
AUC_{24}	Area under the plasma concentration-time profile from time zero to time 24 hours.	AUC_t (area under the plasma concentration-time profile where t = 0 to 24 hours).
C_{max}	Maximum plasma concentration observed from time zero to 24 hours.	Observed directly from data.
T_{max}	Time for C_{max}.	Observed directly from data as time of first occurrence.
A single trough concentration sample will be obtained for semaglutide at 0h on Weeks 5, 9, 13, and 17 during Period 2 and prior to dosing in Period 3, Day 1.		

9.3.2. Statistical Methods for Pharmacokinetic Data

The PK data for midazolam, 1-hydroxymidazolam, omeprazole, 5-hydroxyomeprazole, LE, EE, and PF-07081532 will be analyzed and reported separately.

Plasma concentrations will be listed and summarized descriptively by PK sampling time and treatment (dosing alone vs. coadministration or dose by Cohort of study, as applicable). Individual participant and median profiles of the concentration-time data will be plotted by treatment. For summary statistics and median plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time for plasma samples will be used. Median profiles will be presented on both linear-linear and log-linear scales.

Cohort 1

Natural log_e-transformed AUC_{inf} (as data permit), AUC_{last} and C_{max} of omeprazole administered without PF-07081532 or coadministered with PF-07081532 will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted mean differences (Test-reference) and corresponding 90% CIs will be obtained from the models. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. The 2 test treatments will be 'omeprazole and PF-07081532 80 mg QD' (Period 4) and 'omeprazole and PF-07081532 260 mg QD' (Period 7), which will be reported separately in comparison to the reference treatment of 'omeprazole without PF-07081532' (Period 1).

Natural log_e-transformed AUC_{inf} (as data permit) of the 5-hyroxyomeprazole/omeprazole ratios (MR) administered without PF-07081532 or coadministered with PF-07081532 will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted mean differences (Test-reference) and corresponding 90% CIs will be obtained from the models. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. The 2 test treatments

will be 'omeprazole and PF-07081532 80 mg QD' (Period 4) and 'omeprazole and PF-07081532 260 mg QD' (Period 7), which will be reported separately in comparison to the reference treatment of 'omeprazole without PF-07081532' (Period 1).

Natural $\log_e$transformed AUC_{inf} (as data permit), C_{max} and AUC_{last} of midazolam administered without PF-07081532 or coadministered with PF-07081532 in Cohort 1 will be analyzed and reported separately using the same mixed effect model as described above for omeprazole. The 2 test treatments will be 'midazolam and PF-07081532 80 mg QD' (Period 4) and 'midazolam and PF-07081532 260 mg QD' (Period 7), which will be reported separately in comparison to the reference treatment of 'midazolam without PF-07081532' (Period 1).

Natural $\log_e$transformed AUC_{inf} (as data permit), C_{max} and AUC_{last} of midazolam administered without PF-07081532 or coadministered with PF-07081532 in Cohort 1 will be analyzed and reported separately using the same mixed effect model as described above for omeprazole. The test treatment will be 'midazolam alone following discontinuation of PF-07081532' (Period 9), which will be reported separately in comparison to the 2 reference treatments of 'midazolam without PF-07081532' (Period 1) and 'midazolam and PF-07081532 260 mg QD' (Period 7).

Natural $\log_e$transformed AUC_{inf} (as data permit) of the 1-hyroxymidazolam/midazolam ratios administered without PF-07081532 or coadministered with PF-07081532 in Cohort 1 will be analyzed and reported separately using the same mixed effect model as described above for omeprazole. The 2 test treatments will be 'midazolam and PF-07081532 80 mg QD' (Period 4) and 'midazolam and PF-07081532 260 mg QD' (Period 7), which will be reported separately in comparison to the reference treatment of 'midazolam without PF-07081532' (Period 1).

Natural $\log_e$transformed AUC_{inf} (as data permit), C_{max} and AUC_{last} of LE and EE administered alone or coadministered with PF-07081532 will be analyzed and reported separately using the same mixed effect model as described above for omeprazole. For LE, the 2 test treatments will be 'LE and PF-07081532 80 mg QD' (Period 5) and 'LE and PF-07081532 260 mg QD' (Period 8), which will be reported separately in comparison to the reference treatment of 'LE alone' (Period 2). Similarly for EE, the 2 test treatments will be 'EE and PF-07081532 80 mg QD' (Period 5) and 'EE and PF-07081532 260 mg QD' (Period 8), which will be reported separately in comparison to the reference treatment of 'EE alone' (Period 2).

Cohort 2

Natural $\log_e$-transformed AUC_{inf} (as data permit), C_{max} and AUC_{last} of midazolam administered alone or coadministered with semaglutide will be analyzed and reported separately using the same mixed effect model as described above for omeprazole. The test treatment will be 'midazolam and semaglutide 2.4 mg weekly' (Period 3) which will be reported separately in comparison to the reference treatment of 'midazolam alone' (Period 1).

Natural $\log_e$transformed AUC_{inf} (as data permit), C_{max} and AUC_{last} of midazolam administered without semaglutide or coadministered with semaglutide will be analyzed and reported separately using the same mixed effect model as described above for omeprazole. The test treatment will be 'midazolam alone following discontinuation of semaglutide' (Period 4), which will be reported separately in comparison to the 2 reference treatments of 'midazolam without semaglutide' (Period 1) and 'midazolam and semaglutide 2.4 mg weekly' (Period 3).

Natural $\log_e$transformed AUC_{inf} (as data permit) of the 1-hyroxymidazolam/midazolam ratios administered alone or coadministered with semaglutide will be analyzed and reported separately using the same mixed effect model as described above for omeprazole. The test treatment will be 'midazolam and semaglutide 2.4 mg weekly' (Period 3) which will be reported separately in comparison to the reference treatment of 'midazolam alone' (Period 2).

If less than 12 participants have PK parameters related to coadministration with PF-07081532 260 mg QD, the above mixed effect models may additionally/alternatively include PK parameters from the maximum tolerated dose of PF-07081532 (if applicable), where further details will be included in the SAP.

The above and other PK parameters for midazolam, 1-hydroxymidazolam, omeprazole, 5-hydroxyomeprazole, LE and EE, and PK parameters for PF-07081532, will be separately summarized descriptively by treatment.

If evaluated, the plasma 4β-hydroxycholesterol, cholesterol and CCI data will be summarized descriptively by period (Day 1 in Periods 1, 4, 7 and 9 in Cohort 1 and Day 1 in Periods 1, 3 and 4 in Cohort 2). The plasma ratios of 4β-hydroxycholesterol/cholesterol will also be summarized descriptively by period. Percent change for the 4β-hydroxycholesterol/ cholesterol ratios from baseline (Day 1 Period 1 in Cohorts 1 and 2) will be reported, and further details will be included in the SAP.

CCI

9.3.3. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, body weight and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Participants may undergo collection of ECGs, BP, and PR at the discretion of the investigator. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

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

Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.3.3.1. Electrocardiogram Analyses

Not applicable.

9.3.4. Other Analyse(s)

Tertiary/Exploratory analyses not included in the pharmacokinetic or safety analyses outlined above will be documented in the SAP.

CCI [redacted]

9.4. Interim Analyses

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

9.5. Sample Size Determination

Approximately 12 evaluable participants will complete each cohort of the study.

A sample size of 12 participants will provide 90% CIs for the difference between treatments of ±0.2491, ±0.248 and ±0.1161 on the natural log scale for AUC_{inf} in the assessment of midazolam, omeprazole and LE or EE, respectively, with 80% coverage probability. The width of 90% CIs for different estimated effects is presented in Table 14.

Table 14. Expected Widths of the 90% CIs (with 80% Coverage Probability) for Different Possible Estimated Effects and Parameters of Interest

Reference	Estimated Effect (Test/Reference)	AUC_{inf}	
		Probable 90% CI	Probable CI Width
Midazolam	50%	39% - 64%	25%
	75%	58% - 96%	38%
	100%	78% - 128%	50%
	125%	97% - 160%	63%
	150%	117% - 192%	75%
	200%	156% - 257%	101%
Omeprazole	50%	39% - 64%	25%
	75%	58% - 96%	38%
	100%	78% - 128%	50%
	125%	97% - 160%	63%
	150%	117% - 192%	75%
	200%	156% - 256%	100%
LE or EE	50%	45% - 56%	11%
	75%	67% - 84%	17%
	100%	89% -112%	23%
	125%	111% - 140%	29%
	150%	134% - 168%	35%
	200%	178% - 225%	47%

These estimates are based on data from previous internal DDI studies of midazolam, omeprazole, and an oral contraceptive containing LE/EE. These estimates are based on the assumption that within-participant standard deviations are 0.294 and 0.137 for $lnAUC_{inf}$ of midazolam and LE or EE, respectively, as obtained from previous Pfizer studies in obese participants. For omeprazole, these estimates are based on an assumed conservative within-participant standard deviation of 0.293 for $lnAUC_{inf}$ in obese participants.

Participants who fail to complete the study may be replaced at the discretion of the sponsor.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date 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 ICD(s) during their participation in the study.

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

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

10.1.4. Data Protection

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data sharing

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

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

10.1.7. 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 clinical study report.

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 clinical monitoring plan, which is maintained by the sponsor.

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

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

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

10.1.9. 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. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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

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

10.1.10. Publication Policy

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

The investigator agrees to refer to the primary publication in any subsequent publications, such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention- related information necessary for the appropriate scientific presentation or understanding of the study results.

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

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

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

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

10.1.11. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the SToD system.

To facilitate access to appropriately qualified medical personnel for study related medical questions or problems, 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 investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 15. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine eGFR Cystatin-C Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST ALT Total bilirubin Direct bilirubin Indirect bilirubin GGT Alkaline phosphatase Uric acid Albumin Total protein	Urinalysis: • pH • Glucose (qual) • Protein (qual) • Blood (qual) • Ketones • Nitrites • Leukocyte esterase • Urobilinogen • Urine bilirubin • Microscopy[a]	HbA1c Serum pregnancy test (β-hCG)[b] Lipid panel: • Total cholesterol • Direct LDL-C • HDL-C • Triglycerides TSH Free T4 Calcitonin Amylase Lipase Serum TBA SARS-CoV-2 test Urine drug screening[c] Screening only: FSH[d] C-peptide (fasting) HIV HBsAgHCVAb HCV RNA
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin (repeat) Indirect bilirubin (repeat) CK GGT (repeat) PT/INR Total bile acids (repeat) Acetaminophen drug and/or protein adduct levels		

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. Serum β-hCG for all WOCBP.
c. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific). At screening, Period 1 Day-1and at the discretion of the investigator.

d. For confirmation of postmenopausal status only.

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

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

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

10.3.2. Definition of an SAE

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

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

g. 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.

h. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

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

Assessment of Intensity

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

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

Assessment of Causality

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

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

Follow-Up of AEs and SAEs

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

- If a participant dies during participation in the study or during a recognized follow-up- period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male

Males will not participate in this study.

10.4.2. Female Participant Reproductive Inclusion Criteria

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 definitions below in Section 10.4.3).

OR

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

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition, a second effective method of contraception, as described below, must be used. 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 an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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

2. Postmenopausal female.
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
     - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.

10.4.4. Contraception Methods

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

Highly Effective Methods That Have Low User Dependency

1. Intrauterine device.
2. Bilateral tubal occlusion.
3. 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 nonhormonal.
   - Nonhormonal contraception should be used. The spermatogenesis cycle is approximately 90 days.

4. **Highly Effective Methods That Are User Dependent**

Sexual abstinence.

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

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

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

CCI

[redacted]

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

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

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

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

In addition to repeating measurements of AST and ALT and TBili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, TBA, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.7. Appendix 7: 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. Age-Specific Kidney Function Calculation Recommendations

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

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

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

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

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free 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 (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

10.9. Appendix 9 Abbreviations

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

Abbreviation	Term
Abs	absolute
ADL	activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
AM	before noon
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	area under the plasma concentration-time profile from time zero extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})
AUC_t	area under the plasma concentration-time profile where t = 0 to 24 hours
AUC_{tau}	area under the plasma concentration-time profile over the dosing interval, tau
AUC_{24}	area under the plasma concentration-time profile from time zero to time 24 hours
AV	atrioventricular
BBS	Biospecimen Banking System
β-hCG	beta human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
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 Collaboration
CL	clearance
CL/F	apparent oral clearance
C_{last}	predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
CL_p	plasma clearance
C_{max}	maximum plasma concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CRF	case report form

Abbreviation	Term
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	clinical trial
%CV	percent coefficient of variation
CYP	cytochrome P450
D/C	discharge
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
EC	ethics committee
ECC	Emergency Contact Card
eCrCl	estimated creatinine clearance
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EE	ethinyl estradiol
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
CCI	
FSBG	fingerstick blood glucose
FSH	follicle-stimulating hormone
F/U	follow-up
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide 1
GLP-1R	glucagon-like peptide 1 receptor
HAE	hypoglycemic adverse event
HbA1c	hemoglobin A_{1c}
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HDL-C	high-density lipoprotein cholesterol
Hep	hepatitis
HIV	human immunodeficiency virus
HR	heart rate

Abbreviation	Term
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IL	Interleukin
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	intravenous(ly)
KDIGO	Kidney Disease: Improving Global Outcomes
k_{el}	first-order elimination rate constant
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LBBB	left bundle branch block
LDL-C	low density lipoprotein cholesterol
LE	levonorgestrel
LFT	liver function test
LLN	Lower limit of normal
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	multiple dose
MDZ	midazolam
MEN2	multiple endocrine neoplasia syndrome type 2
MHP	mental health professional
MR	metabolite to parent ratio
mRNA	messenger ribonucleic acid
MTC	medullary thyroid carcinoma
N/A	not applicable
NOAEL	no observed adverse effect level
OATP	organic anion transporting polypeptides
OC	oral contraceptive
OH	hydroxy
OMP	omeprazole
PBPK	physiologically based pharmacokinetics
PCR	polymerase chain reaction
pH	potential of hydrogen
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic(s)

Abbreviation	Term
PM	post-menopausal
PR	pulse rate
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	once daily
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
QTL	quality tolerance limits
RA	rheumatoid arthritis
RBC	red blood cell
RSE	Relative Standard Error
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scr	serum creatinine
Scys	serum cystatin C
SD	single dose; standard deviation
SIB	Suicidal Ideation and Behavior
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SToD	study team on demand
ST-T	ST segment to T wave changes on 12-lead ECG
SSID	study-specific subject identification number
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	terminal elimination half-life
T2DM	type 2 diabetes mellitus
T4	thyroxine
TBA	total bile acids
TBili	total bilirubin
TEAE	treatment emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time to C_{max}
TNF-α	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
UGT	uridine 5'-diphospho glucuronosyltransferase
ULN	upper limit of normal
US	United States
USPI	United States Package Insert
V_{ss}	volume of distribution at steady state
Vz/F	apparent volume of distribution

Abbreviation	Term
WBC	white blood cell
WOCBP	woman/women of childbearing potential

11. REFERENCES

1. Ørskov C, Holst JJ, Knuhtsen S,et al. Glucagon-like peptides GLP-1 and GLP-2, predicted products of the glucagon gene, are secreted separately from pig small intestine but not pancreas. Endocrinology. 1986;119(4):1467-75.

2. Kreymann B, Williams G, Ghatei MA, et al. Glucagon-like peptide-1 7-36: a physiological incretin in man. Lancet. 1987;2(8571):1300-3.

3. Nauck MA, Niedereichholz U, Ettler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. Am J Physiol. 1997;273(5):E981-8.

4. Flint A, Raben A, Astrup A, et al. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest. 1998;101(3):515-20.

5. IDF Diabetes Atlas; 9th Edition. Available from: IDF Diabetes Atlas. Accessed 5Nov2022.

6. Menke A, Casagrande S, Geiss L,et al. Prevalence of and trends in diabetes among adults in the United States,1988-2012. JAMA. 2015;314(10):1021-9.

7. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321:405-12.

8. Guh DP, Zhang W, Bansback N, et al. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009;9:88.

9. Flegal KM, Kit BK, Orpana H, et al. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013;309(1):71-82.

10. The GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377(1):13-27.

11. Anderson JW, Konz EC, Frederich RC, et al. Long-term weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nutr. 2001;74(5):579-84.

12. Drucker DJ. The ascending GLP-1 road from clinical safety to reduction of cardiovascular complications. Diabetes. 2018;67:1710-9.

13. Midazolam Injection, USP. United States Prescribing Information. March 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208878Orig1s000lbl Accessed 3Nov2022.

14. Prilosec (omeprazole). Highlights of Prescribing Information. December 2014. Available from: 022056s017lbl019810s101lbl.pdf (fda.gov). Accessed 5Nov2022.

15. Levonorgestrel and Ethinyl Estradiol Tablets USP, 0.15 mg /0.03 mg. United States Prescribing Information. Revised May, 2016. Available from: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=068199a9-ef22-4061-bb76-1ee58f726018. Accessed 3Nov2022.

16. Wegovy® (semaglutide). United States Prescribing Information. June 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215256s000lbl.pdf. Accessed 27Oct2022.

17. OZEMPIC® (semaglutide). United States Prescribing Information. January 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209637s003lbl Accessed 3Nov2022.

18. Turpault S, Brian W, Van Horn R, et al. Pharmacokinetic assessment of a five-probe cocktail for CYPs 1A2, 2C9, 2C19, 2D6 and 3A. Br J Clin Pharmacol. 2009;68(6):928-35.

19. Ryu, JY, Sing, IS, Sunwoo IE, et al., Development of the "Inje cocktail" for high-throughput evaluation of five human cytochrome P450 isoforms *in vivo*. Clin Pharmacol Ther. 2007;82(5):531-40.

20. Kapetas AJ, Sorich MJ, Rodrigues AD, and Rowland A. Guidance for rifampin and midazolam dosing protocols to study intestinal and hepatic cytochrome P450 (CYP) 3A4 induction and de-induction. The AAPS Journal. 2019;21(78):1-11.

21. Greenblatt DJ, Abernethy DR, Locniskar A, et.al. Effect of age, gender, and obesity on midazolam kinetics. Anesthesiology. 1984;61(1):27-35.

22. Brill MJ, Diepstraten J, van Rongen A, et al. Impact of obesity on drug metabolism and elimination in adults and children. Clin Pharmacokinet. 2012;51(5):277-304.

23. Desta Z, Zhao X, Shin J-G, and Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clin Pharmacokinet. 2002;41(12):913-58.

24. Tassaneeyakul W, Tassaneeyakul W, Vannaprasaht S, and Yamazoe Y. Formation of omeprazole sulphone but not 5-hydroxyomeprazole is inhibited by grapefruit juice. Br J Clin Pharmacol. 2000;49:139–44.

25. Derungs A, Donzelli M, Berger B, et al. Effects of Cytochrome P450 inhibition and induction on the phenotyping metrics of the Basel cocktail: A randomized crossover study. Clin Pharmacokinet. 2016;55:79–91.

26. Furuta T, Ohashi K, Kobayashi K, et al. Effects of clarithromycin on the metabolism of omeprazole in relation to CYP2C19 genotype status in humans. Clin Pharmac Ther. 1999;66(3):265-74.

27. Nichols M, Robinson, G, Bounds, W, et al. Effect of four combined oral contraceptives on blood pressure in the pill-free interval. Contraception. 1993;47:367-76.

28. Eder K, Baffy N, Falus A, and Fulop AK. The major inflammatory mediator interleukin-6 and obesity. Inflamm Res. 2009,58:727–36.

29. Ellulu MS, Patimah I, Khaza'ai H, et al. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci. 2017;13(4):851–863.

30. Wellen KE and Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest. 2005;115(5):1111-1119.

31. Trayhurn P and Wood IS. Signalling role of adipose tissue: adipokines and inflammation in obesity. Biochemical Society Transactions. 2005;33(5):1078-1081.

32. Marantos G, Daskalakis N, Karkavitsas N, et al. Changes in metabolic profile and adipoinsular axis in morbidly obese premenopausal females treated with restrictive bariatric surgery. World J Surg. 2011;35:2022–30.

33. Bastard J-P, Jardel C, Bruckert E, et al. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. J Clin Endocrinology Metabolism. 2000;85(9):3338-42.

34. Bruun JM, Verdich C, Toubro S, et al. Association between measures of insulin sensitivity and circulating levels of interleukin-8, interleukin-6 and tumor necrosis factor-α. Effect of weight loss in obese men. European J Endocrinology. 2003;148:535–42.

35. Schmitt C, Kuhn B, Zhang X, et al. Disease–drug–drug interaction involving tocilizumab and simvastatin in patients with rheumatoid arthritis. Clin Pharmacol Ther. 2011;89(5):735-40.

36. Lee EB, Daskalakis N, Xu C, et al. Disease–drug interaction of sarilumab and simvastatin in patients with rheumatoid arthritis. Clin Pharmacokinet. 2017;56:607–615.

37. Abernethy DR, Greenblatt DJ, Divoll M, et al. The influence of obesity on the pharmacokinetics of oral alprazolam and triazolam. Clin Pharmacokinet. 1984;9(2):177-83.

38. Caraco Y, Zylber-Katz E, Berry EM, and Levy M. Significant weight reduction in obese subjects enhances carbamazepine elimination. Clin Pharmacol Ther. 1992;51(5): 501-6.

39. Lloret-Linares C, Daali Y, Abbara C, et al. CYP450 activities before and after Roux-en-Y gastric bypass: correlation with their intestinal and liver content. Surg Obes Relat Dis. 2019;15(8):1299–1310.

40. Rodríguez-Morató J, Goday A, Langohr K, et al. Short- and medium-term impact of bariatric surgery on the activities of CYP2D6, CYP3A4, CYP2C9, and CYP1A2 in morbid obesity. Sci Rep. 2019;9(1):1–9.

41. Brill MJE, van Rongen A, van Dongen EP, et al. The pharmacokinetics of the CYP3A substrate midazolam in morbidly obese patients before and one year after bariatric surgery. Pharm Res. 2015;32:3927–36.

42. Sall C, Alifrangis L, Dahl K, et al. In vitro CYP450 enzyme down-regulation by GLP-1/glucagon co-agonist does not translate to observed drug-drug interactions in the clinic. Drug Metab Dispos. 2022;Jun 9. doi: 10.1124/dmd.122.000865. Online ahead of print.

43. TRULICITY® (dulaglutide). United States Prescribing Information. February 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125469s033lbl.pdf Accessed 3Nov2022.

44. SAXENDA® (liraglutide). United States Prescribing Information. March 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/206321s011lbl.pdf. Accessed 3Nov2022.

45. VICTOZA® (liraglutide). United States Prescribing Information. June 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022341s031lbl.pdf Accessed 3Nov2022.

46. BYETTA® (exenatide). United States Prescribing Information. June 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021773s046s047lbl.pdf. Accessed 27Oct2022.

47. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.

48. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-13.

49. Crawford P, Chadwick DJ, Martin C, et al. The interaction of phenytoin and carbamazepine with combined oral contraceptive steroids. Br J Clin Pharmac. 1990;30:892-96.

50. Jordy AB, Albayaty M, Breitschaft A, et al. Effect of oral semaglutide on the pharmacokinetics of levonorgestrel and ethinylestradiol in healthy postmenopausal women and furosemide and rosuvastatin in healthy subjects. Clin Pharmacokinet. 2021;60(9):1171–85.

51. American Diabetes Association. Standards of medical care in diabetes-2019. Diabetes Care. 2019;42(Suppl 1): S1-S193.

52. Rodrigues AD, van Dyk M, Sorich MJ, et al. Exploring the use of serum-derived small extracellular vesicles as liquid biopsy to study the induction of hepatic cytochromes P450 and organic anion transporting polypeptides. Clin Pharmacol Ther. 2021;110(1):248-58.