Protocol C3991040

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

Statistical Analysis Plan
(SAP)

Version: 1

Date: 23 Dec 2022

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NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 / 23 Dec 2022	Original 07 Nov 2022	N/A	N/A

2. INTRODUCTION

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.

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.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3991040.

2.1. Modifications to the Analysis Plan Described in the Protocol

None.

2.2. Study 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.*

Objectives	*Endpoints*
	• *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, V_z/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}.*

Objectives	*Endpoints*
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*	• *Midazolam plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Period 4.*

Objectives	*Endpoints*
of semaglutide administration in obese adult female participants.	
• *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, V_z/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.*

2.3. Study 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

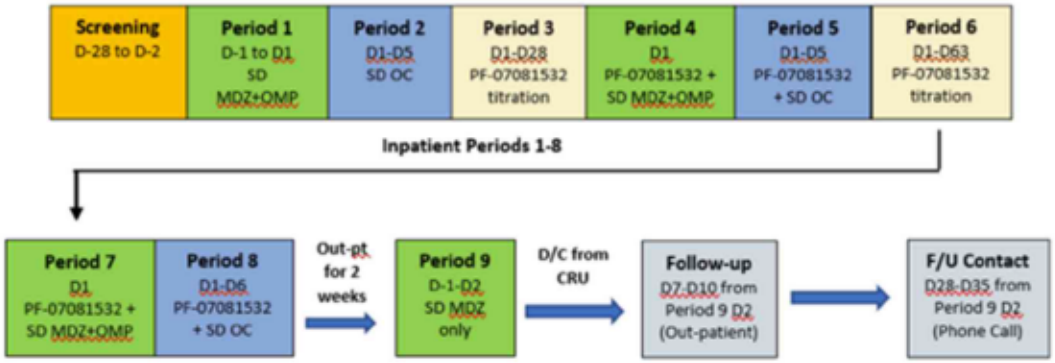
GLP-1R agonists. Participants will participate in either Cohort 1 or Cohort 2 (not both), and Cohort 1 and Cohort 2 are preferred to be conducted in parallel, if possible.

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 ≥30 kg/m^2. Approximately 16 participants will be enrolled in Cohort 1.

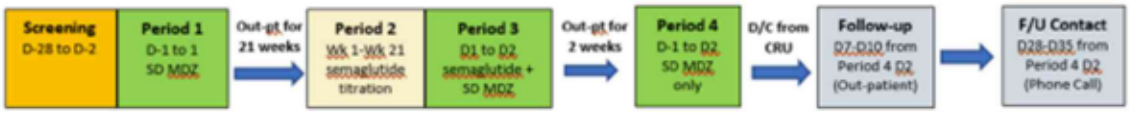
Cohort 2 is an open-label, 4-period, fixed-sequence design to evaluate the effect of steady-state semaglutide on the SD PK of midazolam in obese adult female participants with a BMI ≥30 kg/m^2. Approximately 16 participants will be enrolled in Cohort 2.

Figure 1. Study 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.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

Cohort 1

The primary endpoints are the AUC_{inf} (if data permit, otherwise AUC_{last}) of midazolam and omeprazole in Periods 1, 4 and 7; and AUC_{inf} (if data permit, otherwise AUC_{last}) of LE and EE in Periods 2, 5 and 8. In addition, the test/reference ratios for AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} will be derived for the following comparisons:

- test treatments will be "midazolam (or omeprazole) and PF-07081532 80 mg QD" (Period 4) and "midazolam (or omeprazole) and PF-07081532 260 mg QD" (Period 7) and the reference treatment will be "midazolam (or omeprazole) without PF-07081532" (Period 1);
- test treatments will be "LE (or EE) and PF-07081532 80 mg QD" (Period 5) and "LE (or EE) and PF-07081532 260 mg QD" (Period 8) and the reference treatment will be "LE (or EE) alone" (Period 2).

Cohort 2

The primary endpoints are the AUC_{inf} (if data permit, otherwise AUC_{last}) of midazolam in Periods 1 and 3. In addition, the test/reference ratios for AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} will be derived for the following comparison:

- test treatment will be "midazolam and semaglutide 2.4 mg weekly" (Period 3) and the reference treatment will be "midazolam alone" (Period 1).

3.2. Secondary Endpoints

Cohort 1

The secondary endpoints are the following:

- Safety and tolerability data, discussed in Section 3.5.
- AUC_{inf} (if data permit, otherwise AUC_{last}) of midazolam in Period 9. In addition, the test/reference ratios for AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} will be derived for the following comparisons:
  - test treatment will be "midazolam alone following discontinuation of PF-0708153" (Period 9) and reference treatments will be "midazolam without PF-07081532" (Period 1) and "midazolam and PF-07081532 260 mg QD" (Period 7).
- Additional plasma PK parameters (C_{max}, T_{max}, CL/F, V_z/F, $t_{1/2}$, as data permit) for midazolam and omeprazole in Periods 1, 4 and 7, and for LE and EE in Periods 2, 5 and 8.

- MRAUC$_{inf}$ (1-hydroxymidazolam AUC$_{inf}$/midazolam AUC$_{inf}$) in Periods 1, 4 and 7.
- MRAUC$_{inf}$ (5-hydroxyomeprazole AUC$_{inf}$/omeprazole AUC$_{inf}$) in Periods 1, 4 and 7.
- AUC$_{24}$, C_{max} and T_{max} of PF-07081532 at Days 34 and 103.

Cohort 2

The secondary endpoints are the following:

- Safety and tolerability data, discussed in Section 3.5.
- AUC$_{inf}$ (if data permit, otherwise AUC$_{last}$) of midazolam in Period 4. In addition, the test/reference ratios for AUC$_{inf}$ (if data permit, otherwise AUC$_{last}$) and C_{max} will be derived for the following comparisons:
  - test treatment will be "midazolam alone following discontinuation of semaglutide" (Period 4) and reference treatments will be "midazolam without semaglutide" (Period 1) and "midazolam and semaglutide 2.4 mg once weekly" (Period 3).
- Additional plasma PK parameters (C_{max}, T_{max}, CL/F, V_z/F, $t_{1/2}$, as data permit) for midazolam in Periods 1 and 3.
- MRAUC$_{inf}$ (1-hydroxymidazolam AUC$_{inf}$/midazolam AUC$_{inf}$) in Periods 1 and 3.

3.3. Other Endpoints

Cohort 1

The tertiary/exploratory endpoints are the following:

- AUC$_{last}$, C_{max}, T_{max}, AUC$_{inf}$ and $t_{1/2}$ as data permit for 1-hydroxymidazolam in Periods 1, 4 and 7
- Test/reference ratios for metabolite/parent (1-hydroxymidazolam/midazolam) for AUC$_{inf}$ (as data permit), AUC$_{last}$ and C_{max} where test treatments will be "midazolam and PF-07081532 80 mg QD" (Period 4) and "midazolam and PF-07081532 260 mg QD" (Period 7) and the reference treatments will be "midazolam without PF-07081532" (Period 1) and "midazolam alone following discontinuation of PF-0708153" (Period 9)
- AUC$_{last}$, C_{max}, T_{max}, AUC$_{inf}$ and $t_{1/2}$ as data permit for 5-hydroxyomeprazole in Periods 1, 4 and 7
- Test/reference ratios for metabolite/parent (5-hydroxyomeprazole/omeprazole) for AUC$_{inf}$ (as data permit), AUC$_{last}$ and C_{max} where test treatments will be "omeprazole and PF-07081532 80 mg QD" (Period 4) and "omeprazole and PF-07081532 260 mg

QD" (Period 7) and the reference treatment will be "omeprazole without PF-07081532" (Period 1)

- Morning predose 4β-hydroxycholesterol/cholesterol plasma ratio on Day 1 in Periods 1, 4, and 7

Cohort 2

The tertiary/exploratory endpoints are the following:

- AUC_{last}, C_{max}, T_{max}, AUC_{inf} and $t_{1/2}$ as data permit for 1-hydroxymidazolam in Periods 1 and 3

- Test/reference ratios for metabolite/parent (1-hydroxymidazolam/midazolam) for AUC_{inf} (as data permit), AUC_{last} and C_{max} where test treatment will be "midazolam and semaglutide 2.4 mg once weekly" (Period 3) and the reference treatments will be "midazolam alone" (Period 1) and "midazolam alone following discontinuation of semaglutide" (Period 4)

- Morning predose 4β-hydroxycholesterol/cholesterol plasma ratio on Day 1 in Periods 1 and 3

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 2 below. The plasma PK parameters for PF-07081532 following MD administration will be derived from the concentration-time profiles as detailed in Table 3 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 2. 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 observed concentration.*	*Observed directly from data.*
T_{max}	*Time for C_{max}.*	*Observed directly from data as time of first occurrence.*
$t_{½}$*	*Terminal half-life.*	*$Log_e(2)/k_{el}$, where kel 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 3. 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.*	*Linear/Log trapezoidal method*
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.

3.4. Baseline Variables

Baseline characteristics will be collected according to the schedule of activities (SoA) as specified in the protocol.

3.5. Safety Endpoints

The following data are considered in standard safety summaries (see protocol for collection days, baseline assessment, and list of parameters):

- adverse events (AE)
- laboratory data
- body weight
- mental health
- vital signs data
- electrocardiogram (ECG) results

3.5.1. Adverse Events

Any adverse events occurring following start of treatment will be considered as treatment emergent adverse event (TEAE). Events that occur during follow-up within the lag time of up to 35 days after the last dose of study intervention will be counted as treatment emergent and attributed to the last treatment taken. The time period for collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent.

3.5.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol. To determine if there are any clinically significant laboratory abnormalities, the hematological, clinical chemistry

(serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor's reporting standards. The assessment will not take into account whether each participants's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

For both cohorts, the baseline measurement is the latest predose measurement on Period 1 .

3.5.3. Body Weight

Body weight will be measured at times specified in the SoA given in the protocol.

For both cohorts, the baseline measurement is the predose measurement on Period 1 Day 1.

3.5.4. Vital Signs

Supine blood pressure (BP), pulse rate (PR) and temperature will be measured at times specified in the SoA given in the protocol.

For both cohorts, the baseline measurement is the latest predose measurement on Period 1.

3.5.5. Electrocardiograms

QT interval, QTcF, PR, QRS and heart rate (HR) will be recorded at each assessment time indicated in the SoA given in the protocol. QTcF will be derived using Fridericia's heart rate correction formula:

$$QTcF = QT / (RR)^{(1/3)} \text{ where } RR = 60/HR \text{ (if not provided)}$$

For both cohorts, the baseline measurement is the latest measurement at Screening.

3.5.6. Mental health

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

The C-SSRS is an interview-based rating scale to systematically assess suicidal ideation and suicidal behavior. The "since last visit"version of the C-SSRS will be administered at the time points specified in the SoA. A participant with a postbaseline assessment with response of "yes" to question 4 or 5, or on any suicidal behavioral question on the C-SSRS should be referred to a Mental Health Professional (MHP). Participants who have recurrent suicidal ideation or behavior during the 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) should be discontinued from the study and treated appropriately.

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

The PHQ-9 is a 9 item self-report scale for the assessment of depressive symptoms. The PHQ-9 will be completed by participants and reviewed by site staff at the pre-defined time points outlined in the SoA. The total score will be derived by adding the corresponding values

of responses to each item. The total score ranges from 0 to 27, with the following interpretation:

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

A participant with a postbaseline assessment with a score of ≥15 should be referred to a MHP.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

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.*

5. GENERAL METHODOLOGY AND CONVENTIONS

Final analysis will be performed after study participant data set release following last participant last visit.

5.1. Hypotheses and Decision Rules

No statistical hypothesis will be tested in this study.

5.2. General Methods

5.2.1. Analyses for Binary/Categorical Endpoints

For binary or categorical variables, number of participants, and numbers and percentages of participants meeting the categorical criteria will be presented in accordance with the Clinical Data Interchange Standards Consortium and Pfizer Standards (CaPS).

5.2.2. Analyses for Continuous Endpoints

For continuous variables, the data will be summarized using the number of participants, mean, median, standard deviation (SD), minimum, and maximum in accordance with the CaPS. For appropriate PK parameters, geometric mean and geometric coefficient of variation (%CV) will also be summarized.

5.3. Methods to Manage Missing Data

5.3.1. Pharmacokinetic Data

Methods to handle missing PK data are described below.

Concentrations Below the Limit of Quantification:

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings, BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.).

Deviations, Missing Concentrations and Anomalous Values:

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, no sample).
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

An anomalous concentration value is one that, after verification of bioanalytical validity, is grossly inconsistent with other concentration data from the same individual or from other

participants. For example, a BLQ concentration that is between quantifiable values from the same dose is considered as anomalous. Anomalous concentration values may be excluded from PK analysis at the discretion of the PK analyst.

PK Parameters:

Actual PK sampling times will be used in the derivation of PK parameters. If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a participant discontinues).

In summary tables, statistics will not be presented for a particular treatment group if more than 50% of the data are NC. For statistical analyses, PK parameters coded as NC will also be set to missing.

If an individual participant has a known biased estimate of a PK parameter (due for example to dosing error or an unexpected event, such as vomiting, before all the compound is adequately absorbed from the gastrointestinal tract), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses. For instance, if a participant has a vomiting event post dose that is within a duration of time that is 2-times the derived median T_{max} for the population for the administered treatment, then the pharmacokineticist should consider the exclusion of the PK concentration data collected following the initial vomiting event in that treatment period and the PK parameter data reported for that treatment period from the datasets used to calculate summary statistics or statistical analyses.

5.3.2. Safety Data

Missing values in standard summaries of AEs, laboratory data, vital signs, and ECGs will be imputed according to CaPS.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

Cohort 1

For the evaluation of the effects of PF-07081532 on the pharmacokinetics of omeprazole, *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).*

For the evaluation of the effects of PF-07081532 on the pharmacokinetics of midazolam, *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).*

For the evaluation of the effects of PF-07081532 on the pharmacokinetics of an oral contraceptive, *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).*

For all mixed effect models, residuals will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals, but these will not be included in the CSR. If there are major deviations from normality or outliers, then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

Cohort 2

For the evaluation of the effects of semaglutide on the pharmacokinetics of midazolam, *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).*

6.2. Secondary Endpoints

Cohort 1

Analyses and summaries of safety data are described in Section 6.6.

For the evaluation of the pharmacokinetics of midazolam following discontinuation of PF-07081532, *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).

For the evaluation of the effects of PF-07081532 on additional pharmacokinetic parameters (C_{max}, T_{max}, CL/F, V_z/F, $t_{1/2}$, as data permit) for midazolam and omeprazole (Periods 1, 4 and 7 [including Period 9 for midazolam]), and LE and EE (Periods 2, 5 and 8), descriptive statistics will be provided, as outlined in Table 4.

For the evaluation of the effects of PF-07081532 on the metabolite/parent ratios ($MRAUC_{inf}$) for midazolam and omeprazole (Periods 1, 4 and 7 [including Period 9 for midazolam]), descriptive statistics will be provided, as outlined in Table 4.

For the evaluation of MD pharmacokinetics of PF-07081532 (AUC_{24}, C_{max}, T_{max}), descriptive statistics at Days 28 and 63 of Periods 3 and 6, respectively, will be provided, as outlined in Table 4.

Cohort 2

Analyses and summaries of safety data are described in Section 6.6.

For the evaluation of the pharmacokinetics of midazolam following discontinuation of semaglutide, *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).*

For the evaluation of the effects of semaglutide on additional pharmacokinetic parameters (C_{max}, T_{max}, CL/F, V_z/F, $t_{1/2}$, as data permit) for midazolam (Periods 1, 3 and 4), descriptive statistics will be provided, as outlined in Table 4.

For the evaluation of the effects of semaglutide on the metabolite/parent ratios ($MRAUC_{inf}$) for midazolam (Periods 1, 3 and 4), descriptive statistics will be provided, as outlined in Table 4.

6.3. Other Endpoints

Cohort 1

For the evaluation of the effects of PF-07081532 on the pharmacokinetics of 1-hydroxymidazolam (AUC_{last}, C_{max}, T_{max}, AUC_{inf}, $t_{1/2}$, as data permit) in Periods 1, 4, 7 and 9, descriptive statistics will be provided, as outlined in Table 4. In addition, *natural log_e-transformed AUC_{inf} (as data permit)*, AUC_{last} and C_{max} *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 treatments of 'midazolam without PF-07081532' (Period 1) and 'midazolam alone following discontinuation of PF-07081532' (Period 9).

For the evaluation of the effects of PF-07081532 on the pharmacokinetics of 5-hydroxyomeprazole (AUC_{last}, C_{max}, T_{max}, AUC_{inf}, $t_{1/2}$, as data permit) in Periods 1, 4 and 7, descriptive statistics will be provided, as outlined in Table 4. In addition, *natural log_e-transformed AUC_{inf} (as data permit)*, AUC_{last} and C_{max} *of the 5-hyroxyomeprazole/omeprazole ratios (MR) 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 '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).*

For the evaluation of the effects of PF-07081532 on biomarkers of CYP3A induction, observed value and percent change from baseline in morning predose 4β-hydroxycholesterol/cholesterol plasma ratio will be summarized descriptively by period (Day 1 in Periods 1 [baseline], 4, 7 and 9).

Cohort 2

For the evaluation of the effects of semaglutide on the pharmacokinetics of 1-hydroxymidazolam (AUC_{last}, C_{max}, T_{max}, AUC_{inf}, $t_{1/2}$, as data permit) in Periods 1, 3 and 4, descriptive statistics will be provided, as outlined in Table 4. In addition, *natural log_e-transformed AUC_{inf} (as data permit)*, AUC_{last} and C_{max} *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 treatments of 'midazolam alone' (Period 1)* and 'midazolam alone following discontinuation of semaglutide' (Period 4).

For the evaluation of the effects of semaglutide on biomarkers of CYP3A induction, observed value and percent change from baseline in morning predose 4β-hydroxycholesterol/cholesterol plasma ratio will be summarized descriptively by period (Day 1 in Periods 1 [baseline], 3 and 4).

6.3.1. PK Concentration

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.

Presentations of concentrations will include:

- A listing of all concentrations sorted by participant ID, treatment and nominal time postdose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.
- A summary of concentrations by treatment and nominal time postdose, where the set of statistics will include n, mean, median, SD, %CV, minimum, maximum and the number of concentrations above the LLQ.
- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).
- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).
- Individual concentration time plots by treatment (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each treatment per scale).
- Individual concentration time plots by participant (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each participant (containing all treatments) per scale].

6.3.2. PK parameter

The PK parameters will be summarized descriptively by treatment group in accordance with Pfizer data standards on the PK Parameter Analysis Set, as data permit. *For AUC_{inf} (if data permits), AUC_{last}, and C_{max}, a listing of the individual participant ratios (Test/Reference) will be provided. Box and whisker plots for AUC_{inf} (if data permits), AUC_{last}, and C_{max}, will be plotted by treatment.* Missing values will be handled as detailed in Section 5.3.1. Each PK parameter will be summarized by treatment group and will include the set of summary statistics as specified in Table 4.

Table 4. PK Parameters to be Summarized Descriptively by Treatment

Parameter	Summary Statistics
AUC_{inf}, AUC_{last}, C_{max}, CL/F, V_z/F, MR, AUC_{24}	N, arithmetic mean, median, SD, %CV, minimum, maximum, geometric mean and geometric %CV
T_{max}	N, median, minimum, maximum
$t_{½}$	N, arithmetic mean, median, SD, %CV, minimum, maximum

Supporting data from the estimation of $t_{½}$ and AUC_{inf} will be listed by analyte and group: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation (AUC_{extrap}%); and the first, last, and number of time points used in the estimation of k_{el}. This data may be included in the clinical study report.

6.4. Subset Analyses

There are no planned subset analyses.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Demographic Summaries

Demographic characteristics will be summarized for the enrolled population in accordance with the CaPS.

6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show end of study participant disposition. Frequency counts will be supplied for participant discontinuation(s) by treatment. Data will be reported in accordance with the CaPS.

6.5.3. Study Treatment Exposure

Study treatment exposure will be listed.

6.5.4. Concomitant Medications and Nondrug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be reported in the listings.

6.6. Safety Summaries and Analyses

All safety analyses will be performed on the Safety Analysis Set.

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

6.6.1. Adverse Events

Adverse events will be reported in accordance with the CaPS.

Participant discontinuations due to adverse events will be detailed by treatment. Data will be reported in accordance with the CaPS.

6.6.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the CaPS.

6.6.3. Body Weight

Observed value and change from baseline in body weight will be summarized descriptively by treatment.

6.6.4. Vital Signs

Vital sign data will be databased and available upon request.

6.6.5. Electrocardiograms

ECG data will be databased and available upon request.

6.6.6. Mental Health

C-SSRS and PHQ-9 data will be listed.

7. INTERIM ANALYSES

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

Final analysis will follow the official database release. As this will be an open-label study, there is no formal unblinding of the randomization code.

APPENDICES

Appendix 1. SAS Code for Analyses

An example of the PROC MIXED code is provided below:

For primary objectives:

Cohort 1

```
proc mixed data=tab.pk;
where period in ("1", "4") and ppcat="midazolam";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'D vs A' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

proc mixed data=tab.pk;
where period in ("1", "7") and ppcat="midazolam";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'G vs A' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

proc mixed data=tab.pk;
where period in ("1", "4") and ppcat="omeprazole";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'D vs A' trt -1 1 /cl alpha=0.1;
```

```
        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

proc mixed data=tab.pk;
where period in ("1", "7") and ppcat="omeprazole";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'G vs A' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

proc mixed data=tab.pk;
where period in ("2", "5") and ppcat="LE";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'E vs B' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

proc mixed data=tab.pk;
where period in ("2", "8") and ppcat="LE";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'H vs B' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
```

```
run;
proc mixed data=tab.pk;
where period in ("2", "5") and ppcat="EE";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'E vs B' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

proc mixed data=tab.pk;
where period in ("2", "8") and ppcat="EE";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'H vs B' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;


/* Letter assignments for treatments (trt) within the estimate statement above are as follows
A: SD midazolam 2 mg + SD omeprazole 20 mg (Reference);
B: SD OC (LE 015 mg/EE 0.03 mg) (Reference);
D: PF-07081532 80 mg QD + SD midazolam 2 mg + SD omeprazole 20 mg (Test)
E: PF-07081532 80 mg QD + SD OC (LE 0.15 mg/EE 0.03 mg) (Test)
G: PF-07081532 260 mg QD + SD midazolam 2 mg + SD omeprazole 20 mg (Test)
H: PF-07081532 260 mg QD + SD OC (LE 0.15 mg/EE 0.03 mg) (Test)    */
```

Cohort 2

```
proc mixed data=tab.pk;
where period in ("1", "3") and ppcat="midazolam";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
```

```
        estimate 'L vs J' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

/* Letter assignments for treatments (trt) within the estimate statement above are as follows
J: SD midazolam 2 mg (Reference);
L: semaglutide 2.4 mg once weekly + SD midazolam 2 mg (Test);  */
```

For secondary objectives:

Cohort 1

```
proc mixed data=tab.pk;
where period in ("1", "9") and ppcat="midazolam";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'I vs A' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

proc mixed data=tab.pk;
where period in ("7", "9") and ppcat"midazolam";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'I vs G' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

/* Letter assignments for treatments (trt) within the estimate statement above are as follows;
A: SD midazolam 2 mg + SD omeprazole 20 mg (Reference);
```

```
G: PF-07081532 260 mg QD + SD midazolam 2 mg + SD omeprazole 20 mg (Reference)
I: SD midazolam 2 mg only (Test)    */
```

Cohort 2

```
proc mixed data=tab.pk;
where period in ("1", "4");
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'M vs J' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

proc mixed data=tab.pk;
where period in ("3", "4");
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'M vs L' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

/* Letter assignments for treatments (trt) within the estimate statement above are as follows;
J: SD midazolam 2 mg (Reference);
L: semaglutide 2.4 mg once weekly + SD midazolam 2 mg (Reference);
M: SD midazolam 2 mg only (Test) */
```

For tertiary/exploratory objectives:

Cohort 1

```
proc mixed data=tab.pk;
where period in ("1", "4") and ppcat="1-hyroxymidazolam/midazolam";
        class trt participant;
```

```
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'D vs A' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

proc mixed data=tab.pk;
where period in ("1", "7") and ppcat="1-hyroxymidazolam/midazolam";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'G vs A' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

proc mixed data=tab.pk;
where period in ("1", "4") and ppcat="5-hyroxyomeprazole/omeprazole";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'D vs A' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

proc mixed data=tab.pk;
where period in ("1", "7") and ppcat="5-hyroxyomeprazole/omeprazole";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'G vs A' trt -1 1 /cl alpha=0.1;
```

```
        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

proc mixed data=tab.pk;
where period in ("9", "4") and ppcat="1-hyroxymidazolam/midazolam";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'D vs I' trt 1 -1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

proc mixed data=tab.pk;
where period in ("9", "7") and ppcat="1-hyroxymidazolam/midazolam";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'G vs I' trt 1 -1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;


/* Letter assignments for treatments (trt) within the estimate statement above are as follows
A: SD midazolam 2 mg + SD omeprazole 20 mg (Reference);
D: PF-07081532 80 mg QD + SD midazolam 2 mg + SD omeprazole 20 mg (Test)
G: PF-07081532 260 mg QD + SD midazolam 2 mg + SD omeprazole 20 mg (Test)
I: SD midazolam 2 mg only (Reference) */
```

Cohort 2

```
proc mixed data=tab.pk;
where period in ("1", "3") and ppcat="1-hyroxymidazolam/midazolam";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'L vs J' trt -1 1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

proc mixed data=tab.pk;
where period in ("4", "3") and ppcat="1-hyroxymidazolam/midazolam";
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /subject=participant;
        lsmeans trt;
        estimate 'L vs M' trt 1 -1 /cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

/* Letter assignments for treatments (trt) within the estimate statement above are as follows
J: SD midazolam 2 mg (Reference);
L: semaglutide 2.4 mg once weekly + SD midazolam 2 mg (Test);
M: SD midazolam 2 mg only (Reference)     */
```

Appendix 2. List of Abbreviations

Abbreviation	Term
%CV	coefficient of variation
AE	adverse event
AUC_{24}	area under the plasma concentration-time profile from time zero to time 24 hours
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})
BLQ	below the limit of quantitation
BMI	body mass index
BP	blood pressure
CaPS	Clinical Data Interchange Standards Consortium and Pfizer Standards
CI	confidence interval
C_{last}	predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
CL/F	apparent oral clearance
C_{max}	maximum plasma concentration
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	clinical study report
ECG	electrocardiogram
EE	ethinyl estradiol
GLP-1R	glucagon-like peptide 1 receptor
HR	heart rate
k_{el}	the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve
LE	levonorgestrel
LLQ	lower limit of quantitation
MD	multiple dose
mg	milligram
MHP	mental health professional
MR	metabolite to parent ratio
$MRAUC_{inf}$	1-hydroxymidazolam AUC_{inf}/midazolam AUC_{inf}; 5-hydroxyomeprazole AUC_{inf}/omeprazole AUC_{inf}
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
OC	oral contraceptive
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic(s)

Abbreviation	Term
PR	pulse rate
QD	once daily
QRS	Combination of Q-, R- and S- wave on an electrocardiogram representing ventricular depolarization
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
RR	respiratory rate
SAP	statistical analysis plan
SD	single dose; standard deviation
SoA	schedule of activities
$t_{1/2}$	terminal elimination half-life
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
T_{max}	time to C_{max}
V_z/F	apparent volume of distribution