Statistical Analysis Plan J2A-MC-GZPI(v3.0)

A Multiple-Dose Study to Investigate the Bioequivalence of Orforglipron (LY3502970) Capsules and Orforglipron Tablets in Participants with Obesity or Overweight who are Otherwise Healthy.

NCT06440980

Approval Date: 10 Mar 2025

Statistical Analysis Plan

A Multiple-Dose Study to Investigate the Bioequivalence of Orforglipron (LY3502970) Capsules and Orforglipron Tablets in Participants with Obesity or Overweight who are Otherwise Healthy.

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LIST OF ABBREVIATIONS

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

ADaM	Analysis Data Model
AE	adverse event
AUC	area under the concentration versus time curve
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
$AUC_{(0-\tau),ss}$	area under the concentration versus time curve during one dosing interval at steady state
$AUC_{(0-\tau)}$	area under the concentration versus time curve during one dosing interval
BE	bioequivalence
BLQ	below the limit of quantification
$C_{av,ss}$	average concentration under steady state conditions during multiple dosing
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL_{ss}/F	apparent total body clearance of drug calculated after extra-vascular administration at steady state
C_{last}	last quantifiable drug concentration
C_{max}	maximum observed drug concentration during a dosing interval
$C_{min,ss}$	minimum observed drug concentration during a dosing interval at steady state
CRU	clinical research unit
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
DMP	data management plan
ECG	electrocardiogram
GLSM	geometric least squares mean
GMR	geometric mean ratio
GZGN	J2A-MC-GZGN
LLOQ	lower limit of quantification
LSM	least squares mean
PHQ-9	patient health quesionaire-9
PK	pharmacokinetic

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

1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version (c) dated 17 July 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 (eg, objectives, study design) is given to help the reader's interpretation.

Version 1 of 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*.[1,2,3]

The document history is presented in Appendix 1.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the bioequivalence of orforglipron tablets and capsules at capsule dose levels of CCI [redacted] mg (Part B).	• Steady-state $AUC_{(0-\tau)}$ and C_{max}
Secondary	
• To evaluate the bioequivalence of orforglipron tablets and capsules at	• Steady-state $AUC_{(0-\tau)}$ and C_{max}

capsule dose levels of CCI mg (Part B). • To assess the safety and tolerability of orforglipron tablets and capsules in participants with obesity or overweight who are otherwise healthy (Parts A and B)	Number and incidence of • SAEs • TEAEs
Exploratory	
• To evaluate the relative bioavailability of orforglipron tablets and capsules at capsule dose levels of CCI mg (Part A).	• Steady-state $AUC_{(0-\tau)}$ and C_{max}

Abbreviations: $AUC_{(0-\tau)}$ = area under the concentration versus time curve from time 0 to τ hour time point (τ is 24 hours for QD dosing); C_{max} = maximum observed drug concentration; QD = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

3. STUDY DESIGN

3.1. Overall

Study GZPI is an open-label, randomized, dose-escalating, multiple-dose, Phase 1 study to investigate the BE of tablets and capsules of orforglipron in participants with obesity or overweight who are otherwise healthy.

Study GZPI is planned to have 2 parts.

- Part A (pilot relative bioavailability study) will have 4 sequences for each of the 2 cohorts to assess 3 tablet dose strengths corresponding to each capsule dose level. The PK data from Part A will be reviewed to select a single tablet dose strength for each capsule dose level for Part B of the study.
- Part B (BE study) will have 3 sequences for each cohort, to accommodate replicate sampling of capsule PK.

Each part includes 2 cohorts. Each cohort will evaluate 3 capsule dose levels (Cohort 1: CCI and Cohort 2: CCI mg). Participants will receive QD oral doses of orforglipron as capsules and tablets. In Cohort 1 from both Parts A and B, the participants will be dosed in the CRU. In Cohort 2 from both Parts A and B, the participants will have a dose escalation at home followed by in-CRU dosing.

Based on the results from Study GZGN, it is anticipated that orforglipron tablets will result in higher exposure compared to the capsule when dosed at the same molar dose. To demonstrate

BE in Part B, tablets will be administered at an adjusted dose compared to the capsules. BE will be evaluated in a pairwise manner between a given capsule dose level and 1 selected tablet dose strength chosen from 3 possible options in Part A. The 3 tablet dose strengths are designated as

- "Tablet N," corresponding to the nominal tablet dose strength
- "Tablet N–," corresponding to slightly lower tablet dose strength than the nominal tablet dose strength, and
- "Tablet N+," corresponding to a slightly higher tablet dose strength than the nominal tablet dose strength.

The tablet dose strengths (N, N-, N+) being administered in the study were determined using statistical modeling of the exposure data at multiple tablet and capsule doses from Study GZGN and drug product dissolution data. The analysis predicts the nominal tablet dose strength that results in the same $AUC_{(0-24)}$ as a given capsule dose level. This analysis was also performed on C_{max} and resulted in similar nominal tablet dose strength. There is uncertainty in the determination of the tablet dose strength from the model arising from multiple sources, including

- the high intersubject variability at a given dose
- variability among doses over which the model is fit
- variability in dissolution results, and
- the uncertainty in the accuracy of the model extrapolation to predict doses that were not administered in Study GZGN.

In addition to the uncertainty associated with the model, the tablets administered in Study GZPI will be slightly different formulation compared to those in Study GZGN and scaled up to be representative of commercial tablets. To address this uncertainty, 2 additional tablet dose strengths (N-, N+) will be administered in Part A of the study.

These dose strengths (N, N-, N+) are anticipated to cover an adequate range of potential true tablet dose strength for each capsule dose level.

BE between the capsule and the selected tablet dose strengths in Part B will be assessed for all 6 capsule dose levels: CCI [redacted] mg. The design of each study part and the study visits are described below.

3.1.1. Part A: Pilot Study

Screening and baseline

Participant eligibility will be determined at a screening visit up to 42 days prior to admission to the CRU.

After completing all screening assessments, eligible participants will be admitted to the CRU on Day -1 for baseline procedures.

For Cohort 2A orforglipron at-home dosing, capsules will be dispensed on Day 1 for self-administration at home. Self-administration training will be conducted (that is, on Day 1, self-administration of the study drug will occur under CRU supervision), and a participant diary will be provided, to track the at-home dosing compliance and will be discharged on Day 1 of Period 1.

Treatment period

Cohort 1A

Participants will be randomly assigned to 1 of 4 (1:1:1:1) sequences. Accordingly, they will receive QD oral doses of orforglipron tablets and capsules in a crossover manner, in the sequence as indicated in the schema in Figure 1. The dose strengths are presented in Table 1.

Table 1: Cohort 1A dose strengths

Capsule (mg)	Tablet N– (mg)	Tablet N (mg)	Tablet N+ (mg)
CCI			

- Each participant will receive study medication from Periods 1 to 12 (7 days each).
- Participants may be allowed to leave the CRU after completing the safety assessments on Day 8 of Period 12, or later at the investigator's discretion.

Cohort 2A

- Participants will be admitted to the CRU on Day -1. On Day 1, participants will be discharged after they receive training on in-home dosing and documentation of daily dosing in their diaries (that is, on Day 1, self-administration of the study drug and documentation in diaries will occur under CRU supervision).
- Participants will self-administer a QD oral dose of orforglipron capsule (CCI mg) at home for Periods 1 to 6 (7 days per period).
- On Day 7 of Periods 1 to 5, participants will come to the CRU for an outpatient visit. During the outpatient visit, participants will be assessed for dosing compliance and will receive a re-supply of study medication per schedule.

- Participants will be admitted to the CRU for an inpatient stay on Day 7 of Period 6 and will be randomly assigned to 1 of 4 (1:1:1:1) sequences for Periods 7 to 18. Accordingly, they will receive QD oral doses of orforglipron tablet or capsule. The dose strengths are presented in Table 2.

Table 2: Cohort 2A dose strengths

Capsule (mg)	Tablet N– (mg)	Tablet N (mg)	Tablet N+ (mg)
CCI			

- Participants may be allowed to leave the CRU after completing the safety assessments on Day 8 of Period 18, or later at the investigator's discretion.

Follow-up period

- A follow-up visit will be performed approximately 7 days after last dose.

3.1.2. Part B: BE Study

Screening and baseline

Participant eligibility will be determined at a screening visit up to 42 days prior to Day -1.

After completing all screening assessments, eligible participants will undergo baseline procedure.

For Cohort 2B orforglipron at-home dosing, capsules will be dispensed on Day -1 for self-administration at home. Self-administration training will be conducted, and a participant diary will be provided, to track the at-home dosing compliance (that is, on Day 1, self-administration of the study drug and documentation in diaries will occur under CRU supervision). Participants will be discharged on Day 1 of Period 1.

Treatment period

Cohort 1B

- Participants will be randomly assigned to 1 of 3 (1:1:1) sequences. Accordingly, they will receive QD oral doses of orforglipron tablets and capsules. The tablet dose strengths for Cohort 1B will be determined based on the interim analysis of relative bioavailability conducted at each dose level in the Cohort 1A pilot study.
- Each participant will receive study medication from Periods 1 to 9 (7 days each).
- Participants may be allowed to leave the CRU after completing the safety assessments on Day 8 of Period 9, or later at the investigator's discretion.

Cohort 2B

- Participants will be admitted to the CRU on Day -1. On Day 1, participants will be discharged after they receive training on in-home dosing and documentation of daily dosing in their diaries (that is, on Day 1, self-administration of the study drug and documentation in diaries will occur under CRU supervision).
- Participants will self-administer a QD oral dose of orforglipron capsule CCI mg) at home for Periods 1 to 6 (7 days per period).
- On Day 7 of Periods 1 to 5, participants will come to the CRU for an outpatient visit. During the outpatient visit, participants will be assessed for dosing compliance and will receive a re-supply of study medication per schedule.
- Participants will be admitted to the CRU for an inpatient stay on Day 7 of Period 6 and will be randomly assigned to 1 of 3 (1:1:1) sequences for Periods 7 to 15. Accordingly, they will receive QD oral doses of orforglipron tablet or capsule as indicated in the schema in Figure 4. The tablet dose strengths for Cohort 2B will be determined based on the interim analysis of relative bioavailability conducted at each dose level in the Cohort 2A pilot study.
- Participants may be allowed to leave the CRU after completing the safety assessments on Day 8 of Period 15, or later at the investigator's discretion.

Follow-up period

A follow-up visit will be performed approximately 7 days after last dose.

Schematics of the study designs are presented in Figure 1 (Cohort 1a), Figure 2 (Cohort 2a), Figure 3 (Cohort 1b), and Figure 4 (Cohort 2b).

Figure 1: Cohort 1A (CCI mg) Study Schema

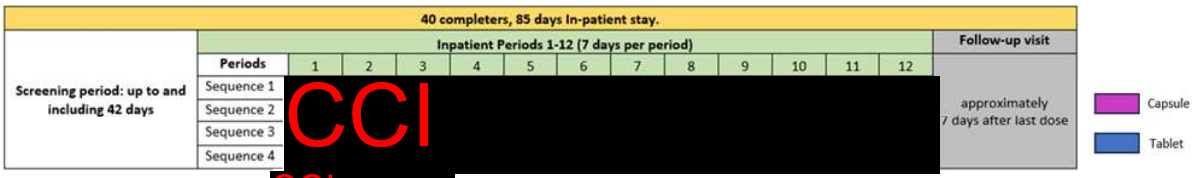


Figure 2: Cohort 2A (CCI mg) Study Schema

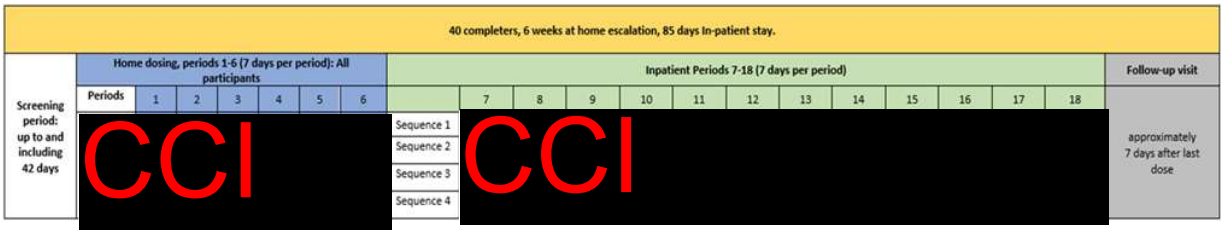
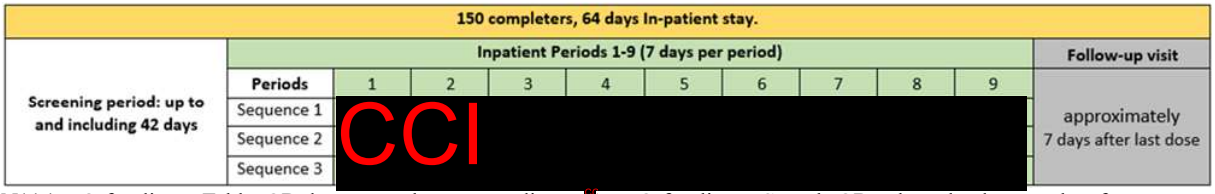
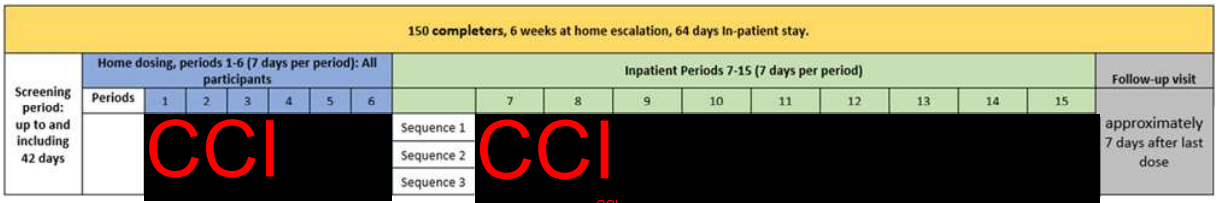


Figure 3: Cohort 1B (CCI mg) Study Schema



N1(±) = Orforglipron Tablet QD dose strength corresponding to [redacted] mg Orforglipron Capsule QD, where the dose can be of nominal strength, slightly lower, or slightly higher than the Capsule dose.
N3(±) = Orforglipron Tablet QD dose strength corresponding to [redacted] mg Orforglipron Capsule QD, where the dose can be of nominal strength, slightly lower, or slightly higher than the Capsule dose.
N6(±) = Orforglipron Tablet QD dose strength corresponding to [redacted] mg Orforglipron Capsule QD, where the dose can be of nominal strength, slightly lower, or slightly higher than the Capsule dose.

Figure 4: Cohort 2B (CCI mg) Study Schema



N12(±) = Orforglipron Tablet QD dose strength corresponding to [redacted] mg Orforglipron Capsule QD, where the dose can be of nominal strength, slightly lower, or slightly higher than the Capsule dose.
N24(±) = Orforglipron Tablet QD dose strength corresponding to [redacted] mg Orforglipron Capsule QD, where the dose can be of nominal strength, slightly lower, or slightly higher than the Capsule dose.
N36(±) = Orforglipron Tablet QD dose strength corresponding to [redacted] mg Orforglipron Capsule QD, where the dose can be of nominal strength, slightly lower, or slightly higher than the Capsule dose.

4. BLINDING

This is a randomized, open-label study.

5. SAMPLE SIZE JUSTIFICATION

The sample size has been calculated to ensure the trial satisfies BE requirement for PK parameters and is considered sufficient to evaluate the primary objective of this study.

Approximately 508 participants (108 for Part A and 400 for Part B) will be enrolled so that approximately 40 participants with evaluable PK in each cohort for Part A and 150 participants with evaluable PK in each cohort for Part B complete the study. The sample size for Part A will provide at least 90% chance to ensure that the 90% CI of the GMR of AUC and C_{max} between tablet (test) and capsule (reference) of a given dose strength will fall within (0.85, 1.18) of the estimated GMR, assuming a within-subject coefficient of variation of 40%. The sample size for Part B will provide at least 90% chance to ensure that the 90% CI of the GMR of AUC and C_{max} between tablet (test) and capsule (reference) of a given dose strength will fall within the equivalence boundary of a widened CI when $S_{wr} \geq 0.294$, or (0.8 to 1.25) if $S_{wr} < 0.294$, assuming an expected GMR of 1.09 (test vs reference) and a within-subject coefficient of variation of 40%.

Participants who are enrolled but not administered treatment may be replaced to ensure that enough participants may complete the study. If a participant does not complete the entire treatment period of the study, they may be replaced by another participant if decided by the sponsor.

6. STUDY TREATMENTS

The study treatment names, and ordering to be used in the TFLs are presented in Table 3.

Table 3: Presentation of Study Treatments in TFLs

Part	Cohort	Study Treatment	Order in TFLs
A	1A	[redacted] mg Orforglipron Capsule QD	1
		[redacted] mg Orforglipron Tablet QD	2
		[redacted] mg Orforglipron Tablet QD	3
		[redacted] mg Orforglipron Tablet QD	4
		[redacted] mg Orforglipron Capsule QD	5
		[redacted] mg Orforglipron Tablet QD	6
		[redacted] mg Orforglipron Tablet QD	7
		[redacted] mg Orforglipron Tablet QD	8
		[redacted] mg Orforglipron Capsule QD	9
		[redacted] mg Orforglipron Tablet QD	10
		[redacted] mg Orforglipron Tablet QD	11
		[redacted] mg Orforglipron Tablet QD	12
	2A	[redacted] mg Orforglipron Capsule QD (Home dosing)	13
		[redacted] mg Orforglipron Capsule QD	14
		[redacted] mg Orforglipron Tablet QD	15
		[redacted] mg Orforglipron Tablet QD	16
		[redacted] mg Orforglipron Tablet QD	17
		[redacted] mg Orforglipron Capsule QD	18
		[redacted] mg Orforglipron Tablet QD	19
		[redacted] mg Orforglipron Tablet QD	20
		[redacted] mg Orforglipron Tablet QD	21
		[redacted] mg Orforglipron Capsule QD	22
		[redacted] mg Orforglipron Tablet QD	23
		[redacted] mg Orforglipron Tablet QD	24
		[redacted] mg Orforglipron Tablet QD	25
B	1B	[redacted] mg Orforglipron Capsule QD	26
		[redacted] ± mg Orforglipron Tablet QD*	27
		[redacted] mg Orforglipron Capsule QD	28
		[redacted] ± mg Orforglipron Tablet QD*	29
		[redacted] mg Orforglipron Capsule QD	30
		[redacted] ± mg Orforglipron Tablet QD*	31
	2B	[redacted] mg Orforglipron Capsule QD (Home dosing)	32
		[redacted] mg Orforglipron Capsule QD	33

	CCI ± Orforglipron mg Tablet QD*	34
	CCI mg Orforglipron Capsule QD	35
	CCI ± mg Orforglipron Tablet QD*	36
	CCI mg Orforglipron Capsule QD	37
	CCI ± mg Orforglipron Tablet QD*	38

* Actual dosage level administered will replace NX ± in the treatment level in the TFLs.

The tablet dose strengths for Cohort 1B will be determined based on the interim analysis of relative bioavailability conducted at each dose level in the Cohort 1A pilot study.

All TFLs will be based on actual treatments.

All dose levels described above are the potential dose levels, and therefore are subject to change. The TFLs will reflect the dose levels utilized in the study, and these will be displayed in increasing order.

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 randomly assigned to study intervention.

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 have received at least 1 dose of study intervention and have evaluable PK data. Participants will be excluded from the PK summary statistics and statistical analysis if a participant has an AE of vomiting that occurs at or before 2 times median t_{max}. Participants will be excluded from the BE statistical analysis if a clinician documents in a case report form that the participant did not swallow the capsule or tablet, based on a mouth check of the subjects for PK days.

8. STATISTICAL METHODOLOGY

8.1. General

Listings may 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 1.3 (or higher if a new version is issued during the study). Pinnacle 21 Enterprise Version 5.3.1 (or higher if a new version is issued during the study) will be utilized to ensure compliance with CDISC standards.

For statistical analyses in Part A, the hypothesis testing will be 2 1-sided test procedure, and each will be carried out on 0.05 significance level, unless specifically stated otherwise. For statistical analyses in Part B, the hypothesis testing will be 2 1-sided test procedure, and each will be carried out on 0.05 significance level, unless specifically stated otherwise.

Where reference is made to ‘valid’ data, this refers to non-missing data which meet the predetermined criteria (eg, 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.

When data for both replicated capsule periods of each capsule treatment are collected, the mean should be used in summaries. For PK data, the geometric mean of the 2 replicate reference treatments will be used for each capsule dose.

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 of summary statistics and statistical analyses. Exceptions may be made where justified.

For categorical data the following rules will be applied:

- For ordered categorical data (eg, 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 (eg, 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.

8.1.3. Definitions of Baseline, and Change from Baseline

The baseline will be defined as the last scheduled value recorded prior to dosing in each period. 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 dosing in each period.

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 participant' values (eg, 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 part, and cohort will be provided, based on the safety population.

8.3. Screening Demographics and Baseline Characteristics

The screening demographics and baseline characteristics including age, sex, race, ethnicity, site ID, height, body weight, and body mass index will be listed.

Summary tables by part, cohort, and sequence 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 WHO Drug Dictionary (version number is documented in the DMP).

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

Noncompartmental methods applied with a validated software program [WinNonlin Phoenix v8.3.5 or later] to the plasma concentrations of orforglipron will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
$AUC(0\text{-}\tau)_{,ss}$	ng.h/mL	Area under the concentration versus time curve during one dosing interval (τ is 24 hours for QD dosing)
$C_{max,ss}$	ng/mL	Maximum observed drug concentration during a dosing interval at steady state
$t_{max,ss}$	h	Time to maximum observed drug concentration during a dosing interval at steady state
$AUC(0\text{-}t_{last})$	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
CL_{ss}/F	L/h	Apparent total body clearance of drug calculated after extra-vascular administration at steady state
V_{ss}/F	L	Apparent volume of distribution at steady state after extra-vascular administration
$V_{z,ss}/F$	L	Apparent volume of distribution at steady state after extra-vascular administration

$C_{min,ss}$	ng/mL	Minimum observed drug concentration during a dosing interval at steady state
$C_{av,ss}$	ng/mL	Average drug concentration under steady state conditions during multiple QD dosing as follows: $(AUC(0-\tau),_{ss}/24$
degree of fluctuation	NA	The degree of fluctuation is defined as follows: $[(C_{max,ss}-C_{min,ss})/C_{av,ss}]$
swing	NA	The swing is defined as follows: $[(C_{max,ss}-C_{min,ss})/C_{min,ss}]$
C_0	ng/mL	Observed drug concentration at time 0 (pre-dose)
C_{24}	ng/mL	Observed drug concentration at time 24 hr

NA = Not applicable

Additional PK parameters may be calculated, as appropriate. 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 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.

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

- 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 $t_{max,ss}$ and then the logarithmic trapezoidal method will be used after $t_{max,ss}$. 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 $C_{max,ss}$.

- 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 observed 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 BLQ concentration occurs before the first quantifiable concentration.
- All other BLQ 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 PK sample is missing, then the 24-hour concentration value will be used as pre-dose in a sensitivity analysis assuming steady state has been attained. If 24-hour concentration is missing, then pre-dose value may be used in a sensitivity analysis.

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 mean 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 CSR.

- A concentration average will be plotted for a given sampling time only if two-thirds 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 two-thirds, 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 CSR.

Treatment of Outliers during Pharmacokinetic 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 there are fewer than 6 data points, 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 there are 6 or more data points, 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 there are still 6 or more data points 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 concentration will be listed for final PK analysis.

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 part and treatment will be provided for all PK 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}.

A participant may be excluded from primary PK statistical analysis should they miss a dose within 4 days of PK sampling day (PK Day 7), in a given period. This is due to the missing

dose potentially impacting the steady-state PK parameters. The PK parameter and concentration data will also be excluded from summary statistics for the primary analysis.

Sensitivity PK statistical analysis may be conducted to include a participant who missed a dose within 4 days of PK sampling day (PK Day 7) and/or had an emesis event within 2 times median t_{max} on PK Day 7. The PK parameter and concentration data will also be included in summary statistics for sensitivity analysis.

8.5.3. Pharmacokinetic Statistical Methodology

Primary Analysis (Part B)

Data from Part A will be used to select a test tablet dose strength for each corresponding capsule dose level for Part B. Data from Part B will then be used to assess bioequivalence between the chosen test tablet dose strength and the reference capsule for each capsule dose level.

On the Part B data, a statistical analysis will be conducted to investigate the bioequivalence of NX± mg Orforglipron Tablet QD (test treatment) to CCI mg Orforglipron Capsule QD (reference treatment). Only participants that have valid data for all 3 treatment periods corresponding to the relevant dose level will be included in the analysis.

Two 1-sided t-tests will be applied to the GMR between each dose $AUC_{(0-\tau),ss}$ and $C_{max,ss}$ using capsule as the reference and the selected tablet as test separately for CCI mg. Test limits of the GMRs to establish BE will be applied using the mixed scaling approach.

The reference capsule's S_{wr} for replicate periods will be estimated based on the difference in the log-transformed PK parameter calculated between the 2 replicate periods from each study participant at each capsule dose level.

Calculation for S_{wr} can be seen as follows:[10]

$$S^2_{WR,ss} = \frac{\sum_{i=1}^{m}\sum_{j=1}^{n_i}\left(D_{ij} - \bar{D}_i\right)^2}{2(n-m)}$$

Where:

- i is the index corresponding to the sequence
- j is the index for the j^{th} subject within sequence i
- $D_{ij} = R_{ij1} - R_{ij2}$ (where 1 and 2 represent replicate reference treatments)

- $\overline{D_i} = \frac{\sum_{j=1}^{n_i} D_{ij}}{n_i}$
- $n = \sum_{j=1}^{m} n_j$ (i.e., total number of subjects used in the study, while n_j is number of subjects used in sequence j)
- m = number of sequences

The following quantities must also be defined:

- T = Test treatment
- R = Reference treatment
- T_{ij} = the observation on T for subject j within sequence i.
- R_{ijk} = kth observation (k = 1 or 2) on R for subject j within sequence i
- $I_{ij} = T_{ij} - \frac{R_{ij1}+R_{ij2}}{2}$

Examples of the SAS code that will be used to calculate S_{WR} are as follows:

```
proc glm data=scavbe;
   by parcat1n parcat1 paramn paramcd;
   class trtseq;
   model dlat=trtseq;
   ods output overallanova=dglm1;
   ods output NObs=dglm3;
   title1 'scaled average BE';
run;
```

Where dlat is defined as D_{ij} above.

```
data dglm1_1;
   set dglm1(where=(source='Error'));
   s2wr=ms/2;
   swr=sqrt(s2wr);
run;
```

If the estimated $S_{wr} \geq 0.294$, the reference-scaled procedure will be applied to determine BE for the individual parameter together with a point estimate of the estimated test/reference GMR within (0.8, 1.25) and the 90% CI of the GMR is within: $(0.8^{Swr/0.25}, 1.25^{Swr/0.25})$.

Examples of the SAS code that will be used to calculate the confidence intervals are as follows:

```
proc glm data=scavbe;
```

```
    class seq;
    model ilat=seq/clparm alpha=0.1;
    estimate 'average' intercept 1 seq 0.3333333333 0.3333333333
    0.3333333333;
    ods output overallanova=iglm1;
    ods output Estimates=iglm2;
    ods output NObs=iglm3;
    title1 'scaled average BE';
run;
```

Where ilat is defined as I_{ij} above.

Results from the output can be calculated as follows:

If the estimated S_{wr} <0.294, the two 1-sided t-test procedure (the unscaled average BE approach) will be used to determine BE for the individual PK parameter with bioequivalent boundary of (0.8, 1.25).

The natural log-transformed[4] $AUC_{(0-\tau)}$ and C_{max} will be analyzed using a mixed model.[5] The model will include planned treatment sequence, period, and treatment (capsule and selected tablet) as fixed effects, and participant as a random effect. Within-subject variance will be estimated for each treatment group. If this model fails in convergence, a simpler structure to estimate the within-subject variability will be applied in the order of common intrasubject variability across treatment, or removing repeated statement until the first convergence is reached.

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.

It will be concluded that the test treatment is bioequivalent to the reference treatments if, for PK parameters $AUC_{(0-\tau)}$ and C_{max}, the 90% CI for the ratio of GLSMs is completely contained within the predefined interval of (0.8, 1.25).[6] This procedure is equivalent to Schuirmann's[7] two one-sided tests at the 0.05 level of significance.

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

```
proc mixed data=pk;
    class seq subj per trt;
    model lauct = seq per trt/ ddfm=kr2;
    random subj;
    repeated/grp=trt sub=subj;
    estimate 'T vs. R' trt 1 -1/cl alpha=0.1;
    ods output Estimates=unsc1;
    title1 'unscaled BE 90% CI - guidance version';
    title2 'AUCt';
run;
```

```
data unsc2;
   set unsc1;
   unscabe_lower=exp(lower);
   unscabe_upper=exp(upper);
run;
```

The parameter t_{max} will be analyzed non-parametrically. For the reference capsule treatment, the median of the two measures will be taken and used as the observation for the capsule treatment for this analysis. Estimates of the median of the within-participant differences and approximate 90% CI will be calculated using the Hahn and Meeker method.[8] The p-value from the Wilcoxon signed-rank[9] test will also be calculated.

Secondary Analysis (Part B)

The $AUC_{(0-\tau),ss}$ and $C_{max,ss}$ at capsule dose level of CCI mg from Part B will follow the same model as described in the primary analysis. Only participants that have valid data for all 3 treatment periods corresponding to the relevant dose level will be included in the analysis.

Exploratory Analysis (Part A)

Six statistical analyses will be conducted separately to investigate the relative bioavailability of NX± mg Orforglipron Tablet QD (test treatment) to corresponding CCI mg Orforglipron Capsules QD (reference treatment). No multiplicity adjustment is needed for this analysis. For each analysis, each PK parameter ($AUC_{(0-\tau)}$and C_{max}) will be log transformed and analyzed in a linear mixed effect model with treatment, sequence, period as fixed effects, subject nested within sequence as a random effect. The geometric mean ratio of each tablet to corresponding capsule along with its 90% CI will be reported.

tmax comparison between each tablet and corresponding capsule will be analyzed via Wilcoxon signed-rank test. Median and approximately 90% CI will be reported.

8.6. Safety and Tolerability Assessments

8.6.1. Adverse Events

All AEs will be coded using MedDRA (version number is documented in the DMP).

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 first dose. A TEAE will be defined as an AE that starts during or after dosing or starts prior to dosing and increases in severity after dosing.

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

TEAE's, SAE's and AE's leading to discontinuation 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, and leading to death) by treatment
- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) 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

AEs of special interest will be listed separately if the data are sufficient, and are the following for this study:

- pancreatic events
- cardiovascular events
- hepatic and biliary events
- hypoglycemia, and
- thyroid C-cell hyperplasia and malignancy.

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 (eg, 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. If the start time is missing for an adverse event that occurs on the first dosing day, and there is evidence that the AE occurs post treatment, then the above calculations will be amended to assume the time of treatment as the start time.

- 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 (eg, 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.

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.

- The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.

- If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

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

Clinical laboratory parameters outside the reference range will be listed and flagged.

Summary tables by part, cohort, and time point will be provided for clinical chemistry and hematology parameters.

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

Summary tables by part, cohort, 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 part and treatment.

8.6.5. 12-lead Electrocardiogram 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. Depression, Suicidal Ideation, and Behavior Risk Monitoring

Columbia Classification Algorithm of Suicide Assessment

C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior via a questionnaire. If there are any positive responses and there are sufficient data, the responses will be summarized by treatment and time point via a frequency table and listed. If any positive responses are observed for a participant, all available C-SSRS data over all timepoints will be listed for that participant.

PHQ-9

The C-SSRS questionnaire will be used to capture the occurrence, severity, and frequency of suicidal ideation and behaviors during the assessment period. If there are any positive responses and there are sufficient data, the responses will be summarized by treatment and time point via a frequency table and listed.

The PHQ-9 will also be used to assess the specific diagnostic symptoms that determine the presence of a clinical depressive disorder, with the questionnaire assessing the previous 2 weeks. Nine symptoms are diagnosed and rated on a 0 to 3 scale, with a higher score indicating greater dysfunction. The total sum of these scores is used to interpret the level of depression, which can be seen in Table 4.

Table 4: Interpretation of Depression using PHQ-9 score

Interpretation of Depression	Total Score
Minimal to none	0-4
Mild	5-9
Moderate	10-14
Moderately severe	15-19
Severe	20-27

If there are sufficient data, a listing and summary table by cohort will be produced for total score.

8.6.7. Hepatic Monitoring

If a participant experiences elevated laboratory parameters, as detailed in Section 8.3.6 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.

8.6.8. Other Assessments

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

8.6.9. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9. INTERIM ANALYSES

Six interim analyses are planned for Part A of this study to determine the corresponding tablet dose strength for each capsule dose level that will be assessed in Part B for bioequivalence. No interim analyses are planned with data from Part B.

10. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

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

11. REFERENCES

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12. 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 Version 2.0	13AUG2024	Protocol Amendment: Study design updates / AE removed from endpoints / Definition of populations wording updates / Glucose listing and summary removed
Final Version 3.0	07MAR2025	Amendment to PK handling rules

NA = not applicable

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Approval	PPD PKPDPMx 07-Mar-2025 14:03:13 GMT+0000

Approval	PPD Statistician 07-Mar-2025 14:07:10 GMT+0000

Approval	PPD Statistician 07-Mar-2025 15:13:39 GMT+0000

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