Protocol J2A-MC-GZPI(d)

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: 14 Aug 2024

Title Page

Protocol Title:

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.

Protocol Number: J2A-MC-GZPI

Amendment Number: J2A-MC-GZPI(d)

Compound: Orforglipron (LY3502970)

Brief Title:

A Multiple-Dose Study to Compare Tablets and Capsules of Orforglipron

Study Phase: 1

Acronym: GZPI

Sponsor Name: Eli Lilly and Company (Lilly)

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s): IND: 156143

Approval Date: Protocol amendment (d) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-132296

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment c	17 Jul 2024
Amendment b	24 May 2024
Amendment a	05 Apr 2024
Original Protocol	07 Dec 2023

Amendment [d]

Overall rationale for the amendment

The protocol is amended to update the information on clinical chemistry, clinical laboratory tests and blood sampling summary for consistency with other orforglipron clinical study protocols.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	Updated to include clinical chemistry every 4 weeks in all the cohorts (cohorts 1A, 2A and 1B, 2B) Updated clinical laboratory tests at the end of the treatment phase in all cohorts (cohorts 1A, 2A and 1B, 2B)	Consistency with other orforglipron clinical study protocols
Appendix 2: Clinical Laboratory Tests	Removed uric acid from "other tests" and updated under "Clinical Chemistry" and other minor editorial changes	Updated for consistency
10.2.1. Blood Sampling Summary	Added clinical chemistry tests and updated central clinical laboratory tests	Revised as per the updated changes

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1. Protocol Summary

1.1. Synopsis

Protocol Title: 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

Brief Title: A Multiple-Dose Study to Compare Tablets and Capsules of Orforglipron.

Regulatory Agency Identifier Number(s): IND: 156143

Rationale:

Study J2A-MC-GZPI (GZPI) is a Phase 1, multiple-dose study designed to assess the pharmacokinetics (PK), safety, and tolerability of orforglipron (LY3502970) following oral administration of a capsule or a tablet in participants with obesity or overweight who are otherwise healthy. This study will provide PK data for orforglipron when it is administered as tablets versus capsules.

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 capsule dose levels of CCI [redacted] 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)	• Steady-state $AUC_{(0-\tau)}$ and C_{max} Number and incidence of • SAEs • TEAEs

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.

Overall Design:

Brief Summary:

Study GZPI is a Phase 1, open-label, multiple-dose study to evaluate the bioequivalence of orforglipron tablets and capsules in participants with obesity or overweight who are otherwise healthy.

Study GZPI will have 2 parts (Parts A and B). Part A will be a pilot relative bioavailability (RBA) design that will assess 3 tablet dose strengths for each capsule dose level. This RBA assessment will be used to select a single tablet dose strength for each capsule dose level to be assessed in Part B. Part B will assess BE (bioequivalence) of each of the 6 capsule dose levels with 1 corresponding tablet dose strength selected from the pilot study (that is, Part A). Parts A and B will run with 2 separate sets of participants. Each part will have 2 cohorts.

Participants will receive once-daily (QD) oral doses of orforglipron as capsules and tablets. The duration of treatment ranges from 9 to 18 weeks as indicated in the schema. Cohort 1 from both Parts A and B will be dosed in clinical research unit (CRU) whereas Cohort 2 from both Parts A and B will have a dose escalation at home followed by in-CRU dosing.

Study Population:

Participants with obesity or overweight who are otherwise healthy

Number of Participants:

Approximately 508 participants may be enrolled so that approximately 40 participants with evaluable PK in each cohort for Part A and approximately 150 participants with evaluable PK in each cohort for Part B complete the study.

Intervention Groups and Duration:

The study involves a comparison of multiple doses of orforglipron capsules and tablets.

Part A: Pilot Study

Cohort 1A

The study duration for individual participants, inclusive of screening, is expected to be approximately 19 weeks, divided as follows:

- Screening: up to 42 days prior to Day -1
- Inpatient period: Periods 1 to 12 (7 days per period), including QD oral dose of orforglipron tablet or capsule
- Follow-up period: approximately 7 days after last dose

Cohort 2A

The study duration for individual participants, inclusive of screening, is expected to be approximately 25 weeks, divided as follows:

- Screening: up to 42 days prior to Day -1

- In-home dose escalation: Periods 1 to 6 (7 days per period), which includes QD oral dose of orforglipron capsule
- Inpatient period: Periods 7 to 18 (7 days per period), which includes QD oral dose of orforglipron tablet or capsule
- Follow-up period: approximately 7 days after last dose

Part B: BE Study

Cohort 1B

The study duration for individual participants, inclusive of screening, is expected to be approximately 16 weeks, divided as follows:

- Screening: up to 42 days prior to Day -1
- Inpatient period: Periods 1 to 9 (7 days per period), including QD oral dose of orforglipron tablet or capsule
- Follow-up period: approximately 7 days after last dose.

Cohort 2B

The study duration for individual participants, inclusive of screening, is expected to be approximately 22 weeks, divided as follows:

- Screening: up to 42 days prior to Day -1
- In-home dose escalation: Periods 1 to 6 (7 days per period), which includes QD oral dose of orforglipron capsule
- Inpatient period: Periods 7 to 15 (7 days per period), which includes QD oral dose of orforglipron tablet or capsule
- Follow-up period: approximately 7 days after last dose

Ethical Considerations of Benefit/Risk :

No safety or tolerability concerns have been seen that prevent further investigation of orforglipron. The highest doses of orforglipron studied are [redacted]-mg capsule as a single dose and [redacted]-mg capsule as multiple doses.

Data from Phase 2 studies show that orforglipron treatment causes a decrease in body weight. Some participants may experience a decrease in body weight as a result of participation in this trial; however, given the study duration and doses being tested, no therapeutic benefit should be expected.

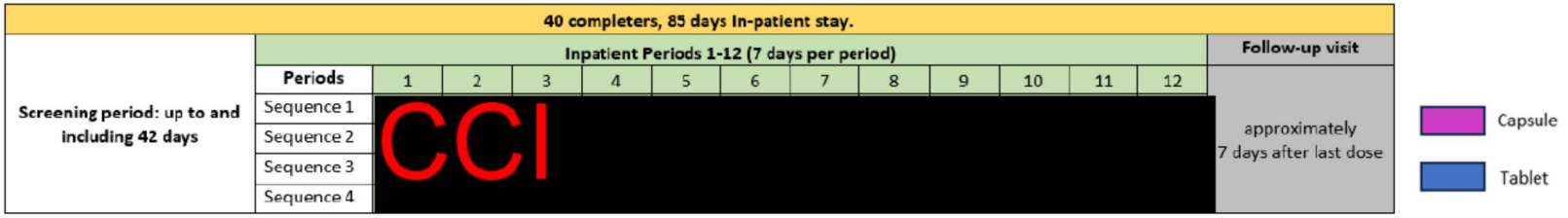
The highest dose assessed in this study will be the [redacted]-mg capsule and tablet doses that are anticipated to be equivalent to this dose.

Data Monitoring Committee: No

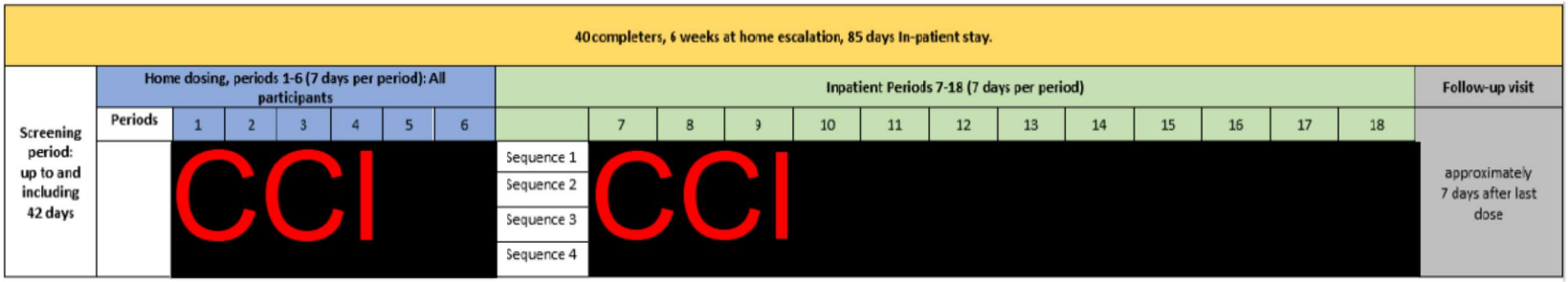
1.2. Schema

Part A: Pilot Study

Cohort 1A (CCI mg)



Cohort 2A CCI mg)



Part B: BE Study

Cohort 1B (CCI mg)

150 completers, 64 days In-patient stay.										
Screening period: up to and including 42 days	Inpatient Periods 1-9 (7 days per period)									Follow-up visit
	Periods	1	2	3	4	5	6	7	8	9	approximately 7 days after last dose
	Sequence 1	CCI									
	Sequence 2										
	Sequence 3										

Cohort 2B (CCI mg)

150 completers, 6 weeks at home escalation, 64 days In-patient stay.																
Screening period: up to and including 42 days	Home dosing, periods 1-6 (7 days per period): All participants							Inpatient Periods 7-15 (7 days per period)								Follow-up visit
	Periods	1	2	3	4	5	6		7	8	9	10	11	12	13	14	15	approximately 7 days after last dose
		CCI						Sequence 1	CCI									
								Sequence 2										
								Sequence 3										

Abbreviation: N (+/-) = single tablet dose strength (higher / lower) selected from pilot study.

Refer to details in Section 4.1.

1.3. Schedule of Activities (SoA)

Part A: Pilot Study

Cohort 1A:

	Screening	Inpatient Period (12 periods of 7 days)					FU/ED	Notes
Days	**≤42 days**	**-1 (Baseline: for Period 1 only)**	**1**	**2 to 6**	**7**	**8 (for Period 12 only)**		
Informed consent	X							
Admission to CRU		X						
Discharge from CRU						X		
Medical history	X							
Randomization		X						
Outpatient visit							X	
Physical examination	X	X				X	X	Refer to details in Section 8.2.1.
Weight	X	X			X		X	
Height	X							
Vital signs	X	X			P		X	Should be measured before blood sample collection.
Clinical laboratory tests	X	X				X	X	See Appendix 2 in Section 10.2 for details.
Clinical Chemistry			X					Periods 4, 8 and 12. Does not include amylase and lipase.
Pregnancy test	X	X						Screening: Serum beta HCG pregnancy test Baseline visit: Urine pregnancy test.
Ethanol test and urine drug screen	X	X						Screening: Urine alcohol test Baseline visit: Breath or urine test
Single 12-lead ECG	X	X		P* Day 6 only			X	*Periods 4, 8, and 12.

	Screening	Inpatient Period (12 periods of 7 days)					FU/ED	Notes
Days	**≤42 days**	**-1 (Baseline: for Period 1 only)**	**1**	**2 to 6**	**7**	**8 (for Period 12 only)**		
								Should occur before blood sample collection
C-SSRS baseline	X							
C-SSRS since last assessed		X			X			To be done once every 4 weeks (Day 7 of Periods 4, 8, and 12).
PHQ-9	X	X			X			To be done once every 4 weeks (Day 7 of Periods 4, 8, and 12).
Pharmacogenetic sample		X						
PK sampling during tablet and capsule dosing			P*		P, 0.5h, 1h, 2h, 4h, 6h, 8h, 12h, 16h	24hr (relative to Day 7 dosing)		*Periods 2-12 (Day 1 PK sample should be collected at 24 hr relative to Day 7 dosing in previous period) and prior to dosing on Day 1.
HbA1c – local laboratory	X							
Study intervention administration			X	X	X			
AE review	←						→	
Concomitant medication review	←						→	

Abbreviations: AE = adverse event; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; FU = follow up; HbA1c = glycated hemoglobin; HCG = human gonadotropic hormone; P = predose; PHQ-9 = patient health questionnaire; PK = pharmacokinetics; SAE = serious adverse event.

Cohort 2A:

	Screening	**Baseline**	**Home Dosing (each period is 7 days)**			**Inpatient Period (each period is 7 days)**					**FU/ED**	**Notes**
			Period 1 to 5		**Period 6**	**Period 6**	**Period 7 to 18**					
Days	**≤42 days**	**-1**	**1 to 6**	**7**	**1 to 6**	**7**	**1**	**2 to 6**	**7**	**8 (For Period 18 only)**		
Informed consent	X											
Admission to CRU		X*				X						*Admission to CRU on Day -1 (Period 1 only)
Training on self-administration and diary entry			X									Training will be given to participants on Day 1 (Period 1 only)
Discharge from CRU			X*							X		*Discharge from CRU on Day 1 (Period 1 only)
Outpatient visit				X							X	
Compliance (diary review)				X		X						
Medical history	X											
Randomization						X						
Weight	X	X							X		X	
Height	X											
Physical examination	X	X				X				X	X	Refer to details in Section 8.2.1
Vital signs	X			X			P		P		X	Should be measured before any blood sample collection.
Clinical laboratory tests	X	X								X	X	See Appendix 2 in Section 10.2 for details.

	Screening	Baseline	Home Dosing (each period is 7 days)			Inpatient Period (each period is 7 days)					FU/ED	Notes
			Period 1 to 5		Period 6	Period 6	Period 7 to 18					
Days	**≤42 days**	**-1**	**1 to 6**	**7**	**1 to 6**	**7**	**1**	**2 to 6**	**7**	**8 (For Period 18 only)**		
Clinical Chemistry				X (Period 3)			X					Period 3, 8, 12 and 16 only. Does not include amylase and lipase
Pregnancy test	X	X				X						Screening: Serum beta HCG pregnancy test Baseline visit: Urine pregnancy test Admission to CRU: Urine pregnancy test
Ethanol test and urine drug screen	X	X				X						Screening: Urine alcohol test Baseline visit: Breath or urine test Admission to CRU: Breath or urine test
Single 12-lead ECG	X							P* Day 6 only			X	*Periods 10, 14, and 18 Should occur before blood sample collection.
PHQ-9	X	X							X		X	To be done once every 4 weeks (Periods 10, 14, and 18).
C-SSRS baseline	X											
C-SSRS since last assessed		X				X			X			To be done once every 4 weeks (Periods 10, 14, and 18).
Pharmacogenetic sample		X										

	Screening	Baseline	Home Dosing (each period is 7 days)			Inpatient Period (each period is 7 days)					FU/ED	Notes
			Period 1 to 5		Period 6	Period 6	Period 7 to 18					
Days	**≤42 days**	**-1**	**1 to 6**	**7**	**1 to 6**	**7**	**1**	**2 to 6**	**7**	**8 (For Period 18 only)**		
PK sampling during tablet and capsule dosing							P*		P, 0.5h, 1h, 2h, 4h, 6h, 8h, 12h, 16h	24hr (relative to Day 7 dosing)		*Periods 8-18 (Day 1 PK sample should be collected at 24 hr relative to Day 7 dosing in the previous period) and prior to dosing on Day 1.
HbA1c – local laboratory	X											
Study intervention administration			X	X	X	X	X	X	X			For Periods 1-6: Study intervention dispensed on Day 1 of Period 1, Day 7 of Periods 2 and 4
Home recording of dosing			X	X	X	X						Participant diary will be issued on Day 1 of Period 1 and Day 7 of Periods 1-5.
AE review	←										→	
Concomitant medication review	←										→	

Abbreviations: AE = adverse event; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; HbA1c = glycated hemoglobin; HCG = human gonadotropic hormone; P = predose; PHQ-9 = patient health questionnaire-9; PK = pharmacokinetics.

Part B: BE Study

Cohort 1B

	Screening	Inpatient Period (9 periods of 7 days)					FU/ED	Notes
Days	**≤42 days**	**-1 (Baseline: for Period 1 only)**	**1**	**2 to 6**	**7**	**8 (For Period 9 only)**		
Informed consent	X							
Admission to CRU		X						
Discharge from CRU						X		
Medical history	X							
Randomization		X						
Outpatient visit							X	
Physical examination	X	X				X	X	Refer to details in Section 8.2.1
Weight	X	X			X		X	
Height	X							
Vital signs	X	X			P		X	Should be measured before blood sample collection.
Clinical laboratory tests	X	X				X	X	See Appendix 2 in Section 10.2 for details.
Clinical Chemistry			X					Period 4 and 8 only. Does not include amylase and lipase.
Pregnancy test	X	X						Screening: Serum beta HCG pregnancy test Baseline visit: Urine pregnancy test.
Ethanol test and urine drug screen	X	X						Screening: Urine alcohol test Baseline visit: Breath or urine test
Single 12-lead ECG	X	X		P* Day 6 only			X	*Periods 3, 6, and 9 Should occur before blood sample collection
C-SSRS baseline	X							

	Screening	Inpatient Period (9 periods of 7 days)					FU/ED	Notes
Days	**≤42 days**	**-1 (Baseline: for Period 1 only)**	**1**	**2 to 6**	**7**	**8 (For Period 9 only)**		
C-SSRS since last assessed		X			X			To be done once every 4 weeks (Day 7 of Periods 4 and 8).
PHQ-9	X	X			X			To be done once every 4 weeks (Day 7 of Periods 4 and 8).
Pharmacogenetic sample		X						
PK sampling during tablet and capsule dosing			P*		P, 0.5h, 1h, 2h, 4h, 6h, 8h, 12h, 16h	24hr (relative to Day 7 dosing)		*Periods 2-9 (Day 1 PK sample should be collected at 24 hr relative to Day 7 dosing in previous period) and prior to dosing on Day 1.
HbA1c – local laboratory	X							
Study intervention administration			X	X	X			
AE review	◄	———	———	———	———	———	►	
Concomitant medication review	◄	———	———	———	———	———	►	

Abbreviations: AE = adverse event; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; FU = follow up; HbA1c = glycated hemoglobin; HCG = human gonadotropic hormone; P = predose; PHQ-9 = patient health questionnaire; PK = pharmacokinetics; SAE = serious adverse event.

Cohort 2B

	Screening	Baseline	Home Dosing (each period is 7 days)			Inpatient Period (Each Period is 7 days)					FU/ED	Notes
			Period 1 to 5		Period 6	Period 7 to 15						
Days	**≤42 days**	**-1**	**1 to 6**	**7**	**1 to 6**	**7**	**1**	**2 to 6**	**7**	**8 (For Period 15 only)**		
Informed consent	X											
Admission to CRU		X*				X						*Admission to CRU on Day -1 (Period 1 only)
Training on self-administration and diary entry			X									Training will be given to participants on Day 1 (Period 1 only)
Discharge from CRU			X*							X		*Discharge from CRU on Day 1 (Period 1 only)
Outpatient visit				X							X	
Compliance (diary review)				X								
Medical history	X											
Randomization						X						
Weight	X	X							X		X	
Height	X											
Physical examination	X	X				X				X	X	Refer to details in Section 8.2.1.
Vital signs	X			X			P		P		X	Should be measured before any blood sample collection.
Clinical laboratory tests	X	X								X	X	See Appendix 2 in Section 10.2 for details.
Clinical Chemistry				X (Period 3)			X					Periods 3, 8 and 12 only. Does not include amylase and lipase.

	Screening	Baseline	Home Dosing (each period is 7 days)			Inpatient Period (Each Period is 7 days)					FU/ED	Notes
			Period 1 to 5		Period 6	Period 6	Period 7 to 15					
Days	**≤42 days**	**-1**	**1 to 6**	**7**	**1 to 6**	**7**	**1**	**2 to 6**	**7**	**8 (For Period 15 only)**		
Pregnancy test	X	X				X						Screening: Serum beta HCG pregnancy test Baseline visit: Urine pregnancy test Admission to CRU: Urine pregnancy test
Ethanol test and urine drug screen	X	X				X						Screening: Urine alcohol test Baseline visit: Breath or urine test Admission to CRU: Breath or urine test
Single 12-lead ECG	X							P* Day 6 only			X	*Periods 9, 12, and 15 Should occur before blood sample collection.
PHQ-9	X	X							X		X	To be done once every 4 weeks (Day 7 of Periods 10 and 14).
C-SSRS baseline	X											
C-SSRS since last assessed		X				X			X			To be done once every 4 weeks (Day 7 of Periods 10 and 14).
Pharmacogenetic sample		X										
PK sampling during tablet and capsule dosing							P*		P, 0.5h, 1h, 2h, 4h, 6h, 8h, 12h, 16h	24hr (relative to Day 7 dosing)		*Periods 8-15 (Day 1 PK sample should be collected at 24 hr relative to Day 7 dosing in previous period) and prior to dosing on Day 1.
HbA1c – local laboratory	X											

	Screening	Baseline	Home Dosing (each period is 7 days)			Inpatient Period (Each Period is 7 days)					FU/ED	Notes
			Period 1 to 5		Period 6	Period 7 to 15						
Days	**≤42 days**	**-1**	**1 to 6**	**7**	**1 to 6**	**7**	**1**	**2 to 6**	**7**	**8 (For Period 15 only)**		
Study intervention administration			X	X	X	X	X	X	X			For Periods 1-6: Study intervention dispensed on Day 1 of Period 1, Day 7 of Periods 2 and 4.
Home recording of dosing			X	X	X	X						Participant diary will be issued on Day 1 of Period 1 and Day 7 of Periods 1-5.
AE review	←									→		
Concomitant medication review	←									→		

Abbreviations: AE = adverse event; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; HbA1c = glycated hemoglobin; HCG = human gonadotropic hormone; P = predose; PHQ-9 = patient health questionnaire-9; PK = pharmacokinetics.

2. Introduction

Orforglipron, also known as LY3502970, is a chemically synthesized, oral GLP-1 RA that exhibits the antihyperglycemic actions of GLP-1.

Orforglipron is being developed as a daily oral therapy as an adjunct to diet and exercise to improve glycemic control in adults with T2DM and as an adjunct therapy to healthy diet and physical activity for the treatment of overweight or obesity.

2.1. Study Rationale

Study J2A-MC-GZPI (GZPI) is a Phase 1, open-label, multiple-dose escalation study designed to assess the PK, safety, and tolerability of orforglipron tablets and capsules in participants with obesity or overweight who are otherwise healthy.

2.2. Background

There is an unmet medical need for efficacious, safe, and well-tolerated oral formulations of GLP-1 RAs for the management of T2DM and for the treatment of overweight or obesity.

Orforglipron is being investigated for its potential use as a therapy for chronic weight management and T2DM. Orforglipron is a chemically synthesized molecule that shows agonist activity for human GLP-1 receptor. To date, no off-target toxicity has been identified in the clinical studies.

GLP-1 RAs are highly effective peptide drugs that mimic the incretin hormone GLP-1 (Werner et al. 2010; Lau et al. 2015; Scheen 2017). The hormone is secreted from the intestine upon food consumption, and its effects include augmented glucose-dependent insulin secretion, prolonged satiety, reduced glucagon release, and delayed gastric emptying (Bayliss and Starling 1902; Baggio and Drucker 2007; Nauck et al. 1997). The GLP-1 RAs have demonstrated beneficial effects on weight management (Frias et al. 2018; Newsome et al. 2019).

2.3. Benefit/Risk Assessment

To date, in participants administered orforglipron up to the highest single dose of [redacted] mg and multiple doses of [redacted] mg for a maximum of 36 weeks, the common safety or tolerability concerns have been

- GI-related effects that are consistent with GLP-1 pharmacology, and
- changes in vital signs (increase in heart rate, and so on) that have resolved spontaneously over time.

To date, approximately 268 healthy participants, 72 healthy participants with obesity or overweight, 222 participants with obesity or overweight with weight-related comorbidities, and 381 participants with T2DM have received orforglipron and no safety or tolerability concerns that preclude further investigation of orforglipron have been identified. Additionally, as with in-home dosing in the recently completed Phase 2 studies and the ongoing Phase 3 studies, any safety or tolerability concerns arising in the portions of this study that involve in-home dosing will be adequately monitored and managed.

Some participants may experience a decrease in body weight as a result of participation in this trial; however, given the study duration and doses being tested, no therapeutic benefit should be expected.

The highest dose assessed in this study will be the [redacted]-mg capsule and tablet doses that are anticipated to be equivalent to this dose.

More information about the known and expected benefits, risks, SAEs, and adverse drug reactions of orforglipron is to be found in the IB.

3. 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 capsule dose levels of CCI [redacted] 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)	• Steady-state $AUC_{(0-\tau)}$ and C_{max} Number and incidence of • SAEs • TEAEs
Exploratory	
• To evaluate the relative bioavailability of orforglipron tablets and capsules at capsule dose levels of CCI [redacted] 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.

4. Study Design

4.1. Overall Design

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 [redacted] mg and Cohort 2: CCI [redacted] mg). Participants will receive once-daily (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 J2A-MC-GZGN (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 (N) 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.

The schema in Section 1.2 illustrates the study design and includes the actual tablet dose strengths that will be assessed for each capsule dose level. Safety and PK assessments will be performed according to the SoA in Section 1.3.

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

4.1.1. 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 Section 1.2. The dose strengths are presented in the following table.

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 as indicated in the schema in Section 1.2. The dose strengths are presented in the following table.

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.

4.1.2. 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 as indicated in the schema in Section 1.2. 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 Section 1.2. 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.

4.2. Scientific Rationale for Study Design

This study will evaluate relative bioavailability of each of the 6 capsule dose levels, each with 3 tablet dose strengths in the pilot study (Part A). From this evaluation, 1 tablet dose strength will be selected for each capsule dose level. In Part B of the study, the bioequivalence of each dose level of the capsules will be assessed against the tablet dose strengths selected from Part A. This study will be conducted in participants with obesity or overweight who are otherwise healthy.

In this study, collection of demographic information includes race and ethnicity.

The study design includes 2 parts as indicated in the schema. Part A is the pilot part of the study and Part B is the BE part of the study. Participants in Cohorts 1A and 2A will be randomly assigned to 1 of 4 sequences as indicated in the schema, such that they will receive each of the 3 tablet dose strengths and the capsule dose levels for the corresponding dose levels in the specified order for each sequence. Relative bioavailability of 3 tablet dose strengths will be assessed against each capsule dose level. The tablet dose strength that best matches the PK profile of the corresponding capsule dose level in terms of AUC and C_{max} will be selected for assessment of BE in Part B of the study. Participants in Cohorts 1B and 2B will be randomly assigned into 1 of 3 sequences such that each participant receives the capsule dose (reference formulation) and 1 dose strength of tablet dose (test formulation) selected from Part A for the BE assessment.

Each period of each part of the study will last 7 days as indicated in the schema. In Part B, both cohorts include a third period at each capsule dose level for each cross-over, to allow for collection of replicate PK for the capsule administration. The collection of replicates allows to use a reference scale approach to assess BE at capsule dose levels at which within subject variability (Swr) is greater than or equal to 0.294.

This multiple-dose study with steady-state PK evaluation is required because of the need for an escalation period to reach higher doses, and to mitigate GI tolerability associated with GLP-1 RA pharmacology. This design also allows each individual participant to be used as their own control to limit the number of participants needed for the assessment.

Participants with obesity or overweight who are otherwise healthy will be enrolled, rather than healthy participants because the pharmacologic activity of orforglipron includes weight loss and it is anticipated that the participants will experience some body weight loss during this study. Participants without a history of alcohol or drug abuse or regular co-medication are proposed to avoid interaction on drug metabolism and to avoid noncompliance.

IOCBP can participate in this study based on a review of developmental and reproductive toxicology studies.

4.3. Justification for Dose

Orforglipron doses of CCI [redacted] mg in the capsule formulations administered orally will be compared with dose-adjusted tablet formulations of orforglipron in this study.

These orforglipron capsule dose levels of CCI mg administered orally QD are being studied in the Phase 3 studies and were selected based on the following:

- Orforglipron capsule dose levels of CCI mg QD are anticipated to span a dose range producing increasing magnitudes of clinically relevant HbA1c reduction in patients with T2DM based on assessment of safety, efficacy (glycemic control), and GI tolerability data from Phase 1 and 2 clinical studies.
- Orforglipron capsule dose levels of CCI mg QD are anticipated to span a dose range producing increasing magnitudes of clinically relevant weight reduction in individuals with obesity or overweight, potentially providing multiple treatment options tailored to individual weight reduction goals and tolerability based on assessment of safety, efficacy (weight reduction), and GI tolerability data from Phase 1 and 2 clinical studies.

Orforglipron capsule dose escalation method was selected to optimize GI tolerability with a lower starting dose of CCI mg prior to escalating to CCI mg, followed by CCI mg until the target dose is attained.

Orforglipron tablet doses were selected based on results from the Study GZGN:

- Data from Study GZGN compared various dose strengths of capsules and tablets and indicate that the tablets result in higher exposure compared to capsules when dosed at the same molar dose.
- A detailed description of the scientific basis of dose adjustments and the resulting tablet dose strengths is in Section 4.1.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA. If any assessments are missed, the designation of completion status can be determined by the sponsor.

5. Study Population

Eligibility of participants for enrollment in the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG. The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

The inclusion and exclusion criteria used to determine eligibility should be applied at screening only, unless otherwise specified, and not continuously throughout the study.

Screening may occur up to 42 days prior to enrollment. Participants who are not enrolled within 42 days of screening may undergo an additional medical assessment or clinical measurements to confirm their eligibility. In such instances, at minimum, the following screening tests and procedures will need to be repeated: weight, vital signs, ECG, clinical laboratory tests, and pregnancy test (females only).

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply at screening, unless otherwise specified:

Age

1. Participant must be 18 years or the legal age of consent in the jurisdiction in which the study is taking place to 65 years of age, inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

2. Are overtly healthy as determined through medical evaluation including medical history and physical examination.

Weight

3. Have a stable body weight for 1 month prior to screening (≤5% body weight gain or loss) and body mass index of ≥27 kg/m^2 and ≤40 kg/m^2.

Sex and contraceptive/barrier requirements

4. Assigned male at birth or assigned female at birth.

   Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Appendix 4, Section 10.4.

Informed consent

5. Are capable of giving signed informed consent as described in Appendix 1 in Section 10.1.2, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other inclusion criteria

6. have venous access sufficient to allow for blood sampling as per the protocol.
7. are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply at screening, unless otherwise specified:

Medical conditions and diagnostic tests

8. Have a HbA1c ≥6.5%.
9. Have a history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders or other significant active, uncontrolled medical condition, or history of any medical problem that could, in the opinion of the investigators,
    - significantly alter the absorption, metabolism, or elimination of drugs
    - constitute a risk when taking the study drug, and
    - interfere with the interpretation of data.
10. Have a history of significant active or unstable major depressive disorder or other severe psychiatric disorder, for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder within the past 2 years of screening.
11. Participants with a history of alcohol or drug abuse.
12. Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk of suicide and have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS and the ideation occurred within the past month OR
    have answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS and the behavior occurred within the past 3 months.
13. Have a PHQ-9 score of 15 or more.
14. Have
    - a history or presence of acute or chronic pancreatitis
    - an elevation in serum lipase or amylase levels greater than 3 times the ULN.

    A potential participant with a history of acute pancreatitis caused by gallstones may be included in the study if the participant has a cholecystectomy to resolve the problem.
15. Have obesity induced by other endocrine disorders such as Cushing's syndrome or Prader-Willi syndrome.
16. Have
    - known clinically significant gastric emptying abnormality, such as severe gastroparesis or gastric outlet obstruction,
    - undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®) or
    - chronically taken medications that directly affect GI motility.

17. Have abnormal vital signs including BP, pulse rate, or both, including
    - seated systolic BP ≥160 mm Hg
    - seated diastolic BP ≥100 mm Hg, or
    - pulse rate <50 or >100 bpm,

    or otherwise deemed to be clinically significant by the investigator. In case a white coat effect is suspected, 2 repeat measurements may be made at the discretion of the investigator.
18. Have a known self or family history (first-degree relative) of multiple endocrine neoplasia type 2A or type 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma.
    - Evidence of hypothyroidism or hyperthyroidism based on clinical evaluation that, in the opinion of the investigator, would need thyroid replacement therapy.
19. Have a QTcF >470 milliseconds for females, >450 milliseconds for males, or a clinically significant ECG abnormality that, per the investigator, may represent a safety risk.
20. Have had any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin, or in situ carcinoma of the cervix that have been resected with no evidence of metastatic disease for 3 years.
21. Evidence of hepatitis B, positive hepatitis B surface antigen, or both.
22. Have a positive HCV antibody test. Participants with a positive HCV antibody test at screening can be included only if a confirmatory HCV RNA test is negative.
23. Evidence of HIV based on clinical laboratory test at screening.
24. Have a history of a transplanted organ; corneal transplants (keratoplasty) are allowed.
25. Have donated blood of more than 500 mL within the previous 8 weeks of screening, had a blood transfusion or severe blood loss within 3 months, or have a hemoglobin value <11 g/dL (males) or <10 g/dL (females).
26. Have difficulty swallowing capsules or tablets.
27. Fasting serum triglyceride level of >500 mg/dL at screening.
28. Have a serum calcitonin level at screening of ≥20 ng/L.
29. Have signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease, or any of the following, as determined by the local laboratory during screening:
    - ALT level >3.0 times the ULN for the reference range (as determined by the local laboratory at study entry)
    - ALP level >1.5 times the ULN for the reference range, or
    - TBL >1.5 times the ULN for the reference range (except for cases of known or suspected Gilbert's syndrome).
30. Have a glomerular filtration rate <60 mL/min based on CKD EPI (Chronic Kidney Disease Epidemiology Collaboration).

Prior or concomitant therapy

31. Have used or intend to use any prescription or OTC medications within 14 days prior to screening and throughout the study. Vitamin or mineral supplements, occasional acetaminophen, are allowed.

32. Have any exposure to GLP-1 analogs, or other related compounds within 3 months of screening or any history of hypersensitivity or allergies to orforglipron.
    - Participants who previously took GLP-1 analogs or related compounds and who discontinued those medications for intolerability should not be randomly assigned.
33. Have taken any prescribed, OTC or alternative remedies (including herbal / nutritional supplements) intended to promote weight loss within 14 days prior to screening. See Section 10.7.1 for examples of excluded medications.
34. Are receiving or have received within 3 months of screening chronic (>2 weeks) systemic glucocorticoid therapy, excluding topical, intraocular, intranasal, single intraarticular injection, or inhaled preparations, or have received such therapy within 4 weeks immediately prior to screening.
35. Are receiving or have taken 14 days prior to screening, moderate or strong CYP3A inhibitors, moderate or strong CYP3A inducers, moderate or strong OATP inhibitors, and drugs with a narrow therapeutic index that are either substrates of P-gp or BCRP transporters. See Section 10.7.2 for further details.
36. Have a positive test for marijuana or tetrahydrocannabinol-containing products at screening.
37. Have alcohol intake that exceeds recommended average weekly alcohol consumption limits per local regulation, or an amount deemed excessive by the investigator.

Prior/concurrent clinical study experience

38. Are currently enrolled in a clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study.
39. Have participated in a clinical study involving an IP, where they received the last dose of the IP within 90 days or 5 half-lives of the drug (whichever is longer), should have passed before dosing with orforglipron.
40. Have previously completed or withdrawn from this study.

Other exclusion criteria

41. Are women who are
    - currently pregnant or breastfeeding, or
    - who intend to become pregnant or to breastfeed at any time during the study or within 5 weeks after receiving the last dose of study intervention.
42. Are CRU site personnel directly affiliated with this study or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
43. Are employees of Eli Lilly and Company (Lilly) or are employees of a third-party organization involved in the study which requires exclusion of their employees.
44. Are, in the opinion of the investigator or sponsor, unsuitable for inclusion in the study.

5.3. Lifestyle Considerations

Throughout the study, participants must adhere to lifestyle restrictions as outlined by the CRU and in the study procedures.

5.3.1. Meals and Dietary Restrictions

Since CYP3A is involved in the elimination of orforglipron, participants will be required to refrain from consumption of red wine, grapefruits, grapefruit-containing products, Seville oranges, Seville orange-containing products, star fruits, or star fruit-containing products, pomelo, or commercial apple juice or orange juice from 7 days before the start of study intervention until discharge from the study.

On all dosing days participants need to be overnight fasting for at least 10 hours prior to taking an oral dose of orforglipron.

On PK sample collection days, no food will be allowed for at least 4 hours after orforglipron dose. On other days, participants may consume their meal 30 minutes after orforglipron dose.

On PK sample collection days, fluids will be restricted from 1 hour prior to and until 1 hour after orforglipron dosing, except for the water required for dose administration. Water may be consumed freely at all other times.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

Participants will be allowed to maintain their regular caffeine consumption throughout the study period except during in-clinic stay where site restrictions for caffeine will apply.

No alcohol will be allowed at least 24 hours before each CRU admission and outpatient visit and throughout the duration of each CRU visit. Between CRU visits daily alcohol should not exceed recommended average weekly alcohol consumption limits per local regulations or an amount deemed significant by the investigator. No red wine allowed from 7 days before the start of study intervention until discharge from the study.

No nicotine use will be permitted while at the CRU. While not resident in the CRU, participants must consume no more than 10 cigarettes or equivalent per day.

5.3.3. Activity

Participants will be advised to maintain their regular levels of physical activity and exercise during the study; strenuous exercise within 24 hours prior to all visits should be avoided if possible.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the study is not subsequently enrolled in the study.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. Repeating laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention of a Participant

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any medicinal product or medical device intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

While inpatient at the CRU, orforglipron capsules or tablet will be administered orally, as per the SoA in Section 1.3, with approximately 240 mL of room temperature water in the morning of each dosing day in a sitting position.

Orforglipron capsules or tablet will be administered following an overnight fast of at least 10 hours.

Participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

When participants self-administer orforglipron capsules, they will be advised to take 1 orforglipron capsule with approximately 240 mL of room temperature water before breakfast in the morning after an overnight fast of at least 10 hours, but if they forget, it must be taken as soon as possible on that day, or once daily dosing must continue per plan beginning the following day. Participants must maintain a daily record of capsule administration in the diary provided for the study.

Table GZPI.1 lists the interventions used in this clinical study.

Table GZPI.1. Study Intervention Administered

Intervention Name	Orforglipron	Orforglipron
Type	Drug	Drug
Dose Formulation	Capsule	Tablet
Dosage Level(s)	CCI	
Route of Administration	Oral	Oral
Use	Experimental	Experimental

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current good manufacturing practice. Study interventions will be labeled as appropriate for country requirements.

6.2. Preparation, Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention, except for the in-home dosing period when participants will self-administer the study intervention.

All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance, that is, receipt, reconciliation, and final disposition records.

Further guidance and information for the final disposition of unused study interventions are provided separately.

In some cases, the CRU may destroy the material if, during the CRU selection, the evaluator has verified and documented that the CRU has appropriate facilities and written procedures to dispose of clinical materials.

Participant responsibilities

Study participants will be trained on the proper storage and handling of the study interventions and should follow in-use storage conditions according to the instructions for use provided by the sponsor.

6.3. Assignment to Study Intervention

All participants will be clearly assigned to randomized study intervention using as IWRS. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site. Study intervention will be dispensed at the study visits summarized in SoA. Study intervention returned to the site pharmacy should not be re-dispensed to the participants.

6.4. Blinding

This is an open-label study.

6.5. Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee while in the CRU. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in the source documents and will be provided to the sponsor as requested.

When participants self-administer study intervention at home, compliance with study intervention will be assessed at next CRU visit. Compliance will be assessed by direct questioning and counting returned capsules and documented in the source documents.

A record of the number of orforglipron capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records.

Participants who have multiple instances of noncompliance, as judged by the investigator and sponsor, will be discontinued from the study. The assessment of study intervention compliance will be determined by

- information about study intervention administered at home by the participant via the participant's diary
- information about the participant's adherence to the SoA
- information about the participant's compliance with concomitant medications via the participant's diary, and
- information about any other parameters the investigator considers necessary.

6.6. Dose Modification

Dose reductions or adjustments will not be allowed during this study.

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

Orforglipron will not be made available to participants after conclusion of the study.

6.8. Treatment of Overdose

For this study, any dose of orforglipron greater than CCI mg within a 24-hour period will be considered an overdose. Doses greater than the doses assigned through randomization within a dosing window must be brought to the attention of the investigator.

The treatment for overdose is supportive care; refer to the IB.

In the event of an overdose, the investigator should:

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced
- monitor the participant closely for any AE or SAE and laboratory abnormalities as medically appropriate for the duration of the study
- document the quantity of the excess dose as well as the duration of the overdose in the electronic CRF, and
- obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

6.9. Prior and Concomitant Therapy

Any medication or vaccine (including OTC or prescription medicines, vitamins, herbal supplements, or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with the

- reason for use
- dates of administration including start and end dates, and
- dosage information including dose and frequency of concomitant therapy of special interest.

Allowed concomitant medications should be taken according to label directions. The clinical pharmacologist or clinical research physician should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking strong or moderate CYP3A inhibitors, strong or moderate CYP3A inducers, moderate or strong OATP inhibitors, and drugs that are P-gp or BCRP substrates with a narrow therapeutic index. See Section 10.7.2 for details.

Any medications that transiently affect gastric pH, such as antacids and milk of magnesia, as well as drugs whose absorption may be affected by an increase in gastric pH should be separated from study drug administration by at least 4 hours. See Section 10.7.3 for details.

Throughout the study, participants must also abstain from taking GLP-1 analogs or other related compounds, and glucose-lowering medications. See Section 10.7.4 for details.

Throughout the study, participants will not be allowed to take medications intended to promote weight loss, including prescribed, OTC, or alternative remedies. These drugs must be washed out for at least 14 days prior to screening. See Section 10.7.1 for details.

Acetaminophen

Acetaminophen, at doses of less than 3 g per day, is permitted for use during the study, except as noted below. Acetaminophen during inpatient periods will be administered at the discretion of the investigator. As with all concomitant medications used during the study, any acetaminophen use will be recorded in the CRF.

Other prohibited concomitant medications

OTC or prescription medication that maintains elevated gastric pH, such as H2-receptor blockers and proton pump inhibitors.

Initial doses of orforglipron may delay gastric emptying and have the potential to transiently impact the rate of absorption of concomitantly administered oral medicinal products. Orforglipron should be used with caution in participants receiving oral medicinal products that require rapid GI absorption following the initial doses of orforglipron, as exposure to oral medications may be increased. Dosing of drug products that require rapid GI absorption should therefore be separated from dosing of the study drug orforglipron by 2 to 4 hours.

See Appendix 7 in Section 10.7 for examples of excluded medications.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 in Section 10.1.

7.1. Discontinuation of Study Intervention

Participants discontinuing from study intervention prematurely for any reason should complete AE and other follow-up procedures per the SoA in Section 1.3.

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will discontinue the study intervention (treatment), thereby discontinuing the treatment period, and will remain in the study to complete procedures for an early discontinuation visit and posttreatment follow-up, if applicable as shown in the SoA.

A participant should be permanently discontinued from study intervention if

- the participant becomes pregnant during the study
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons, or
- acute pancreatitis is diagnosed.

In addition, study intervention may be discontinued if participants.

- answered “yes” to Question 4 or Question 5 on the “Suicidal Ideation” portion of the C-SSRS, or
- answered “yes” to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.

7.1.1. Hepatic Criteria for Study Drug Interruption or Discontinuation

See Section 8.3.6.3 for hepatic criteria for study drug interruption or discontinuation.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study.

- at any time at the participant’s own request for any reason or without providing any reason
- at the request of the participant’s designee, for example, parents or legal guardian
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, or
- if enrolled in any other clinical study involving an IP or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit, as shown in the SoA. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the CRU study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the CRU. CRU personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the CRU.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA in Section 1.3.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

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

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

See Section 10.1.10 for details about sample retention and custody.

8.1. Efficacy Assessments

Efficacy is not evaluated in this study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA in Section 1.3.

8.2.1. Physical Examinations

Physical examinations will be conducted as specified in the SoA in Section 1.3, and as clinically indicated.

A complete physical examination (performed at screening) includes, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded as specified in the SoA in Section 1.3.

A symptom-directed physical examination will be performed at other visits, as deemed necessary by the investigator.

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

8.2.2. Vital Signs

For each participant, vital sign measurements should be conducted according to the SoA in Section 1.3.

BP and pulse rate should be measured after at least 5 minutes sitting. When possible, measurements of BP and pulse rate should be performed at approximately the same time of day at each scheduled time point.

Unscheduled vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. For these measurements, participants should be sitting for at least 5 minutes and then, the measurement is obtained between 2 and 3 minutes after standing. If the participant feels unable to stand, supine vital signs only will be recorded. Additional vital signs may be measured throughout the study per investigator discretion.

8.2.3. Electrocardiograms

For each participant, a single 12-lead digital ECG will be collected according to the SoA in Section 1.3. All single ECGs recorded should be stored at the CRU.

Single 12-lead ECGs may be obtained at additional times when deemed clinically necessary, for example to assess participants' safety.

ECGs must be recorded before collecting any blood samples. Participants must be supine for at least 5 to 10 minutes before ECG collection, and remain supine and awake, during ECG collection. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of study intervention should be reported to the sponsor, or its designee, as an AE via the electronic CRF.

ECGs will be interpreted by the investigator or qualified designee at the CRU as soon as practically possible after the time of ECG collection, to determine whether the participant meets entry criteria.

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2, Section 10.2 for the list of clinical laboratory tests to be performed and the SoA in Section 1.3 for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

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

All protocol-required laboratory assessments, as defined in Appendix 2, Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

If laboratory values from non-protocol-specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator, for example, SAE or AE or dose modification, then report the information as an AE.

8.2.5. Pregnancy Testing

Pregnancy testing will be performed for all females at the time points according to the SoA in Section 1.3. See Section 8.3.3 for details on pregnancy.

8.2.6. Depression, Suicidal Ideation, and Behavior Risk Monitoring .

Participants who have obesity or are overweight are at increased risk of depression (Luppino et al. 2010). Depression can increase the risk of SIB. Therefore, participants will be screened at study entry and monitored during the study for depression, suicidal ideation, and behavior.

8.2.6.1. Suicide Monitoring

For each participant, SIB risk monitoring will be performed according to the SoA in Section 1.3.

Participants should be monitored appropriately and observed closely for SIB or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

Baseline assessment of SIB, and intervention-emergent SIB, will be monitored during the study using C-SSRS.

C-SSRS

The C-SSRS is a scale that captures the occurrence, severity, and frequency of SIB during the assessment period via a semistructured interview by a trained rater. The scale was developed by the National Institute of Mental Health trial group for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events.

For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

Timing of collection and AE monitoring

Nonleading AE collection should occur prior to the collection of the C-SSRS.

Only report a suicide-related event discovered during collection of the C-SSRS on the AE form if it is an AE that leads to discontinuation or an SAE.

Follow standard procedures for reporting SAEs.

Depression Monitoring

Monitor participants receiving study intervention for depression or any other unusual changes in behavior, especially at the beginning and end of the course of treatment, or at the time of dose escalations.

CRU personnel should alert family members and caregivers of participants receiving study intervention about the need to monitor participants for the emergence of depression or unusual changes in behavior, and to report such symptoms immediately to the investigator.

Depression is monitored using PHQ-9.

8.2.6.1.1. PHQ-9

The PHQ-9 (Spitzer et al. 1999; Moriarty et al. 2015) is a validated, participant-reported instrument that assesses the specific diagnostic symptoms that determine the presence of a

clinical depressive disorder per the Diagnosis and Statistical Manual for Mental Disorders, fifth Edition.

The questionnaire assesses the previous 2 weeks.

The PHQ-9 assesses 9 diagnostic symptoms:

- mood
- anhedonia
- appetite change
- sleep disturbance
- psychomotor agitation or retardation
- loss of energy
- feelings of worthlessness or guilt
- diminished concentration, and
- suicidal thoughts or attempts.

Each question has 4 response options, with scores ranging from 0 to 3. Higher numbers indicate greater dysfunction.

This table describes the interpretation of results.

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

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 3 in Section 10.3:

- AEs
- SAEs, and
- PCs.

These events will be reported by the participant, or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7).

Care will be taken not to introduce bias when detecting events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow up each participant at subsequent visits/contacts. All SAEs and AESIs will be followed up until resolution,

stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature or causality. Further information on follow-up procedures is provided in Appendix 3 in Section 10.3.

8.3.1. Timing and Mechanism for Collecting Events

Table GZPI.2 describes the timing, deadlines, and mechanism for collecting events.

Table GZPI.2. Timing and Mechanism for Collecting Events

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the informed consent form	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the informed consent form	Start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE* – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	At least 45 days after the last dose	Within 24 hours (see Section 8.3.3)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint Form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint Form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint Form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint Form	

Abbreviations: AE = adverse event; CRF = case report form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

* SAEs should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Adverse Event Monitoring with a Systematic Questionnaire

Nonleading AE collection should occur prior to the collection of the C-*SSRS*.

If a suicide-related event is discovered during the C-SSRS but was not captured during the nonleading AE collection, sites should not change the AE form.

If an AE is serious or leads to discontinuation, it needs to be included on the AE form and the process for reporting SAEs is followed.

8.3.3. Collection of Pregnancy Information

8.3.3.1. Participants Who Become Pregnant

The investigator will collect pregnancy information on any participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed up to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, the investigator may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating in the study will be withdrawn from the study. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3.2. Participants with Partners Who Become Pregnant

When to collect pregnancy information

In most circumstances, the investigator will attempt to collect pregnancy information from a participant's partner who becomes pregnant while the participant is in this study.

After learning about a pregnancy in the partner of a study participant, the investigator

- will obtain a consent to release information from the pregnant partner directly, and
- within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

The partner will be followed up to determine the outcome of the pregnancy. Information on the status of the mother and neonate will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks after the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

When not to collect pregnancy information

It is not necessary to collect information about a pregnancy in the partner of a study participant

in these circumstances

- the partner of the study participant was not exposed to the study intervention, or
- the participant did not contribute the sperm or ova that resulted in the pregnancy.

8.3.4. Adverse Events of Special Interest

Nausea, vomiting, and diarrhea events are considered AESIs and will be recorded as AEs in the electronic CRF. For each event, assessment of severity, duration (start and stop dates and times), and investigator's opinion of relatedness to study treatment and protocol procedure will be captured. Other AESIs for this program include:

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

If any of these AESIs are reported, sites will be prompted to collect additional details and data.

8.3.5. Pancreatic Monitoring

Diagnosis of acute pancreatitis

Acute pancreatitis is an AE of interest in all studies with orforglipron, including this study. The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks and Freeman 2006; Koizumi et al. 2006):

- abdominal pain, characteristic of acute pancreatitis, that is, epigastric pain radiating to the back, often associated with nausea and vomiting
- serum amylase, that is total, pancreatic, or both, and/or lipase equal to or greater than 3 × ULN, or
- characteristic findings of acute pancreatitis on scan or magnetic resonance imaging.

If acute pancreatitis is suspected, the investigator should

- obtain appropriate laboratory tests, including pancreatic amylase and lipase
- perform imaging studies, such as abdominal computed tomography scan with or without contrast, or abdominal magnetic resonance imaging, and
- evaluate for possible causes of acute pancreatitis, including alcohol use, gallstone or gall bladder disease, hypertriglyceridemia, and concomitant medications.

Asymptomatic elevation of serum amylase and/or lipase

Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic patients (Nauck 2016; Steinberg et al. 2017a, 2017b). Therefore, further diagnostic follow-up of cases of asymptomatic elevation of pancreatic enzymes, that is lipase, pancreatic amylase, or both, at levels equal to or greater than 3 × ULN, is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

8.3.6. Hepatic Safety Monitoring, Evaluation, and Criteria for Study Intervention Interruption or Discontinuation

The following tables summarize actions to take based on abnormal hepatic laboratory or clinical changes.

Participants with normal or near normal baseline (ALT, AST, or ALP levels less than 1.5 × ULN)

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation	Interrupt or discontinue study drug
ALT or AST ≥3 × ULN	X		
ALP ≥2 × ULN	X		
TBL ≥2 × ULN[b]	X		
ALT or AST ≥5 × ULN	X	X	
ALP ≥2.5 × ULN	X	X	
ALT or AST ≥3 × ULN with hepatic signs or symptoms[a]	X	X	X
ALT or AST ≥5 × ULN for more than 2 weeks	X	X	X
ALT or AST ≥8 × ULN	X	X	X
ALT or AST ≥3 × ULN and TBL ≥2 × ULN[b] or international normalization ratio (INR) ≥ 1.5	X	X	X
ALP ≥3 × ULN	X	X	X
ALP ≥2.5 × ULN and TBL ≥2 × ULN[b]	X	X	X
ALP ≥2.5 × ULN with hepatic signs or symptoms[a]	X	X	X

[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

[b] In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Participants with elevated baseline (ALT, AST, or ALP levels equal to or greater than 1.5 × ULN)

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation	Interrupt or discontinue study intervention
ALT or AST ≥2 × baseline	X		
ALP ≥2 × baseline	X		
TBL ≥2 × ULN[b]	X		
ALT or AST ≥3 × baseline or ≥250 U/L (whichever occurs first)	X	X	
ALP ≥2.5 × baseline	X	X	
ALT or AST ≥2 × baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a]	X	X	X
ALT or AST ≥3 × baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks	X	X	X
ALT or AST ≥4 × baseline or ≥400 U/L (whichever occurs first)	X	X	X
ALT or AST ≥2 × baseline or ≥250 U/L (whichever occurs first) and TBL ≥2 × ULN[b] or INR ≥1.5	X	X	X
ALP ≥3 × baseline	X	X	X
ALP ≥2.5 × baseline and TBL ≥2 × ULN[b]	X	X	X
ALP ≥2.5 × baseline with hepatic signs or symptoms[a]	X	X	X

a Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

b In participants with Gilbert's syndrome, the threshold for TBL may be higher.

8.3.6.1. Close Hepatic Monitoring

If a participant develops any one of these changes, initiate close hepatic monitoring:

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5 × ULN)	Participants with elevated baseline (ALT, AST, or ALP ≥1.5 × ULN)
ALT or AST ≥3 × ULN **or**	ALT or AST ≥2 × baseline
ALP ≥2 × ULN **or**	ALP ≥2 × baseline
TBL ≥2 × ULN[a]	TBL ≥2 × ULN[a]

a In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Close hepatic monitoring should include these actions:

- Laboratory tests detailed in Appendix 6 in Section 10.6, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, creatine kinase, and complete blood count with differential, should be checked within 48 to 72 hours of the detection of elevated liver test results to confirm the abnormality and to determine if it is increasing or decreasing.

- If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 2 to 3 times weekly until levels normalize or return to approximate baseline values.
- In addition to laboratory tests, basic evaluation for possible causes of abnormal liver test results should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including:
    - current symptoms
    - recent illnesses such as heart failure, systemic infection, hypotension, or seizures
    - recent travel
    - concomitant medications, including OTC, herbal and dietary supplements, and
    - history of alcohol drinking and other substance abuse.

8.3.6.2. Comprehensive Hepatic Evaluation

If a participant develops any one of the following laboratory or clinical changes, initiate a comprehensive hepatic evaluation:

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5 × ULN)	**Participants with elevated baseline (ALT, AST, or ALP ≥1.5 × ULN)**
ALT or AST ≥5 × ULN **or**	ALT or AST ≥3 × baseline or ≥250 U/L (whichever occurs first) **or**
ALP ≥2.5 × ULN **or**	ALP ≥2.5 × baseline **or**
ALT or AST ≥3 × ULN with hepatic signs or symptoms[a] **or**	ALT or AST ≥2 × baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a] **or**
ALT or AST ≥5 × ULN for more than 2 weeks **or**	ALT or AST ≥3 × baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks **or**
ALT or AST ≥8 × ULN **or**	ALT or AST ≥4 × baseline or ≥400 U/L (whichever occurs first) **or**
ALT or AST ≥3 × ULN and TBL ≥2 × ULN[b] or INR ≥ 1.5	ALT or AST ≥2 × baseline or ≥250 U/L (whichever occurs first) and TBL ≥2 × ULN[b] or INR ≥ 1.5

a Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

b In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Comprehensive hepatic evaluation should include these actions:

- At a minimum, comprehensive hepatic evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for:
    - prothrombin time-INR
    - tests for viral hepatitis A, B, C, and E
    - tests for autoimmune hepatitis, and
    - an abdominal imaging study, for example, ultrasound or computed tomography scan.
- Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for:
    - hepatitis D virus

  - cytomegalovirus
  - Epstein-Barr virus
  - acetaminophen levels
  - acetaminophen protein adducts
  - urine toxicology screen
  - Wilson's disease
  - blood alcohol levels
  - urinary ethyl glucuronide, and
  - blood phosphatidylethanol.
- Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, and additional tests including:
  - magnetic resonance cholangiopancreatography
  - endoscopic retrograde cholangiopancreatography
  - cardiac echocardiogram, or
  - a liver biopsy.
- Clinical and laboratory monitoring should continue at a frequency of 1 to 2 times weekly until levels normalize or return to approximate baseline values.
- All the medical information and test results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.3.6.3. Study Intervention Interruption or Discontinuation

If a participant develops any one of the following laboratory or clinical changes, interrupt the study drug and continue close monitoring as described in Section 8.3.6.1 and comprehensive hepatic evaluation as described in Section 8.3.6.2.

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5 × ULN)	**Participants with elevated baseline (ALT, AST, or ALP ≥1.5 × ULN)**
ALT or AST ≥3 × ULN with hepatic signs or symptoms[a] **or**	ALT or AST ≥2 × baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a] **or**
ALT or AST ≥5 × ULN for more than 2 weeks **or**	ALT or AST ≥3 × baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks **or**
ALT or AST ≥8 × ULN **or**	ALT or AST ≥4 × baseline or ≥400 U/L (whichever occurs first) **or**
ALT or AST ≥3 × ULN and TBL ≥2 × ULN[b] or INR≥ 1.5 **or**	ALT or AST ≥2 × baseline or ≥250 U/L (whichever occurs first) and TBL ≥2 × ULN[b] **or**
ALP ≥3 × ULN **or**	ALP ≥3 × baseline **or**
ALP ≥2.5 × ULN and TBL ≥2 × ULN[b] **or**	ALP ≥2.5 × baseline and TBL ≥2 × ULN[b] **or**
ALP ≥2.5 × ULN with hepatic signs or symptoms[a]	ALP ≥2.5 × baseline with hepatic signs or symptoms[a]

a Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

b In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Interruption or discontinuation of study intervention should include these actions:

- While the participant is not receiving the study intervention, clinical and laboratory monitoring should continue at a frequency of 1 to 2 times weekly until liver test results normalize or return to approximate baseline values.
- If the hepatic event continues past the anticipated end of the study, that is, data lock, the investigator should consult with the Lilly-designated medical monitor to determine the need for further data collection beyond the end date of the study, that is, data lock date.
- All the medical information and test results related to the close hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.
- Resumption of the study intervention after interruption for a hepatic reason can be considered only in consultation with the Lilly-designated clinical pharmacologist or clinical research physician and only if the liver test results returned to near baseline and if a self-limited nonstudy intervention etiology is identified. Otherwise, the study intervention should be permanently discontinued.

8.3.7. Hypoglycemia

Participants will be trained by authorized study personnel about signs and symptoms of hypoglycemia and how to treat hypoglycemia. Participants may, at the investigator's discretion, be given a glucometer to assist in the evaluation of these symptoms.

Investigators should use the following classification of hypoglycemia:

Level 1 hypoglycemia:

Glucose less than 70 mg/dL or 3.9 mmol/L, and equal to or greater than 54 mg/dL or 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 less than 54 mg/dL or 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 or 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 (in adults): A severe event characterized by altered mental or physical status, or both, 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.

8.4. Pharmacokinetics

At the visits and times specified in the SoA in Section 1.3, venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of orforglipron. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed on between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

A blood sample for DNA isolation will be collected from participants.

See Appendix 5 in Section 10.5 for information regarding genetic research.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Not applicable.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

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

9. Statistical Considerations

The statistical analysis plan will be finalized prior to first participant first visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypothesis

The primary objective of this study is to evaluate the BE of orforglipron tablet and capsule at capsule dose levels of CCI mg in Part B.

The secondary objective is to assess the bioequivalence of orforglipron tablets and capsules at capsule dose levels of CCI mg in Part B.

9.2. Analyses Sets

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

Participant Analysis Set	Description
Enrolled	All participants randomly assigned to study intervention.
Safety analysis set	All participants who are exposed to at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
PK analysis set	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.

9.2.1. Study Participant Disposition

A detailed description of participant disposition will be provided at the end of the study.

9.2.2. Study Participant Characteristics

The participants' age, sex, weight, height, body mass index, race, and other demographic characteristics will be recorded and summarized using descriptive statistics.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of the sponsor or its designee.

PK analyses will be conducted for the PK analysis set according to the formulation and actual dose received. Safety analyses will be conducted for the safety analysis set.

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the statistical analysis plan, where appropriate. Adjustments to the planned analyses are described in the final CSR.

9.3.2. Primary Endpoint Analysis

9.3.2.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for orforglipron will be calculated using standard noncompartmental methods of analysis.

The primary PK parameters for analysis will be $AUC_{(0-\tau)}$ and C_{max} of orforglipron capsule dose levels of CCI [redacted] mg and the corresponding tablet dose strengths, and the secondary parameters will be $AUC_{(0-\tau)}$ and C_{max} of orforglipron capsule dose levels [redacted] and CCI [redacted] mg and the corresponding tablet dose strengths.

Other noncompartmental parameters, such as apparent clearance, and apparent volume of distribution, t_{max} (time of the C_{max}), $AUC_{(0-tlast)}$, C_{min}, C_{ave} (average concentration during a dosing interval), degree of fluctuation $[(C_{max}-C_{min})/C_{ave}]$, swing $[(C_{max}-C_{min})/C_{min}]$ at steady state may be reported.

9.3.2.2. Pharmacokinetic Statistical Inference

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.

Two 1-sided t-tests will be applied to the ratio of the geometric means (GMR) between each dose steady-state $AUC_{(0-\tau)}$ and C_{max} using capsule as the reference and the selected tablet as test separately for CCI [redacted] mg. Test limits of the GMRs to establish BE will be applied using the mixed scaling approach (Statistical Approaches to Establishing Bioequivalence 2023, Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under ANDA 2021).

The reference capsule's Swr 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.

If the estimated Swr $\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: $(0.8^{Swr/0.25}, 1.25^{Swr/0.25})$.

If the estimated Swr <0.294, the two 1-sided t-test procedure will be used to determine BE for the individual PK parameter with bioequivalent boundary of (0.8, 1.25). In this case, a linear mixed effect model will be fitted at each capsule dose level with sequence, period, and treatment (capsule and selected tablet) as fixed effects, subject 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. The treatment difference between the tablet and the corresponding capsule will be back transformed to present the GMR and the corresponding 90% CIs. If the 90% CI of the GMR falls within the boundary, BE will be claimed.

9.3.3. Secondary Endpoints Analysis

The $AUC_{(0-\tau)}$ and C_{max} at capsule dose level of CCI mg from Part B will follow the same model as described in Section 9.3.2.2.

9.3.3.1. Clinical Evaluation of Safety

All IP and protocol procedure AEs will be listed and, if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of AEs for each treatment will be presented by severity and by association with IP as perceived by the investigator. AEs reported to occur prior to study entry will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities.

The number of IP-related SAEs will be reported.

9.3.3.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include vital signs. Significant ECG abnormalities will be captured as treatment-emergent adverse events. The parameters and changes from baseline (Period 1, Day 1 predose), where appropriate, will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

9.3.4. Other Analyses

9.3.4.1. Analysis of C-SSRS Data

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (C-SSRS WWW).

9.3.4.2. Additional PK Parameters

The t_{max} at each capsule dose level as reference will be analyzed using Wilcoxon signed rank test to compare with the counterpart of tablet form. Estimates of the median difference between each tablet and corresponding capsule at each dose level based on the observed medians, approximately 90% CIs, and p-value from the Wilcoxon signed rank test will be calculated. The t_{max} for capsule will take the median of the 2 measures from the 2 replicate periods from each study participant prior to analysis.

9.4. Interim Analysis

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.

9.5. Sample Size Determination

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 Swr $\geq$0.294, or (0.8 to 1.25) if Swr <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.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

- consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- applicable ICH GCP guidelines, and
- applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

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

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

The investigator will be responsible for the following:

- providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations, and
- reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.

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

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

Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with sponsor and ERB consenting guidance.

A copy of the ICF(s) must be provided to the participant and is kept on file.

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

10.1.3. Data Protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.

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

The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation.

10.1.4. Dissemination of Clinical Study Data

Communication of suspended or terminated dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators (for example, through phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

The sponsor does not proactively share data from Phase 1 clinical trials. Requests for access to Phase 1 clinical trial data are evaluated on a case-by-case basis taking into consideration the ability to anonymize the data and the nature of the data collected.

10.1.5. Data Quality Assurance

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This includes laboratory tests, medical records, and clinical notes.

The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source documents.

Monitoring details describing strategy, for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

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

The sponsor assumes accountability for actions delegated to other individuals, for example, contract research organizations.

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the clinical trial agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data capture system

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports or electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global PC management system.

10.1.6. Source Documents

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

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

Definition of what constitutes source data can be found in the site confirmation of source data.

10.1.7. Study and Site Start and Closure

First act of recruitment

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

The first act of recruitment is the first site open and will be the study start date.

Study or site termination

The sponsor or sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

- for study termination due to discontinuation of further study intervention development
- for site termination due to
    - failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
    - inadequate recruitment, evaluated after a reasonable amount of time of participants by the investigator, or
    - total number of participants included earlier than expected.

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

10.1.8. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication in a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.1.9. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical trial.

10.1.10. Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of orforglipron or after orforglipron becomes commercially available for the studied indication.

Sample Type	Custodian	Retention Period after Last Participant Visit
Pharmacokinetics	Sponsor or designee	1 year
Pharmacogenetics	Sponsor or designee	15 years

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the following table will be performed by the central laboratory or local laboratory.

In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the following table), the local laboratory must be qualified in accordance with applicable local regulations.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of the laboratory safety results.

Clinical Laboratory Tests	Comments
Hematology	• Assayed by local laboratory at screening and baseline • Assayed by central laboratory at baseline and during the study
• Hematocrit • Hemoglobin • Erythrocyte count (red blood cells) • Mean cell volume • Mean cell hemoglobin • Mean cell hemoglobin concentration • Leukocytes (white blood cells) • Platelets • Absolute counts of: o Neutrophils o Lymphocytes o Monocytes o Eosinophils o Basophils	
Clinical Chemistry	• Assayed by local laboratory at screening and baseline • Assayed by central laboratory at baseline and during the study
• Sodium • Potassium • Bicarbonate • Chloride • Calcium • Phosphate • Glucose (fasting) • Urea • Total protein • Albumin • Amylase[a] • Lipase[a] • Creatinine • Creatine kinase	[a] Performed at screening, and on Day 8 of the week(s) specified in the SoA, follow-up visit, and early termination, if applicable. [b] Calculated low-density lipoprotein cholesterol.

Clinical Laboratory Tests	Comments

• Uric acid
• Liver panel
  ○ Total bilirubin
  ○ Direct bilirubin
  ○ Indirect bilirubin
  ○ Alkaline phosphatase
  ○ Aspartate aminotransferase
  ○ Alanine aminotransferase
• Lipid panel
  ○ Total cholesterol
  ○ Triglycerides
  ○ Low-density lipoprotein cholesterol[b]
  ○ High-density lipoprotein cholesterol	

Urinalysis	• Assayed by local laboratory at screening and baseline • Assayed by central laboratory at baseline and during the study.
• Specific gravity • pH • Protein • Glucose • Ketones • Bilirubin • Urobilinogen • Leukocytes • Blood • Nitrite • Microscopic examination of sediment[c]	[c] Microscopic examination of sediment only to be performed if dipstick result is abnormal and is further definable by microscopy. Microscopy to be performed at the local or central safety laboratory, if clinically indicated, at investigator's discretion.
Pregnancy Test (All Females)	Assayed by local laboratory.
• Serum pregnancy test • Urine pregnancy test	Screening: serum pregnancy test. Other time points: urine pregnancy test.
HIV and Hepatitis Serology	
• Hepatitis B surface antigen • Hepatitis B core antibody (total) • Hepatitis C antibody • HCV RNA • HIV	Performed at screening only by a local laboratory, except for HCV RNA test, which may be tested at Lilly central or local laboratory. These tests may be waived if performed within 6 months prior to screening, and if test results are available for "review" for hepatitis B, HCV, and HIV. HCV RNA test performed only to confirm a positive hepatitis C antibody test.
Other Tests	Assayed by local laboratory.
• Follicle-stimulating hormone[d,f] • Calcitonin[d] • Glycated hemoglobin (HbA1c)[d] • Ethanol test[e] • Urine drug screen[g]	[d] Performed at screening only. [e] Urine test performed at screening, and breath or urine test performed on Day -1. [f] Performed for females only. [g] Performed at screening and check in.

Clinical Laboratory Tests	Comments
• Thyroid-stimulating hormone (TSH)[d]	
Genetics Sample	Sample will be assayed and stored by Lilly central laboratory. Results will not be provided to the investigative sites.

Abbreviations: HCV = hepatitis C virus; HIV = human immunodeficiency virus.

Note: complete blood count, urea, creatinine, blood glucose, indirect bilirubin, direct bilirubin, total bilirubin, total protein and albumin, total cholesterol, triglycerides, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase, uric acid, and routine urinalysis, are to be performed on Day -1 and during follow-up visit and additional timepoints as indicated in the SoA.

10.2.1. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Part A: Pilot Study

Protocol J2A-MC-GZPI Sampling Summary: Cohort 1A

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a] (local laboratory)	45	1	45
HbA1c (local laboratory)	2	1	2
Baseline clinical laboratory tests[a] (local laboratory)	12	1	12
Central clinical laboratory tests[a] (Baseline)	6	1	6
Central clinical laboratory tests[a] (other than baseline)	9.5	2	19
Clinical chemistry tests	4	3	12
Pharmacogenetics	10	1	10
Pharmacokinetics[b]	2	123	246
Total			352
Total for clinical purposes			360

Abbreviation: HbA1c = glycated hemoglobin.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Includes additional 3 samples, if required.

Protocol J2A-MC-GZPI Sampling Summary: Cohort 2A

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a] (local laboratory)	45	1	45
HbA1c (local laboratory)	2	1	2
Baseline clinical laboratory tests[a] (local laboratory)	12	1	12
Central clinical laboratory tests[a] (Baseline)	6	1	6

Central clinical laboratory tests[a] (other than baseline)	9.5	2	19
Clinical chemistry tests	4	4	16
Pharmacogenetics	10	1	10
Pharmacokinetics[b]	2	123	246
Total			356
Total for clinical purposes			360

Abbreviation: HbA1c = glycated hemoglobin.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Includes additional 3 samples, if required.

Part B: BE Study

Protocol J2A-MC-GZPI Sampling Summary: Cohort 1B

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a] (local laboratory)	45	1	45
HbA1c (local laboratory)	2	1	2
Baseline clinical laboratory tests[a] (local laboratory)	12	1	12
Central clinical laboratory tests[a] (Baseline)	6	1	6
Central clinical laboratory tests[a] (other than baseline)	9.5	2	19
Clinical chemistry tests	4	2	8
Pharmacogenetics	10	1	10
Pharmacokinetics[b]	2	93	186
Total			288
Total for clinical purposes			290

Abbreviation: HbA1c = glycated hemoglobin.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Includes additional 3 samples, if required.

Protocol J2A-MC-GZPI Sampling Summary: Cohort 2B

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a] (local laboratory)	45	1	45
HbA1c (local laboratory)	2	1	2
Baseline clinical laboratory tests[a] (local laboratory)	12	1	12
Central clinical laboratory tests[a] (Baseline)	6	1	6
Central clinical laboratory tests[a] (other than baseline)	9.5	2	19
Clinical chemistry tests	4	3	12
Pharmacogenetics	10	1	10
Pharmacokinetics[b]	2	93	186

Total	292
Total for clinical purposes	300

Abbreviation: HbA1c = glycated hemoglobin.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Includes additional 3 samples, if required.

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

10.3.1. Definition of AE

- An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, or investigational combination product, whether or not related to the medicinal (investigational) product or investigational combination product.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments, for example, ECG, radiological scans, and vital sign measurements, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of investigational medicinal product, including signs, symptoms, or clinical sequelae.

Events <u>NOT</u> meeting the AE definition

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

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

- Results in death
- Is life threatening
    - The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
    - Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
    - This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma, for example, sprained ankle, which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
    - Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs.
- Other situations:
    - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product complaint

A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:

- deficiencies in labeling information, and
- use errors for device or drug-device combination products due to ergonomic design elements of the product.

PCs related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.

An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

10.3.4. Recording and Follow-Up of AE and/or SAE and PCs

AE, SAE, and PC recording

When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and PC information is reported on the Product Complaint Form.

Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for PCs.

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

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

Assessment of intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

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

Assessment of causality

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

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

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

The investigator will also consult the IB in their assessment.

The investigator **must** review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible.

This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE reporting via paper form

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor or designee.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in the Global Patient Safety Clinical Trial SAE Transmission Cover Sheet and Form.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of suspected unexpected serious adverse reactions according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions and Guidance

Word/Phrase	Definition
Individuals assigned female at birth (AFAB)	Individuals assigned the female sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are potentially capable of gestating a fetus, and thus are capable of exposing an egg, embryo, or fetus to study drug or drug effects.
Individuals assigned male at birth (AMAB)	Individuals assigned the male sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are not capable of gestating a fetus, but are capable of exposing a fetus to study drug or drug effects via their semen. Individuals AMAB are considered to be not of reproductive potential if they have had orchiectomy (orchidectomy) with or without penectomy, confirmed by operative note.
Individuals of childbearing potential (IOCBP)[a]	Adult individuals AFAB are considered IOCBP unless they are INOCBP. Individuals less than 18 years of age are considered IOCBP if they have • had at least 1 cycle of menses, or • Tanner Stage 4 breast development (if Tanner staging assessments are required as part of the specific study protocol) Any amount of spotting should be considered menarche. Menarche status and date of menarche should be monitored for every pediatric study participant who is AFAB, starting at 8 years of age until the onset of menses, and therefore, childbearing potential. It is recommended that such monitoring be conducted every 3 to 6 months at a site visit following evaluation from the provider/investigator. Note: Adolescent or adult individuals AFAB who are receiving hormone therapy as part of gender transition are considered IOCBP unless they meet the conditions outlined below for INOCBP.
Individuals not of childbearing potential (INOCBP)[b]	Individuals AFAB are considered INOCBP if they are not capable of producing ova or embryo, and/or are not capable of potentially gestating a fetus. Such individuals include those who • have a congenital anomaly such as Müllerian agenesis, resulting in confirmed infertility • are infertile due to surgical sterilization, or

	• are postmenopausal. Acceptable surgical sterilization methods are hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Menopausal state[c]	The menopausal state is defined as an individual: • at any age at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[c], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone greater than 40 mIU/mL • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy.

a IOCBP is inclusive of the concept of women of childbearing potential (WOCBP or WCBP), a term often used in literature and regulatory guidance documents.

b INOCBP is inclusive of the concept of women not of childbearing potential (WNOBCP).

c The individual should not be taking medications during amenorrhea such as oral contraceptives, hormone replacement therapy (HRT), gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea. Individuals on HRT and those whose menopausal status cannot be confirmed will be required to comply with the protocol contraception requirements if they wish to continue HRT during the study. Otherwise they must discontinue HRT to allow confirmation of menopausal status before study enrollment.

10.4.2. Contraception Guidance

10.4.2.1. Individuals Assigned Male at Birth

Individuals AMAB may participate in this trial.

For individuals AMAB, no contraception is required except in compliance with specific local government study requirements.

10.4.2.2. Individuals Assigned Female at Birth

IOCBP and INOCBP may participate in this trial. See Section 10.4.1 for definitions and additional requirements related to contraception.

IOCBP who are completely abstinent as their preferred and usual lifestyle, or exclusively engage in sexual relations with other individual(s) who are AFAB as their preferred and usual lifestyle must follow the rules in this table.

Must…	Must not…

agree to either remain abstinent or exclusively engage in sexual relations with other individual(s) who are AFAB, and not plan a pregnancy during the study	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

IOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or who do NOT exclusively engage in sexual relations with other individual(s) who are AFAB as their preferred and usual lifestyle, must follow the rules in this table.

Must…
Agree to use 2 forms of effective contraception, where at least 1 method must be highly effective. These methods of contraception must be used during the study and after the study for at least 45 days after the last dose of the study intervention.

Examples of different methods of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• fallopian tubal sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization). Note: Bilateral salpingectomy is indicative of permanent sterilization. Please refer to INOCBP definition above • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only individuals <198 pounds or 90 kg) • total abstinence • sexual relationships exclusively between individuals who are assigned the same sex at birth • vasectomy – for individuals AMAB in clinical trials and for the partner of an individual AFAB (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • vaginal ring containing combination hormone medication, or • intrauterine devices.
Effective contraception	• penile condom with spermicide • vaginal condom with spermicide • diaphragms with spermicide or cervical sponges • cervical sponge with spermicide, or • cervical cap with spermicide. Note: Penile and vaginal condoms should not be used in combination.
Ineffective methods of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea.

10.5. Appendix 5: Genetics

Use/analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to orforglipron or T2DM, chronic weight management and related diseases. They may also be used to develop tests/assays including diagnostic tests related to orforglipron, T2DM, chronic weight management, and related diseases. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to orforglipron or study interventions of this class to understand study disease or related conditions.

The results of genetic analyses may be reported in the clinical study report or in a separate study summary.

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

The samples will be retained while research on orforglipron continues but no longer than 15 years or other period as per local requirements.

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

Hepatic evaluation testing

See Section 8.3.6 for guidance on appropriate test selection.

The Lilly-designated central laboratory should complete the analysis of all selected testing except for testing listed in the investigator-designated local laboratory table. The central laboratory will report results if a validated test or calculation is available.

Local testing may be performed *in addition to central testing* when necessary for immediate participant management. The local laboratory must be qualified in accordance with applicable local regulations. If testing is not available in certain regions based on local requirements, consult with Lilly-designated medical monitor.

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing:**
Hemoglobin	HAV total antibody[a]
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs - red blood cells)	**Hepatitis B virus (HBV) testing:**
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA[b]
Basophils	**Hepatitis C virus (HCV) testing:**
Eosinophils	HCV total antibody[a]
Platelets	HCV RNA[b]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV total antibody[a]
Total bilirubin	
Direct bilirubin	HDV RNA[b]
Alkaline phosphatase (ALP)	**Hepatitis E virus (HEV) testing:**
Alanine aminotransferase (ALT)	HEV IgG antibody
Aspartate aminotransferase (AST)	HEV IgM antibody
Gamma-glutamyl transferase (GGT)	HEV RNA[b]
Creatine kinase (CK)	**Anti-nuclear antibody (ANA)**
Hepatic Coagulation Panel	**Anti-smooth muscle antibody (ASMA) or anti-actin antibody**
Prothrombin time, INR (PT-INR)	**Immunoglobulin IgA (quantitative)**
Urine Chemistry	**Immunoglobulin IgG (quantitative)**
Drug screen	**Immunoglobulin IgM (quantitative)**
Haptoglobin	**Phosphatidylethanol (PEth)**

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing:**
Acetaminophen protein adducts[c]	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA[b]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (ethanol, EtOH)	HSV (Type 1 and 2) DNA[b]
Urine Chemistry	Liver kidney microsomal type 1 (LKM-1) antibody
Ethyl glucuronide (EtG)	**Microbiology Culture:**
Epstein-Barr virus (EBV) testing:	Blood
EBV antibody	Urine
EBV DNA[b]	

Abbreviation: Ig = immunoglobulin.

a If a laboratory does not offer total antibody testing, IgG and/or IgM are acceptable substitutes.

b Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

c Availability of acetaminophen protein adducts testing is limited, hence testing may be performed at central laboratories, if needed.

10.7. Appendix 7: Examples of Excluded Medications

These lists are intended to be exhaustive, but with available information continually evolving, the status of every relevant drug cannot be guaranteed.

10.7.1. Weight Loss Medications

Throughout the study, participants will not be allowed to take medications intended to promote weight loss, including prescribed, OTC, or alternative remedies, including

- ingested material that transiently occupies space in the stomach, for example, Plenity®
- liraglutide
- tirzepatide
- lorcaserin
- mazindol
- naltrexone/bupropion
- orlistat
- OTC medications, for example, allī®
- phentermine
- phentermine/topiramate
- phenylpropanolamine
- semaglutide
- sibutramine, and
- other incretin-based therapies.

10.7.2. CYP3A4 Inhibitors, CYP3A Inducers, OATP Inhibitors, and P-gp and BCRP Substrates

Throughout the study, during both inpatient and outpatient periods, to avoid altering the PK of orforglipron which is a P-gp and an OATP substrate, participants will not be allowed to take

- moderate or strong CYP3A4 inhibitors
- moderate or strong CYP3A inducers, and
- moderate or strong OATP inhibitors.

It cannot be ruled out that orforglipron may cause inhibition of P-gp or BCRP substrates. Therefore, from 14 days prior to screening and throughout the study participants must abstain from taking drugs that are sensitive P-gp or BCRP substrates with a narrow therapeutic index.

These drugs must be washed out from at least 14 days prior to screening, and the participant should be on a stable dose of alternative medications for at least 14 days prior to screening.

Drugs that may be affected by an increase in gastric pH should be separated from study drug administration by at least 4 hours.

10.7.2.1. Strong CYP3A4 Inhibitors

Participants will not be allowed to take strong CYP3A4 inhibitors including

- atazanavir and cobicistat – HIV

- ceritinib – cancer, metastatic nonsmall cell lung cancer
- clarithromycin – antibiotic to treat bacterial infections
- cobicistat – HIV/AIDS
- conivaptan – to treat low blood sodium levels
- fosamprenavir and ritonavir - HIV/AIDS
- grapefruit juice
- idelalisib – cancer, chronic lymphocytic leukemia
- indinavir and ritonavir – HIV/AIDS
- itraconazole – antifungal – can be applied topically, but caution to be exercised if orally used
- lonafarnib – to treat Hutchinson-Gilford progeria syndrome and for the treatment of certain processing-deficient progeroid laminopathies in those aged 1 year and older
- lopinavir and ritonavir – HIV/AIDS
- mifepristone – medical abortion
- nefazodone – antidepressant - limited use in US
- nelfinavir – HIV/AIDS
- nirmatrelvir and ritonavir (Covid treatment) – Paxlovid™
- posaconazole - antifungal
- ribociclib – cancer, breast cancer
- ritonavir – HIV
- saquinavir and ritonavir – HIV
- telithromycin - antibiotic to treat bacterial infections
- tipranavir and ritonavir – HIV
- tucatinib – cancer, breast cancer, and
- voriconazole – antifungal.

10.7.2.2. Strong CYP3A4 Inducers

Participants will not be allowed to take strong CYP3A4 inducers including

- apalutamide (a prostate cancer treatment)
- carbamazepine (an anticonvulsant)
- enzalutamide (a prostate cancer treatment)
- fosphenytoin (an anticonvulsant)
- ivosidenib (a cancer treatment for leukemia)
- lumacaftor (treats cystic fibrosis)
- mitotane (a cancer treatment for adrenal cortical carcinoma, or for treatment of Cushing's syndrome)
- phenobarbital (for treating seizures)
- phenytoin (for treating seizures)
- rifabutin (tuberculosis treatment)
- rifampin (tuberculosis treatment), and
- rifapentine (tuberculosis treatment).

10.7.2.3. Moderate and Strong OATP Inhibitors

Participants will not be allowed to take strong OATP inhibitors, including

- rifampin
- cyclosporine
- faldaprevir
- tipranavir/ritonavir
- glecaprevir/pibrentasvir
- telaprevir
- sofosbuvir/velpatasvir/voxilaprevir
- lopinavir/ritonavir
- darunavir/ritonavir
- elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
- letermovir
- grazoprevir
- boceprevir
- simeprevir
- atazanavir/ritonavir
- enasidenib
- roxadustat
- velpatasvir
- ombitasvir/paritaprevir/ritonavir/dasabuvir
- teriflunomide
- elbasvir/grazoprevir
- paclitaxel
- glecaprevir/pibrentasvir
- capmatinib, and
- fosamprenavir.

10.7.2.4. Drugs that Are Sensitive P-gp Substrates with a Narrow Therapeutic Index

Participants will not be allowed to take drugs that are sensitive P-gp substrates with a narrow therapeutic index, including

- colchicine
- cyclosporine
- dabigatran etexilate
- digoxin
- everolimus
- pimozide
- quinidine
- quinine
- sirolimus, and
- tacrolimus.

10.7.2.5. Drugs that Are Sensitive BCRP Substrates with a Narrow Therapeutic Index

Participants will not be allowed to take drugs that are sensitive BCRP substrates with a narrow therapeutic index, including

- coumestrol
- daidzein
- genistein
- prazosin, and
- sulfasalazine.

10.7.2.6. Moderate CYP3A4 Inhibitors and Moderate CYP3A Inducers

Participants will not be allowed to take moderate CYP3A4 inhibitors and moderate CYP3A inducers, including

- amprenavir
- aprepitant
- atazanavir
- atazanavir and ritonavir
- berotralstat
- cimetidine
- ciprofloxacin
- clotrimazole
- crizotinib
- cyclosporine
- darunavir
- diltiazem
- dronedarone
- duvelisib
- erythromycin
- fedratinib
- fluconazole
- fluvoxamine
- fosnetupitant and palonosetron
- imatinib
- indinavir
- isavuconazole
- istradefylline
- ledipasvir/sofosbuvir
- lefamulin
- letermovir
- magnolia vine (*Schisandra sphenanthera*)
- netupitant
- nilotinib
- tofisopam

- verapamil, and
- voxelotor.

10.7.3. Drugs Affected by an Increase in Gastric pH

Drugs that may be affected by an increase in gastric pH should be separated from study drug administration by at 4 hours.

10.7.4. GLP-1 Analogs and Glucose-Lowering Medications

These drugs must be washed out for at least 90 days prior to screening.

10.7.4.1. GLP-1 Analogs or Other Related Compounds

Participants will not be allowed to take GLP-1 analogs or other related compounds, including

- dulaglutide
- exenatide
- liraglutide
- semaglutide
- tirzepatide, and
- other incretin-based therapy.

10.7.4.2. Glucose-Lowering Medications

Participants will not be allowed to take glucose-lowering medications, including

- metformin
- canagliflozin
- dapagliflozin
- empagliflozin
- dulaglutide
- liraglutide
- semaglutide
- exenatide
- tirzepatide
- sitagliptin
- saxagliptin
- linagliptin, and
- alogliptin.

10.8. Appendix 10: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency virus
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{(0-\tau)}$	AUC from time 0 to τ hour time point
BCRP	breast cancer resistance protein
BE	Bioequivalence
BP	blood pressure
CI	confidence interval
clinical research physician	Individual responsible for the medical conduct of the study. Responsibilities of the clinical research physician may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
C_{max}	maximum observed drug concentration
C_{min}	lowest concentration in a dosing interval
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, GCP, and applicable regulatory requirements.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450

Term	Definition
ECG	Electrocardiogram
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GMR	geometric mean ratio
HbA1c	glycated hemoglobin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INOCBP	Individuals not of childbearing potential
IOCBP	Individuals of childbearing potential
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational medicinal product (see also "investigational product")	A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.

Term	Definition
IP	investigational product. A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "investigational medicinal product."
IRB	institutional review board
IWRS	interactive web-response system
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
OATP	organic anion-transporting polypeptide
OTC	over the counter
P-gp	P-glycoprotein
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PHQ-9	patient health questionnaire-9
PK	pharmacokinetics
QD	once daily
RA	receptor agonist
SAE	serious adverse event

Term	Definition
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SIB	suicidal ideation behavior
SoA	schedule of activities
Swr	within-subject standard deviation
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
t_{max}	time to maximum observed drug concentration
ULN	upper limit of normal

10.9. Appendix 11: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the table of contents.

Amendment c: (17 Jul 2024)

Overall rationale for the amendment

The protocol is amended to include minor changes in the schedule of activities (home dosing: Cohorts 2A and 2B), secondary endpoints, and other editorial changes throughout the document for clarity and consistency.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis and 3. Objectives and Endpoints	Removed AEs from secondary endpoints	Updated for clarity
1.3. Schedule of Activities (SoA)	Updated information on home dosing in Cohorts 2A and 2B (outpatient visit, vital signs, study intervention administration, and home dose recording)	Updated for clarity and consistency
5.2. Exclusion Criteria	In Exclusion Criterion 19, QTc was updated as QTcF	Edited for clarity
6.3. Assignment to Study Intervention	Modified sentence on re-dispensing of study intervention to the participants	Updated for clarity
6.9. Prior and Concomitant Therapy	Updated washout of drugs intended to promote weight loss as 14 days prior to screening	To align with Exclusion Criterion 33
7.1. Discontinuation of Study Intervention	Minor editorial changes	Edited for clarity

Amendment b: (24 May 2024)

Overall rationale for the amendment

The protocol is amended to update information on home dosing (Cohorts 2A and 2B), inclusion and exclusion criteria, concomitant therapy, and minor editorial changes throughout the document.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Updated treatment duration in brief summary and minor editorial corrections	Edited for clarity and consistency
1.2. Schema	Updated "in-clinic periods" as "inpatient periods" and added abbreviation for N (+/-)	Updated for clarity and consistency
1.3. Schedule of Activities (SoA)	Added details on physical examination, clinical laboratory tests, C-SSRS assessment, PHQ-9, pharmacogenetic sample (cohort 1A, 2A) and PK sampling. Updated information on participants admission and discharge in CRU, compliance, training, orforglipron capsules dispensing for in-home dosing in Cohorts 2A and 2B.	Updated for consistency Updated to provide clarification on home dosing procedures in Cohorts 2A and 2B.
2.3. Benefit/Risk Assessment	Removed information on elevation of liver enzymes in patients receiving orforglipron	To refer the reader to the investigator's brochure for more comprehensive information on the benefit/risk assessment
4.1. Overall Design	Minor editorial corrections	Added for clarity
4.1.1. Part A: Pilot Study 4.1.2. Part B: BE Study	Updated information on participants admission and discharge in CRU, training, orforglipron capsules dispensing for in-home dosing in Cohorts 2A and 2B	To clarify on home dosing procedures in Cohorts 2A and 2B
4.3. Justification for Dose	Removed 4-week time interval for orforglipron capsule dose escalation. Removed details on analysis of CCI [redacted] mg capsule dose level with tablet dose strengths that overlap. Minor editorial changes.	To align with the revised study design
5.1. Inclusion Criteria	Stable body weight for 1 month from "prior to randomization" changed to "prior to screening."	Appropriate wording to align with inclusion criterion

Section # and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria	Updated details on Medical conditions and Diagnostic Tests, Prior / concomitant therapy, Prior / concurrent clinical study experience	Updated for clarity
6.1. Study Intervention(s) Administered	Added details on self administration of orforglipron capsules by participants during home dosing (Cohorts 2A and 2B)	Updated for clarity
6.5. Study Intervention Compliance	Updated information on compliance assessment of study intervention during home dosing (Cohorts 2A and 2B)	Updated for clarity
6.8. Treatment of Overdose	Details updated on greater doses than the doses assigned through randomization	To maintain clarity
6.9. Prior and Concomitant Therapy	Updated details on concomitant medications affecting gastric pH and drug products that require rapid GI absorption. Updated information on drugs intended to promote weight loss and washout of drugs.	To minimize any impact due to concomitant administration of other medications Edited for consistency
8.2.2. Vital Signs	Updated sentence on unscheduled vital signs assessment	Updated for clarity
9.2. Analyses Sets	Updated details on participants exclusion from BE statistical analysis	Updated for clarity
9.3. Statistical Analyses 9.5. Sample Size Determination	Minor editorial corrections	Edited for clarity and consistency
10.2. Appendix 2: Clinical Laboratory Tests	Corrections to blood volumes in line with amendment, and clarifications added with regards to local laboratory collections	Edited for clarity and consistency
10.6. Appendix 6: Liver Safety:	Updated details on HDV IgM antibody	Updated for clarity

Section # and Name	Description of Change	Brief Rationale
Suggested Actions and Follow-Up Assessments		
10.7.1. Weight Loss Medications	Minor sentence correction	To maintain clarity
10.7.2. CYP3A4 Inhibitors, CYP3A Inducers, OATP Inhibitors, and P gp and BCRP Substrates	Updated details on concomitant medications affecting gastric pH	To be consistent with earlier change
10.7.3. Drugs Affected by an Increase in Gastric pH	Time gap changed from "at least 2 - 4 hours to 4 hours" between study drug administration and drugs affected by increase in gastric pH	Edited for clarity and consistency

Amendment a: (05 Apr 2024)

Overall rationale for the amendment

The protocol is amended to modify the study design to include a pilot study prior to the bioequivalence study.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated details on objectives, number of participants, intervention groups, and duration as per the new study design	As per revised study design
1.2. Schema	Updated schema with pilot (Cohorts 1A and 2A) followed by BE (Cohorts 1B and 2B) study	As per revised study design
1.3. Schedule of Activities (SoA)	Updated SoA as per the new study design	As per revised study design
	Updated details on clinical laboratory tests, ECG, C-SSRS, PHQ-9, PK sampling, outpatient visit, pregnancy test, HbA1c, ethanol test, and urine drug screen	As per study site feedback

Section # and Name	Description of Change	Brief Rationale
3. Objectives and Endpoints	Updated with individual objectives for pilot study and BE study Updated capsule dose levels for primary and secondary objectives	As per revised study design and capsule dose levels based on planned maintenance doses.
4.1. Overall Design	Updated with new study design that includes a pilot (RBA study) that will run as Cohorts 1A and 2A, followed by a BE portion that will run as Cohorts 1B and 2B.	Reassessment of study design
4.2. Scientific Rationale for Study Design	Updated scientific rationale as per the new study design	As per revised study design
4.3. Justification for Dose	Updated information on capsule dose levels and tablet dose strengths	As per revised study design
5.1. Inclusion Criteria	Inclusion Criterion 1: updated participants' upper limit of age as 65 years	Adjusted to align with other Phase 1 healthy participant studies with consideration of the benefit risk assessment for the trial population
	Inclusion Criterion 3: updated body mass index with upper limit $\leq$40 kg/m^2	To exclude participants with severe/morbid obesity, to conform to the description of the study population (that is, participants with obesity or overweight who are otherwise healthy)
5.2. Exclusion Criteria	Exclusion Criterion 10: added criterion to include information on drug abuse separately	Revised and updated as per study site feedback
	Exclusion Criterion 18: Updated information on clinical evaluation of hypothyroidism or hyperthyroidism	
	Exclusion Criterion 19: updated time frame for past medical conditions	

Section # and Name	Description of Change	Brief Rationale
	Exclusion Criteria 32 and 35: updated information on medication history	
	Exclusion Criterion 37: removed information on cannabidiol oil	
	Exclusion Criterion 44: updated information on Gilbert's syndrome	
5.3.1. Meals and Dietary Restrictions	Updated sentence on overnight fasting	To maintain consistency
5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco	Updated information on caffeine consumption	Updated for clarity
6.1. Study Intervention(s) Administered	Updated nominal (N), higher (N+), and lower (N-) tablet dose strengths for capsule dose levels CCI mg	As per revised estimates of Dose Adjustment Factors
6.2. Preparation, Handling, Storage, and Accountability	Added details on self-administration for in-home dosing	Updated for consistency
6.5. Study Intervention Compliance	Updated information on study intervention administration	Updated for clarity
6.8. Treatment of Overdose	Added information on orforglipron overdose	Updated for clarity on overdose
6.9. Prior and Concomitant Therapy	Minor sentence correction to clarify as prohibited concomitant medications	Updated for clarity
9.1. Statistical Hypothesis 9.3.2.1. Pharmacokinetic Parameter Estimation 9.3.2.2. Pharmacokinetic Statistical Inference 9.3.3. Secondary Endpoints Analysis 9.3.4.2. Additional PK Parameters	Updated capsule dose levels for primary and secondary objectives Updated details on pilot study and BE study	As per revised study design and capsule dose levels based on planned maintenance doses

Section # and Name	Description of Change	Brief Rationale
9.4. Interim Analysis	Updated information on interim analysis planned for pilot study	As per revised study design
9.5. Sample Size Determination	Updated sample size for pilot study and BE study	As per revised study design
10.2. Appendix 2: Clinical Laboratory Tests	Updated as, safety laboratory tests performed in local laboratory at screening and central laboratory during the study	To maintain consistency
	Updated details on low-density lipoprotein cholesterol, follicle-stimulating hormone, urine drug screen, thyroid-stimulating hormone	Updated for consistency as per study site feedback
10.2.1. Blood Sampling Summary	Updated pharmacokinetic blood samples and total volume of blood as per the new study design	Per revised study design

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