Statistical Analysis Plan J2A-MC-GZPG 2.0

A Drug-Drug Interaction Study to Assess the Effect of Orforglipron on the Pharmacokinetics of Digoxin, Simvastatin, Rosuvastatin, Acetaminophen, and Midazolam in Healthy Overweight and Obese Participants

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LIST OF ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

%AUC(tlast-∞)	percentage of AUC(0-∞) extrapolated
ADaM	Analysis Data Model
AE	adverse event
AUC	area under the concentration versus time curve
$AUC_{(0-\infty)}$	area under the concentration versus time curve from time zero to infinity
$AUC(0-t_{last})$	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
BCRP	breast cancer resistant protein
BCRP	breast cancer resistant protein
BLQ	below the lower limit of quantitation
BMI	body mass index
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL/F	apparent total body clearance of drug calculated after extra-vascular administration
C_{last}	last quantifiable drug concentration
C_{max}	maximum observed drug concentration
C_{min}	minimum observed drug concentration
CRU	clinical research unit
CSR	clinical study report
C-SSRS	Columbia Suicide-Severity Rating Scale
CV	coefficient of variation
DDI	drug-drug interaction
DMP	data management plan
ECG	electrocardiogram
eCRF	electronic case report form
GLSM	geometric least squares mean
ICH	International Council for/Conference on Harmonization
LLOQ	lower limit of quantification
ln	natural log
LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
OATP	organic anion transporting polypeptide
PK	pharmacokinetic(s)

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QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
$t_{1/2}$	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{max}	time of maximum observed drug concentration
V_{ss}/F	apparent volume of distribution at steady state after extra-vascular administration
V_z/F	apparent volume of distribution during the terminal phase after extra-vascular administration
WHODrug	World Health Organization Drug Dictionary

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1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1.0 dated 02 October 2023), protocol amendment (a) (Final Version dated 23 October 2023), protocol amendment (b) (Final Version dated 30 January 2024), and protocol amendment (c) (Final Version dated 28 March 2024).

This SAP describes the planned analysis of the PK, safety, and tolerability data from this study. A detailed description of the planned TFLs to be presented in the CSR is provided in the accompanying TFL shells document.

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information about this study (e.g., objectives, study design) is given to help the reader's interpretation.

This SAP must be finalized prior to first participant visit. Additionally, the SAP and TFL shells should be finalized prior to any programming activities commencing.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Eli Lilly and Company and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the ICH E3 guideline *Structure and Content of Clinical Study Reports*, ICH E8 guideline *General Considerations for Clinical Trials*, ICH E9 guideline *Statistical Principles for Clinical Trials*, and ICH E9 R1 guideline *Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials*.[1,2,3]

The document history is presented in Appendix 1.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect, in healthy overweight or obese participants, of: ○ orforglipron capsule on the PK of digoxin, rosuvastatin, acetaminophen, and midazolam, ○ orforglipron capsule on the PK of simvastatin, following simultaneous or staggered administration, and ○ sodium bicarbonate on the PK of simvastatin	• $AUC_{(0-\infty)}$ and C_{max} of simvastatin, simvastatin acid, digoxin, rosuvastatin, acetaminophen, midazolam, and 1'-hydroxymidazolam

Objectives	Endpoints
Secondary	
• To evaluate the effect of orforglipron tablet on the PK of simvastatin in healthy overweight or obese participants	• $AUC_{(0-\infty)}$ and C_{max} of simvastatin and simvastatin acid
• To describe the safety and tolerability of orforglipron in healthy overweight or obese participants	• TEAEs, SAEs, and discontinuations due to AEs
Exploratory	
• To evaluate the effect of multiple oral doses of orforglipron on endogenous OATP1B biomarker in healthy participants.	• AUC(0-24) and C_{max} of biomarker coproporphyrin 1

3. STUDY DESIGN

Study GZPG is an open-label, non-randomized, dose escalation, fixed-sequence DDI study in healthy overweight or obese participants.

The schema in Figure 1 illustrates the study design. PK blood sampling and safety assessments, including vital signs measurements, physical examinations, clinical laboratory tests, ECGs, and AE recording, will be performed.

Screening

All participants will be screened up to 42 days prior to Day 1. Genotyping for BCRP, also known as *ABCG2*, and OATP1B1, also known as *SLCO1B1*, will be performed for each participant at screening. Upon completion of screening, participants with the specified BCRP and OATP1B1 genotype will be assigned to Cohort 1. Participants of any genotype can be assigned to Cohort 2.

Inpatient Period 1

On Day -1, participants will be admitted to the CRU.

Cohort 1

In Cohort 1, participants will receive:

- CCI mg simvastatin on Day 1
- CCI mg digoxin on Day 2
- CCI mg simvastatin and CCI mg sodium bicarbonate* on Day 7
- CCI mg rosuvastatin on Day 8
- CCI mg acetaminophen on Day 10
- CCI mg midazolam on Day 12, and

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- [redacted] mg orforglipron capsule and [redacted] mg acetaminophen, 2 hours ± 10 minutes after orforglipron administration, on Day 14.

On Day 15, participants in Cohort 1 will be discharged from the CRU following supervised self-administration of [redacted] mg orforglipron and completion of study procedures, provided they are deemed medically fit by the investigator or designee.

Cohort 2

In Cohort 2, participants will receive:

- [redacted] mg simvastatin on Day 1
- [redacted] mg digoxin on Day 2
- [redacted] mg simvastatin and [redacted] mg sodium bicarbonate* on Day 7, and
- [redacted] mg orforglipron capsule on Day 9.

On Day 9, participants in Cohort 2 will be discharged from the CRU following supervised self-administration of [redacted] mg orforglipron and completion of study procedures, provided they are deemed medically fit by the investigator or designee.

* Note: the placebo for the orforglipron capsules contains the same [redacted] mg of sodium bicarbonate that the active orforglipron capsules contain, and therefore this 'placebo' will be used as the sodium bicarbonate study intervention on Day 7 of Cohorts 1 and 2.

Outpatient Period and Dose Escalation

Participants will self-administer an orforglipron capsule QD for 12 weeks. Orforglipron capsule doses will be escalated in a stepwise manner for all participants every 14 days, with the following dose levels and formulations administered QD for 14 days as shown:

- for Cohort 1
  - [redacted] mg orforglipron capsule from Days 16 to 27
  - [redacted] mg orforglipron capsule from Days 28 to 41
  - [redacted] mg orforglipron capsule from Days 42 to 55
  - [redacted] mg orforglipron capsule from Days 56 to 69
  - [redacted] mg orforglipron capsule from Days 70 to 83, and
  - [redacted] mg orforglipron capsule from Days 84 to 95.
- for Cohort 2
  - [redacted] mg orforglipron capsule from Days 10 to 22
  - [redacted] mg orforglipron capsule from Days 23 to 36
  - [redacted] mg orforglipron capsule from Days 37 to 50
  - [redacted] mg orforglipron capsule from Days 51 to 64
  - [redacted] mg orforglipron capsule from Days 65 to 78, and
  - [redacted] mg orforglipron capsule from Days 79 to 90.

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Participants will attend an outpatient visit every week to be dispensed orforglipron capsule and for compliance assessment. Participants will be required to complete a diary daily to ensure that they have been compliant in taking orforglipron capsules daily.

Inpatient Period 2

Cohort 1

In Cohort 1, participants will be admitted to the CRU on Day 95 and will continue to receive CCI mg orforglipron capsule QD until Day 110. Participants will also receive:

- CCI mg simvastatin on Day 98
- CCI mg digoxin on Day 99
- CCI mg simvastatin on Day 104, 2 hours ± 10 minutes after orforglipron administration
- CCI mg rosuvastatin on Day 105
- CCI mg acetaminophen on Day 107, 2 hours ± 10 minutes after orforglipron administration
- CCI mg midazolam on Day 109, and
- CCI mg orforglipron tablet and CCI mg simvastatin on Day 111.

On Day 112, participants will be discharged from the CRU following completion of study procedures, provided they are deemed medically fit by the investigator or designee.

Cohort 2

In Cohort 2, participants will be admitted to the CRU on Day 90 and will continue to receive CCI mg orforglipron capsule QD until Day 100. Participants will also receive:

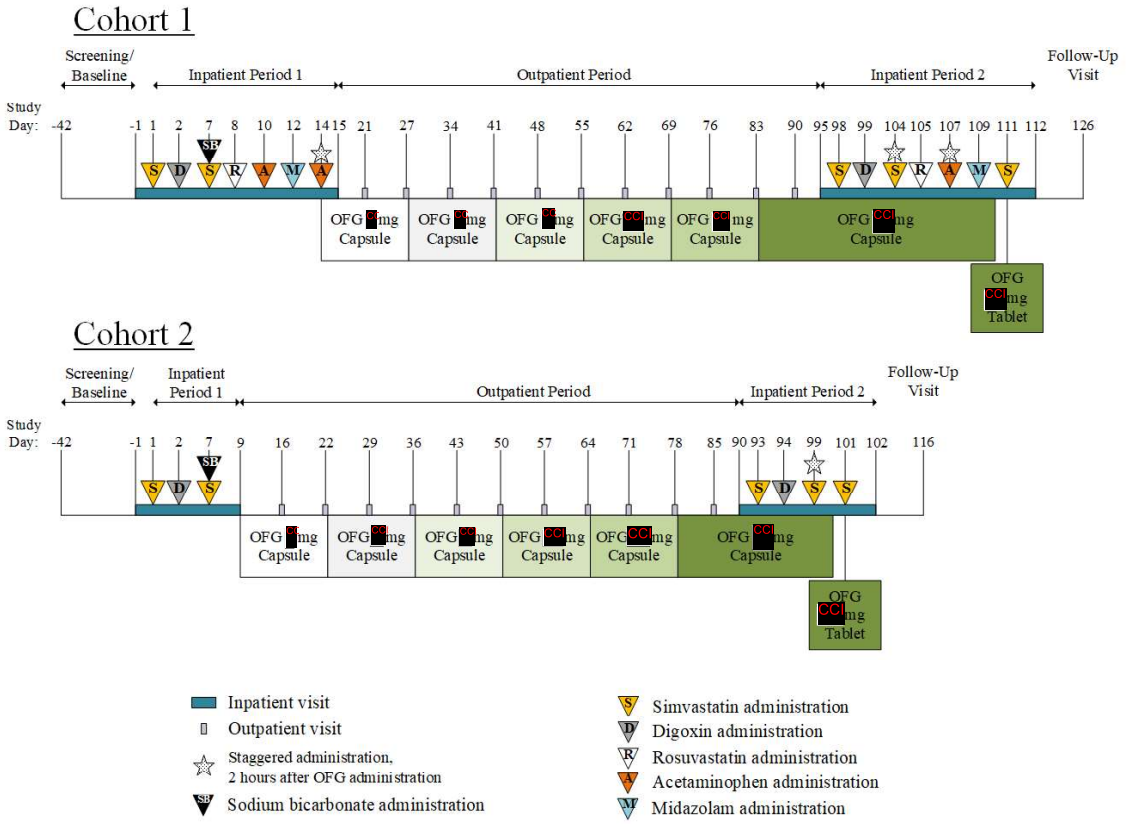
- CCI mg simvastatin on Day 93
- CCI mg digoxin on Day 94
- CCI mg simvastatin on Day 99, 2 hours ± 10 minutes after orforglipron administration, and
- CCI mg orforglipron tablet and CCI mg simvastatin on Day 101.

On Day 102, participants will be discharged from the CRU following completion of study procedures, provided they are deemed medically fit by the investigator or designee.

Follow-up Period

A follow-up visit will be performed 14 ± 3 days after discharge from the CRU.

Figure 1: Study Design



Abbreviations: OFG = orforglipron once daily.

4. BLINDING

This is a non-randomized, open-label study.

5. SAMPLE SIZE JUSTIFICATION

The sample size is customary for Phase 1 studies evaluating PK and is considered sufficient to evaluate the primary objective of this study.

Approximately 50 participants will be enrolled to ensure that at least 32 participants complete the study:

- 30 participants will be enrolled to ensure that at least 20 participants complete Cohort 1, and
- 20 participants will be enrolled to ensure that at least 12 participants complete Cohort 2.

For the DDI drugs used in Cohort 1, assuming a maximum intraparticipant CV of 42.7%, 20 completers are needed to have at least 90% coverage probability to ensure the upper bound of the 90% CI of the geometric mean ratio is within 1.31 of the estimated geometric mean ratios for Cohort 1.

For simvastatin and digoxin, assuming a maximum intraparticipant CV of 23%, 32 completers will provide at least 90% coverage probability to ensure the upper bound of the 90% CI of the geometric mean ratio is within 1.12 of the estimated geometric mean ratios for Cohort 1 and 2 together.

Participants will be genotyped at screening for a BCRP or OATP1B1 impairment genotype. Participants with the specified BCRP and OATP1B1 genotype will be enrolled into Cohort 1. Participants of any genotype can be enrolled into Cohort 2.

If 20 participants with the specified BCRP and OATP1B1 genotype are not identified, additional screening will be required to meet the minimum number required. Participant numbering should be used to identify which dosing group a participant has been allocated to.

Participants who are enrolled but discontinued before Day 23 of the study may be replaced to ensure that enough participants complete the study. If a participant does not complete the entire treatment period of the study, they may be replaced by another participant if the discontinuation occurs before Day 23 of the study.

Participants who are unable to continue with the dose escalation regime before Day 23 of the study will need to be replaced to ensure that enough participants complete the study.

6. STUDY TREATMENTS

The study treatment names, abbreviations, and ordering to be used in the TFLs are presented in Table 1.

Table 1: Presentation of Study Treatments in TFLs

Cohort	Study Treatment	Abbreviation	Order in TFLs
1	[redacted] mg simvastatin (Day 1)	[redacted] mg SIM (D1)	1
	[redacted] mg digoxin (Day 2)	[redacted] mg DIG (D2)	2
	[redacted] mg simvastatin + [redacted] mg sodium bicarbonate (Day 7)	[redacted] mg SIM + [redacted] mg SB (D7)	3
	[redacted] mg rosuvastatin (Day 8)	[redacted] mg ROS (D8)	4
	[redacted] mg acetaminophen (Day 10)	[redacted] mg ACE (D10)	5
	[redacted] mg midazolam (Day 12)	[redacted] mg MID (D12)	6
	[redacted] mg orforglipron capsule + [redacted] mg acetaminophen (Day 14)	[redacted] mg OFG capsule + [redacted] mg ACE (D14)	7
	[redacted] mg orforglipron capsule QD (Days 15 to 27)	[redacted] mg OFG capsule QD (D15 to D27)	8

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Cohort	Study Treatment	Abbreviation	Order in TFLs
	[redacted] mg orforglipron capsule QD (Days 28 to 41)	[redacted] mg OFG capsule QD (D28 to D41)	9
	[redacted] mg orforglipron capsule QD (Days 42 to 55)	[redacted] mg OFG capsule QD (D42 to D55)	10
	[redacted] mg orforglipron capsule QD (Days 56 to 69)	[redacted] mg OFG capsule QD (D56 to D69)	11
	[redacted] mg orforglipron capsule QD (Days 70 to 83)	[redacted] mg OFG capsule QD (D70 to D83)	12
	[redacted] mg orforglipron capsule QD (Days 84 to 97)	[redacted] mg OFG capsule QD (D84 to D97)	13
	[redacted] mg orforglipron capsule + [redacted] mg simvastatin (Day 98)	[redacted] mg OFG capsule + [redacted] mg SIM (D98)	14
	[redacted] mg orforglipron capsule + [redacted] mg digoxin (Day 99)	[redacted] mg OFG capsule + [redacted] mg DIG (D99)	15
	[redacted] mg orforglipron capsule QD (Days 100 to 103)	[redacted] mg OFG capsule QD (D100 to D103)	16
	[redacted] mg orforglipron capsule + [redacted] mg simvastatin (Day 104)	[redacted] mg OFG capsule + [redacted] mg SIM (D104)	17
	[redacted] mg orforglipron capsule + [redacted] mg rosuvastatin (Day 105)	[redacted] mg OFG capsule + [redacted] mg ROS (D105)	18
	[redacted] mg orforglipron capsule (Day 106)	[redacted] mg OFG capsule (D106)	19
	[redacted] mg orforglipron capsule + [redacted] mg acetaminophen (Day 107)	[redacted] mg OFG capsule + [redacted] mg ACE (D107)	20
	[redacted] mg orforglipron capsule (Day 108)	[redacted] mg OFG capsule (D108)	21
	[redacted] mg orforglipron capsule + [redacted] mg midazolam (Day 109)	[redacted] mg OFG capsule + [redacted] mg MID (D109)	22
	[redacted] mg orforglipron capsule (Day 110)	[redacted] mg OFG capsule (D110)	23
	[redacted] mg orforglipron tablet + [redacted] mg simvastatin (Day 111)	[redacted] mg OFG tablet + [redacted] mg SIM (D111)	24
2	[redacted] mg simvastatin (Day 1)	[redacted] mg SIM (D1)	1
	[redacted] mg digoxin (Day 2)	[redacted] mg DIG (D2)	2
	[redacted] mg simvastatin + [redacted] mg sodium bicarbonate (Day 7)	[redacted] mg SIM + [redacted] mg SB (D7)	3
	[redacted] mg orforglipron capsule QD (Days 9 to 22)	[redacted] mg OFG capsule QD (D9 to D22)	4
	[redacted] mg orforglipron capsule QD (Days 23 to 36)	[redacted] mg OFG capsule QD (D23 to D36)	5

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Cohort	Study Treatment	Abbreviation	Order in TFLs
	[redacted] mg orforglipron capsule QD (Days 37 to 50)	[redacted] mg OFG capsule QD (D37 to D50)	6
	[redacted] mg orforglipron capsule QD (Days 51 to 64)	[redacted] mg OFG capsule QD (D51 to D64)	7
	[redacted] mg orforglipron capsule QD (Days 65 to 78)	[redacted] mg OFG capsule QD (D65 to D78)	8
	[redacted] mg orforglipron capsule QD (Days 79 to 92)	[redacted] mg OFG capsule QD (D79 to D92)	9
	[redacted] mg orforglipron capsule + [redacted] mg simvastatin (Day 93)	[redacted] mg OFG capsule + [redacted] mg SIM (D93)	10
	[redacted] mg orforglipron capsule + [redacted] mg digoxin (Day 94)	[redacted] mg OFG capsule + [redacted] mg DIG (D94)	11
	[redacted] mg orforglipron capsule QD (Days 95 to 98)	[redacted] mg OFG capsule QD (D95 to D98)	12
	[redacted] mg orforglipron capsule + [redacted] mg simvastatin (Day 99)	[redacted] mg OFG capsule + [redacted] mg SIM (D99)	13
	[redacted] mg orforglipron capsule (Day 100)	[redacted] mg OFG capsule (D100)	14
	[redacted] mg orforglipron tablet + [redacted] mg simvastatin (Day 101)	[redacted] mg OFG tablet + [redacted] mg SIM (D101)	15

Abbreviations: ACE = acetaminophen; D = day; DIG = digoxin; MID = midazolam; OFG = orforglipron; QD = once daily; ROS = rosuvastatin; SB = sodium bicarbonate; SIM = simvastatin;

All TFLs will be based on actual treatments and will be presented by cohort separately.

The study treatment sequence names, abbreviations, and ordering to be used in the TFLs are presented in Table 2.

Table 2: Presentation of Study Treatment Sequences in TFLs

Cohort	Study Treatment Sequence	Abbreviation	Order in TFLs
1	[redacted] mg simvastatin (Day 1) / [redacted] mg digoxin (Day 2) / [redacted] mg simvastatin + [redacted] mg sodium bicarbonate (Day 7) / [redacted] mg rosuvastatin (Day 8) / [redacted] mg acetaminophen (Day 10) / [redacted] mg midazolam (Day 12) / [redacted] mg orforglipron capsule + [redacted] mg acetaminophen (Day 14) / [redacted] mg orforglipron capsule QD (Days 15 to 27) / [redacted] mg orforglipron capsule QD (Days 28 to 41) / [redacted] mg orforglipron capsule QD (Days 42 to 55) / [redacted] mg orforglipron capsule QD (Days 56 to	[redacted] mg SIM (D1) / [redacted] mg DIG (D2) / [redacted] mg SIM + [redacted] mg SB (D7) / [redacted] mg ROS (D8) / [redacted] mg ACE (D10) / [redacted] mg MID (D12) / [redacted] mg OFG capsule + [redacted] mg ACE (D14) / [redacted] mg OFG capsule QD (D15 to D27) / [redacted] mg OFG capsule QD (D28 to D41) / [redacted] mg OFG capsule QD (D42 to D55) / [redacted] mg OFG capsule QD (D56 to D69) / [redacted] mg OFG capsule QD (D70 to D83) / [redacted] mg OFG capsule QD (D84 to D97) / [redacted] mg OFG capsule + [redacted] mg SIM (D98) / [redacted] mg OFG capsule +	1

Cohort	Study Treatment Sequence	Abbreviation	Order in TFLs
2	[redacted] mg simvastatin (Day 1) / [redacted] mg digoxin (Day 2) / [redacted] mg simvastatin + [redacted] mg sodium bicarbonate (Day 7) / [redacted] mg orforglipron capsule QD (Days 9 to 22) / [redacted] mg orforglipron capsule QD (Days 23 to 36) / [redacted] mg orforglipron capsule QD (Days 37 to 50) / [redacted] mg orforglipron capsule QD (Days 51 to 64) / [redacted] mg orforglipron capsule QD (Days 65 to 78) / [redacted] mg orforglipron capsule QD (Days 79 to 92) / [redacted] mg orforglipron capsule + [redacted] mg simvastatin (Day 93) / [redacted] mg orforglipron capsule + [redacted] mg digoxin (Day 94) / [redacted] mg orforglipron capsule QD (Days 95 to 98) / [redacted] mg orforglipron capsule + [redacted] mg simvastatin (Day 99) / [redacted] mg orforglipron capsule (Day 100) / [redacted] mg orforglipron tablet + [redacted] mg simvastatin (Day 101)	[redacted] mg SIM (D1) / [redacted] mg DIG (D2) / [redacted] mg SIM + [redacted] mg SB (D7) / [redacted] mg OFG capsule QD (D9 to D22) / [redacted] mg OFG capsule QD (D23 to D36) / [redacted] mg OFG capsule QD (D37 to D50) / [redacted] mg OFG capsule QD (D51 to D64) / [redacted] mg OFG capsule QD (D65 to D78) / [redacted] mg OFG capsule QD (D79 to D92) / [redacted] mg OFG capsule + [redacted] mg SIM (D93) / [redacted] mg OFG capsule + [redacted] mg DIG (D94) / [redacted] mg OFG capsule QD (D95 to D98) / [redacted] mg OFG capsule + [redacted] mg SIM (D99) / [redacted] mg OFG capsule (D100) / [redacted] mg OFG tablet + [redacted] mg SIM (D101)	2
	[redacted] mg orforglipron capsule QD (Days 70 to 83) / [redacted] mg orforglipron capsule QD (Days 84 to 97) / [redacted] mg orforglipron capsule + [redacted] mg simvastatin (Day 98) / [redacted] mg orforglipron capsule + [redacted] mg digoxin (Day 99) / [redacted] mg orforglipron capsule QD (Days 100 to 103) / [redacted] mg orforglipron capsule + [redacted] mg simvastatin (Day 104) / [redacted] mg orforglipron capsule + [redacted] mg rosuvastatin (Day 105) / [redacted] mg orforglipron capsule (Day 106) / [redacted] mg orforglipron capsule + [redacted] mg acetaminophen (Day 107) / [redacted] mg orforglipron capsule (Day 108) / [redacted] mg orforglipron capsule + [redacted] mg midazolam (Day 109) / [redacted] mg orforglipron capsule (Day 110) / [redacted] mg orforglipron tablet + [redacted] mg simvastatin (Day 111)	[redacted] mg DIG (D99) / [redacted] mg OFG capsule QD (D100 to D103) / [redacted] mg OFG capsule + [redacted] mg SIM (D104) / [redacted] mg OFG capsule + [redacted] mg ROS (D105) / [redacted] mg OFG capsule (D106) / [redacted] mg OFG capsule + [redacted] mg ACE (D107) / [redacted] mg OFG capsule (D108) / [redacted] mg OFG capsule + [redacted] mg MID (D109) / [redacted] mg OFG capsule (D110) / [redacted] mg OFG tablet + [redacted] mg SIM (D111)	

Abbreviations: ACE = acetaminophen; D = day; DIG = digoxin; MID = midazolam; OFG = orforglipron; QD = once daily; ROS = rosuvastatin; SB = sodium bicarbonate; SIM = simvastatin;

The summaries will be based on planned treatment sequences and listings will be based on actual treatment sequences (e.g., if participant was assigned to receive 'ABC' and was dosed with A in Period 1 and discontinued before start of Period 2, they would be summarized under 'ABC' treatment sequence and listed under 'A--' treatment sequence).

The '(Days X to Y)' part of the treatment and will be kept unchanged even if a participant misses a dose on 1 or more days. Exact dosing regimen details including days on which each dose was received will be presented in the treatment administration listing only.

7. DEFINITIONS OF POPULATIONS

Any protocol deviations will be considered prior to database lock for their importance and taken into consideration when assigning participants to populations.

7.1. Enrolled

The "Enrolled" population will consist of all participants assigned to study intervention. Participants will be analyzed according to the intervention they actually received.

7.2. Safety Population

The "Safety" population will consist of all participants who are exposed to at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.

7.3. Pharmacokinetic Population

The "Pharmacokinetic" population will consist of all enrolled participants who receive at least 1 dose of study intervention and have evaluable PK data.

7.4. Exploratory Biomarker Population

In the event of exploratory biomarker analysis in this study, the "exploratory biomarker" population will consist of all enrolled participants in Cohort 1 who receive at least 1 dose of study intervention and have at least 1 period of evaluable exploratory biomarker data.

8. STATISTICAL METHODOLOGY

8.1. General

Listings will be provided for all data captured in the database. Listings will include all participants assigned to the Enrolled population and include data up to the point of study completion or discontinuation. Participants are generally considered to have completed the study if they complete the scheduled follow-up visit (rather than early discontinuation visit). Any participant who discontinues the study will be identified accordingly in the listings. Summaries and statistical analyses will include the participants assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if a new version is issued during the study).

ADaM datasets will be prepared using CDISC ADaM Version 2.1 (or higher if a new version is issued during the study) and CDISC ADaM Implementation Guide Version 1.1 (or higher

if a new version is issued during the study). Pinnacle 21 Community Validator Version 4.0.2 (or higher if a new version is issued during the study) will be utilized to ensure compliance with CDISC standards.

For all statistical analyses, the hypothesis testing will be 2-sided and carried out on 0.1 significance level, unless specifically stated otherwise.

Caution should be used when interpreting results from the statistical analyses conducted in this study because the sample size is not based on power calculations.

Where reference is made to 'valid' data, this refers to non-missing data which meet the predetermined criteria (e.g., are not flagged for exclusion).

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics, statistical analyses, baseline derivation, changes from baseline and any parameter derivations.

All figures will be produced on linear-linear or discrete-linear scales, as applicable, unless specifically stated otherwise.

8.1.1. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- If the number of participants with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.
- In general, as early discontinuation data are not associated with any scheduled time point, they will be excluded from all calculations. Exceptions may be made where justified.

For categorical data the following rules will be applied:

- For ordered categorical data (e.g., AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category.
- For non-ordered categorical data (e.g., race), only those categories for which there is at least 1 participant represented will be included, unless specifically stated otherwise.
- Missing values will not be imputed, unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

8.1.2. Unscheduled Readings

Any value recorded in addition to the original value will be defined as an unscheduled value. As unscheduled values are not associated with any scheduled time point, they will be excluded from all calculations, with the exception of the baseline derivation (see Section 8.1.3).

8.1.3. Definitions of Baseline and Change from Baseline

The baseline will be defined as the last scheduled value prior to the first dose. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to the first dose.

Individual changes from baseline will be calculated by subtracting the individual participant's baseline value from the value at the postdose time point.

The summary statistics for change from baseline will be derived from individual participants' values (e.g., mean change from baseline will be the mean of the individual changes from baseline for all participants, rather than difference between the mean value at the postdose time point and mean value at baseline).

See Section 8.1.2 for more detail on handling unscheduled readings in the calculations.

8.2. Participant Disposition and Population Assignment

Participant disposition and population assignment will be listed.

A summary table by treatment will be provided, based on the safety population.

8.3. Screening Demographics

The screening demographics including age, sex, race, ethnicity, country of enrolment, site ID, height, body weight, BMI, and genotypes (BCRP and OATP) will be listed.

A summary table by treatment will be provided, based on the safety population.

8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to the first dose. Concomitant medication will be defined as medication that starts during or after the first dose or starts but does not end prior to the first dose.

Prior and concomitant medications will be coded using the WHODrug Global, Format B3, Version September 2023 (or later if a new version is issued during the study; see the DMP for more details). Prior and concomitant medications will be listed.

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

Noncompartmental methods applied with a validated software program (Phoenix WinNonlin Version 8.3.5 or later) to the plasma concentrations of orforglipron, simvastatin, simvastatin acid, digoxin, rosuvastatin, acetaminophen, midazolam, 1-hydroxy-midazolam and, in the event of exploratory biomarker analysis in this study will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	ng.h/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	Percentage of AUC(0-∞) extrapolated
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration[a]
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration[a]
V_{SS}/F	L	apparent volume of distribution at steady state after extra-vascular administration[a]

[a] for orforglipron, simvastatin, digoxin, rosuvastatin, acetaminophen, and midazolam only.

Additional PK parameters may be calculated, or additional analysis may be performed, as appropriate. In the event of exploratory biomarker analysis in this study, plasma concentrations of exploratory biomarker(s) may be listed and summarized, using standard descriptive statistics. If applicable, PK parameters may be calculated for exploratory biomarkers, and PK parameters may be summarized using descriptive statistics.

The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final CSR.

Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus pre-dose sampling times which will be set to zero. For

non-bolus, multiple dose profiles, the pre-dose time will be set to zero unless a time deviation falls outside of the protocol blood collection time window which is considered to impact PK parameter derivation.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the LLOQ, with at least 1 of these concentrations following C_{max}.

- AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- $t_{1/2}$ will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each participant will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{1/2}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{1/2}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on predicted quantifiable drug concentration (C_{last}) will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported BLQ. Plasma concentrations reported as BLQ will be set to a value of zero when all of the following conditions are met:

    - The compound is non-endogenous.

    - The samples are from the initial dose period for a participant or from a subsequent dose period following a suitable wash-out period.

    - The time points occur before the first quantifiable concentration.

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- All other BQL concentrations that do not meet the above criteria will be set to missing.

- Also, where 2 or more consecutive concentrations are BLQ towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

For multiple-dosing data, when pre-dose concentrations are missing, the value to be substituted will be minimum observed drug concentration (C_{min}) for the dosing interval.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.

- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.

- The average concentration profiles will be graphed using arithmetic average concentrations.

- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.

- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.

- Concentrations excluded from the mean calculation will be documented in the final study report.

- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

Treatment of Outliers during PK Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure

describes the methodology for identifying an individual value as an outlier for potential exclusion but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.
- For PK profiles during multiple dosing, the concentration of the pre-dose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.
- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated, and results reported with and without the suspected datum.

Data between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.
2. If $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:
    a. Transform all values in the calculation to the logarithmic domain.
    b. Find the most extreme value from the arithmetic mean of the log-transformed values and exclude that value from the dataset.
    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.
    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.
    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only 1 suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final CSR. Approval of the final CSR will connote approval of the exclusion.

8.5.2. Presentation of Pharmacokinetic Data

All PK parameters will be listed.

Arithmetic mean (+ SD) figures, overlaying individual figures, and individual figures by treatment and time postdose will be provided for plasma PK concentrations. All figures will be produced on both linear-linear and linear-logarithmic scales, with the exception of figures across all days, which will be produced on the linear-linear scale only. The +SD bars will only be displayed on the linear-linear scale.

Summary tables by treatment will be provided for all PK parameters. Separate summary tables by treatment and time interval will be provided for excretion parameters and cumulative excretion parameters.

A participant may be excluded from the PK summary statistics and statistical analysis if the participant has an AE of vomiting that occurs at or before 2 times the median t_{max}.

8.5.3. Pharmacokinetic Statistical Methodology

The following comparisons will be made:

Endpoint	DDI	Analyte	Reference Treatment	Test Treatment
Primary	Acetaminophen – OFG capsule	Acetaminophen	CCI mg ACE (C1 D10)	CCI mg OFG capsule + CCI mg ACE (C1 D14)
Primary	Acetaminophen – OFG capsule	Acetaminophen	CCI mg ACE (C1 D10)	CCI mg OFG capsule + CCI mg ACE (C1 D107)
Primary	Digoxin – OFG capsule	Digoxin	CCI mg DIG (C1 D2 and C2 D2 combined)	CCI mg OGF capsule + CCI mg DIG (C1 D99 and C2 D94 combined)
Primary	Rosuvastatin – OFG capsule	Rosuvastatin	CCI mg ROS (C1 D8)	CCI mg OFG capsule + CCI mg ROS (C1 D105)
Primary	Midazolam – OFG capsule	Midazolam	CCI mg MID (C1 D12)	CCI mg OFG capsule + CCI mg MID (C1 D109)
Primary	Midazolam – OFG capsule	1'-hydroxymidazolam	CCI mg MID (C1 D12)	CCI mg OFG capsule + CCI mg MID (C1 D109)

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Endpoint	DDI	Analyte	Reference Treatment	Test Treatment
Primary	Simvastatin – OFG capsule	Simvastatin	CCI mg SIM (C1 D1 and C2 D1 combined)	CCI mg OFG capsule + CCI mg SIM (C1 D98 and C2 D93 combined)
Primary	Simvastatin Acid – OFG capsule	Simvastatin Acid	CCI mg SIM (C1 D1 and C2 D1 combined)	CCI mg OFG capsule + CCI mg SIM (C1 D98 and C2 D93 combined)
Primary	Simvastatin – OFG capsule	Simvastatin	CCI mg SIM (C1 D1 and C2 D1 combined)	CCI mg OFG capsule + CCI mg SIM (C1 D104 and C2 D99 combined)
Primary	Simvastatin Acid – OFG capsule	Simvastatin Acid	CCI mg SIM (C1 D1 and C2 D1 combined)	CCI mg OFG capsule + CCI mg SIM (C1 D104 and C2 D99 combined)
Primary	Simvastatin + OFG staggered – Simvastatin + OFG unstaggered	Simvastatin	CCI mg OFG capsule + CCI mg SIM (C1 D98 and C2 D93 combined)	CCI mg OFG capsule + CCI mg SIM (C1 D104 and C2 D99 combined)
Primary	Simvastatin Acid + OGF staggered – Simvastatin Acid + OFG unstaggered	Simvastatin Acid	CCI mg OFG capsule + CCI mg SIM (C1 D98 and C2 D93 combined)	CCI mg OFG capsule + CCI mg SIM (C1 D104 and C2 D99 combined)
Primary	Simvastatin – Sodium Bicarbonate	Simvastatin	CCI mg SIM (C1 D1 and C2 D1 combined)	CCI mg SIM + CCI mg SB (C1 D7 and C2 D7 combined)
Primary	Simvastatin Acid – Sodium Bicarbonate	Simvastatin Acid	CCI mg SIM (C1 D1 and C2 D1 combined)	CCI mg SIM + CCI mg SB (C1 D7 and C2 D7 combined)
Primary	Simvastatin + Sodium Bicarbonate – Simvastatin + OFG capsule	Simvastatin	CCI mg SIM + CCI mg SB (C1 D7 and C2 D7 combined)	CCI mg OFG capsule + CCI mg SIM (C1 D98 and C2 D93 combined)
Primary	Simvastatin Acid + Sodium Bicarbonate – Simvastatin Acid + OFG capsule	Simvastatin Acid	CCI mg SIM + CCI mg SB (C1 D7 and C2 D7 combined)	CCI mg OFG capsule + CCI mg SIM (C1 D98 and C2 D93 combined)
Secondary	Simvastatin – OFG tablet	Simvastatin	CCI mg SIM (C1 D1 and C2 D1 combined)	CCI mg OFG tablet + CCI mg SIM (C1 D111 and C2 D101 combined)

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Endpoint	DDI	Analyte	Reference Treatment	Test Treatment
Secondary	Simvastatin Acid – OFG tablet	Simvastatin Acid	[redacted] mg SIM (C1 D1 and C2 D1 combined)	[redacted] mg OFG tablet + [redacted] mg SIM (C1 D111 and C2 D101 combined)

Abbreviations: ACE = acetaminophen; C = cohort; D = day; DDI = drug-drug interaction; DIG = digoxin; MID = midazolam; OFG = orforglipron; QD = once daily; ROS = rosuvastatin; SB = sodium bicarbonate; SIM = simvastatin;

In the event of exploratory biomarker analysis in this study, a further exploratory comparison will be made:

Endpoint	DDI	Analyte	Reference Treatment	Test Treatment
Exploratory	CP1 – OFG capsule	CP1	CPI measured after dosing [redacted] mg ROS (C1 D8)	CPI measured after dosing [redacted] mg OFG capsule + [redacted] mg ROS (C1 D105)

Abbreviations: C = cohort; D = day; DDI = drug-drug interaction; OFG = orforglipron; QD = once daily; ROS = rosuvastatin;

The log-transformed[4] AUC(0-∞), AUC(0-t_{last}), and C_{max} will be analyzed using a linear mixed-effect model.[5] The model will include actual treatment as a fixed effect, and participant as a random effect.

For each PK parameter separately, the LSM for each treatment, difference in LSMs between the test and reference treatments, and corresponding 90% CI will be calculated; these values will then be back-transformed to give the GLSM, ratio of GLSMs, and corresponding 90% CI.

Additionally, the pooled estimate (across treatments) of the within-participant CV will be calculated, and residual plots will be produced to assess the adequacy of the model(s) fitted.

The parameter t_{max} will be analyzed non-parametrically. Estimates of the median of the within-participant differences and approximate 90% CI will be calculated using the Hahn and Meeker method[6]. The p-value from the Wilcoxon signed-rank[7] test will also be calculated.

Examples of the SAS code that will be used are as follows:

Mixed Model Analysis

```
proc mixed data = <data in>;
  by parcat1n parcat1 pkday paramn param;
  class trtan usubjid;
  model lpk = trtan / cl residual ddfm = kr2;
  lsmeans trtan / cl pdiff = control('1') alpha = 0.1;
  random intercept / subject = usubjid;
  ods output lsmeans = <data out>;
  ods output diffs = <data out>;
  ods output covparms = <data out>;
```


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```
run;
```

Wilcoxon Signed-rank Test

```
proc univariate data = <data in> cipctldf(alpha = 0.1);
  by parcat1n parcat1 pkday paramn param;
  var ref test dif;
  ods output quantiles = <data out>;
  ods output testsforlocation = <data out>;
run;
```

8.6. Safety and Tolerability Assessments

8.6.1. Adverse Events

All AEs will be coded using the MedDRA Version 26.1 (or higher if a new version is issued during the study; see the DMP for more details).

A pre-existing condition is defined as a condition that starts before the participant has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A TEAE will be defined as an AE that starts during or after the first dose or starts prior to the first dose and increases in severity after the first dose.

A treatment-related TEAE will be defined as a TEAE that is related to the study treatment, as determined by the investigator.

All AEs, SAEs, and AEs of special interest will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of the last associated dose for TEAEs only. Where the last associated dose is referring to the last dose received prior to the start of a TEAE.

The frequency of participants with TEAEs and the number of TEAEs will be summarized for the following categories:

- TEAEs (overall, serious, leading to discontinuation) by treatment
- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation) by treatment
- Treatment-related TEAEs by severity and treatment

The frequency of participants will be summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class, preferred term, and treatment
- Preferred term and treatment

For the AE data the following rules will apply:

- For the derivation of treatment-emergent status (applicable to all AEs): If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started before the first dose.

- For the derivation of treatment-related status (applicable to TEAEs only): If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.

- For the derivation of onset time (applicable to TEAEs only): If the start date/time of a TEAE is missing, onset time will not be calculated. If the start date/time of a TEAE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (e.g., if the date/time of the last associated dose is 01MAY2019/08:00 and recorded start date/time of a TEAE is 03MAY2019, then the minimum possible onset time will be calculated by assuming a TEAE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing). If the start date of a TEAE is the same as the date of the last associated dose but the start time of a TEAE is missing, an onset time will be presented as '≥00:00:01'. Any clock changes will be accounted for in the derivation.

- For the derivation of duration (applicable to all AEs): If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (e.g., if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming an AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing). Any clock changes will be accounted for in the derivation.

- For the calculation of TEAE summary statistics: If the severity of a TEAE is missing, that TEAE will be counted under the 'missing' category.

- For the calculation of TEAE summary statistics: Where changes in severity are recorded in the eCRF, each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables.

8.6.2. Glucose Monitoring and Hypoglycemia

During the study, plasma glucose concentrations will be monitored for safety assessments. Glucose data will be listed and summarized by treatment together with changes from baseline.

Hypoglycemic events will be appropriately recorded in the eCRF. In the case of a hypoglycemic event, the actual glucose value, if measured, will be recorded in the eCRF, together with any treatments administered. Each category of hypoglycemic events (defined below) will be listed and summarized by treatment. Hypoglycemia is defined as follows:

Level 1 hypoglycemia:

Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L): Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

Level 2 hypoglycemia:

Glucose <54 mg/dL (3.0 mmol/L): Level 2 hypoglycemia is also referred to as documented or blood glucose confirmed hypoglycemia with glucose less than 54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

Level 3 hypoglycemia:

Severe hypoglycemia: A severe event characterized by altered mental or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

Nocturnal hypoglycemia:

Nocturnal hypoglycemia is a hypoglycemia event, including severe hypoglycemia, that occurs at night and presumably during sleep.

8.6.3. Clinical Laboratory Parameters

All clinical laboratory parameters, and their changes from baseline, will be listed, as applicable; any value outside the clinical reference range will be flagged. Separate listings will be provided for any parameter for which there is any individual participant value outside the respective clinical reference range.

Summary tables by treatment and time point will be provided for clinical chemistry, and hematology parameters, and their changes from baseline, as applicable.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the calculation of summary statistics, <x and ≤x values will be set to 0.5 × x, whereas >x and ≥x values will be set to 1.1 × x.

8.6.4. Vital Signs Parameters

All vital signs parameters, and their changes from baseline, will be listed.

Summary tables by treatment and time point will be provided for all vital signs parameters, and their changes from baseline. Figures of mean vital signs and mean changes from baseline will be presented over time by treatment.

8.6.5. 12-lead ECG Parameters

ECGs will be performed for safety monitoring purposes only and will not be presented. Any clinically significant findings from ECGs will be reported as an AE.

8.6.6. Hepatic Monitoring

If a participant experiences elevated laboratory parameters, as detailed in Section 8.3.5 of the protocol, additional tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

The participants' liver disease history and associated person liver disease history data will be listed. Use of acetaminophen during the study, which has potential for hepatotoxicity, will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography scan, and biopsy assessments will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by treatment and listed. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data will be listed. Values outside the reference ranges will be flagged on the individual participant data listings.

8.6.7. Hypersensitivity Reactions

For all drug hypersensitivity reactions that occur, additional follow-up data will be collected to assess the participant's medical history, alternative causes, and symptoms.

These data will be listed.

8.6.8. C-SSRS

The C-SSRS data will be listed and summarized for individual participants.

8.6.9. PHQ-9

The PHQ-9 data will be listed and summarized for individual participants.

8.6.10. Other Assessments

All other safety and tolerability assessments not detailed in the above sections will be listed only.

8.6.11. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9. INTERIM ANALYSES

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

10. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

There were no significant changes from the protocol-specified analyses.

11. REFERENCES

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Appendices

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.
Final v2.0	09 May 2024	Updated treatment names, added treatment sequences, added CP1 analyses, and small other updates from protocol amendments (b) and (c).

NA = not applicable

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Approval	PPD PKPDPMx 09-May-2024 14:36:08 GMT+0000

Approval	PPD Statistician 13-May-2024 09:11:42 GMT+0000

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