Protocol J2A-MC-GZPG(d)

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

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Approval Date: 27-Jun-2024

Title Page

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

Protocol Number: J2A-MC-GZPG

Amendment Number: (d)

Compound: Orforglipron (LY3502970)

Brief Title: A drug-drug interaction study of orforglipron in healthy overweight and obese participants

Study Phase: Phase 1

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Eli Lilly and Company, Indianapolis, Indiana USA 46285.

Regulatory Agency Identifier Number: IND: 156143

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

Document ID: VV-CLIN-126204

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment [c]	28-Mar-2024
Amendment [b]	30-Jan-2024
Amendment [a]	23-Oct-2023
Original Protocol	02-Oct-2023

Amendment [d]

Overall Rationale for the Amendment:

Protocol J2A-MC-GZPG has been amended. The new protocol is indicated by amendment (d) and will be used to conduct the study in place of any preceding version of the protocol. This amendment is considered to be non-substantial and is provided to allow flexibility in the evaluation of exploratory endpoint, coproporphyrin 1.

The overall changes and rationale for the changes made to the protocol are described in the following table.

Section # and Name	Description of Change	Brief Rationale
3. Objectives and Endpoints	Flexible language added for coproporphyrin 1 biomarker evaluations in Cohort 1.	To allow the evaluation of coproporphyrin 1 levels to be flexible depending on team decision and availability of bioanalysis method.
4.2. Scientific Rationale for Study Design		
8.7. Biomarkers		
9.1. Statistical Hypotheses		
9.2. Analyses Sets		
9.3.1. General Considerations		
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10.1.9. Sample Retention		
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1.1. Synopsis

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

Brief Title: A drug-drug interaction study of orforglipron in healthy overweight and obese participants

Regulatory Agency Identifier Number: IND: 156143

Rationale: Study J2A-MC-GZPG, or GZPG, is a Phase 1, open-label, non-randomized, dose escalation, drug-drug interaction (DDI) study in healthy overweight or obese participants designed to evaluate the effect of multiple once daily (QD) doses of orforglipron on the pharmacokinetics (PK) of digoxin, simvastatin, rosuvastatin, acetaminophen, and midazolam.

The potential for orforglipron to affect cytochrome P450 (CYP)3A, P-glycoprotein 1 (P-gp), or breast cancer resistant protein (BCRP) activity cannot be ruled out using in vitro data, therefore midazolam, digoxin, and rosuvastatin are being assessed as clinical substrates of CYP3A, P-gp, and BCRP, respectively. Additionally, as a glucagon-like peptide 1 (GLP-1) receptor agonist, orforglipron delays gastric emptying and acetaminophen is being assessed as a marker substrate to characterize this effect. Finally, sodium bicarbonate in orforglipron capsules is expected to transiently elevate gastric pH. Elevated gastric pH is hypothesized to underlie the increase in simvastatin acid observed with orforglipron capsule coadministration during exploratory clinical assessment, as investigated in Study J2A-MC-GZGA. To assess the gastric pH effect on simvastatin, simvastatin will be administered under a variety of conditions.

An additional objective of the study includes assessment of the effect of the orforglipron tablet on the PK of simvastatin.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effect, in healthy overweight or obese participants, of: o orforglipron capsule on the PK of digoxin, rosuvastatin, acetaminophen, and midazolam o orforglipron capsule on the PK of simvastatin, following simultaneous or staggered administration, and o sodium bicarbonate on the PK of simvastatin	• $AUC_{(0-\infty)}$ and C_{max} of simvastatin, simvastatin acid, digoxin, rosuvastatin, acetaminophen, and midazolam, and 1'-hydroxymidazolam
Secondary	
• To evaluate the effect of orforglipron tablet on the PK of simvastatin in healthy overweight or obese participants • To describe the safety and tolerability of orforglipron in healthy overweight or obese participants	• $AUC_{(0-\infty)}$ and C_{max} of simvastatin and simvastatin acid • TEAEs, SAEs, and discontinuations due to AEs

Abbreviations: AE = adverse event; $AUC_{(0-\infty)}$ = area under the concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Overall Design:

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

Brief Summary:

Screening

All participants will be screened up to 42 days prior to Day 1. Genotyping for BCRP, also known as *ABCG2*, and organic anion transporting polypeptide (OATP)1B1, also known as *SLCO1B1*, will be performed for each participant at screening. Upon completion of screening, participants with the specified BCRP and OATP1B1 genotype will be assigned to Cohort 1. Participants of any genotype can be assigned to Cohort 2.

Inpatient Period 1

On Day -1, participants will be admitted to the clinical research unit (CRU).

Cohort 1

In Cohort 1, participants will receive:

- [redacted] mg simvastatin on Day 1
- [redacted] mg digoxin on Day 2
- [redacted] mg simvastatin and [redacted] mg sodium bicarbonate* on Day 7
- [redacted] mg rosuvastatin on Day 8
- [redacted] mg acetaminophen on Day 10
- [redacted] mg midazolam on Day 12, and
- [redacted] mg orforglipron capsule and [redacted] mg acetaminophen, 2 hours ± 10 minutes after orforglipron administration, on Day 14.

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

Cohort 2

In Cohort 2, participants will receive:

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

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

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

Outpatient Period and Dose Escalation

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

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

- [redacted] mg orforglipron capsule from Days 37 to 50
- [redacted] mg orforglipron capsule from Days 51 to 64
- [redacted] mg orforglipron capsule from Days 65 to 78, and
- [redacted] mg orforglipron capsule from Days 79 to 90.

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

Inpatient Period 2

Cohort 1

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

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

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

Cohort 2

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

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

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

Follow-up Period

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

Study Population:

Participants will:

- be healthy males or females with normal renal function
- be between 18 or the legal age of consent in the jurisdiction in which the study is taking place, to 70 years of age, inclusive, at the time of signing the informed consent

- have a stable body weight, that is equal to or less than 5% body weight change, for 1 month prior to screening, and
- have a body mass index equal to or greater than 27 kg/m^2.

Number of Participants:

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

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

Intervention Groups and Duration:

All participants will be screened up to 42 days prior to dosing. On the days and in the cohorts specified in the brief summary, participants will receive:

- CCI and CCI mg orforglipron capsule
- CCI mg orforglipron tablet
- CCI mg sodium bicarbonate capsule*
- CCI mg midazolam syrup
- CCI mg rosuvastatin tablet
- CCI mg digoxin tablet
- CCI mg simvastatin tablet, and
- CCI mg acetaminophen liquid.

Participants will be followed through to approximately Day 126 in Cohort 1 and approximately Day 116 in Cohort 2. The maximum total study duration is approximately 171 days for Cohort 1 and 161 days for Cohort 2.

* Orforglipron capsules also contain CCI mg of sodium bicarbonate in each strength. The sodium bicarbonate capsules are manufactured as the placebo to match the active capsules, that is, the 'placebo to match LY3502970 C3 capsules' in the IND. The orforglipron tablet contains a lower amount of a different pH modifier.

Ethical Considerations of Benefit/Risk:

In participants administered orforglipron up to the highest single dose of CCI mg and multiple doses of CCI mg for a maximum of 36 weeks to date, the only safety or tolerability concerns have been:

- GI-related effects that are consistent with GLP-1 pharmacology, and
- changes in vital signs that have resolved spontaneously over time.

Elevations in serum bilirubin, transaminase, alkaline phosphatase, and gamma-glutamyl transferase levels have been reported in patients receiving orforglipron.

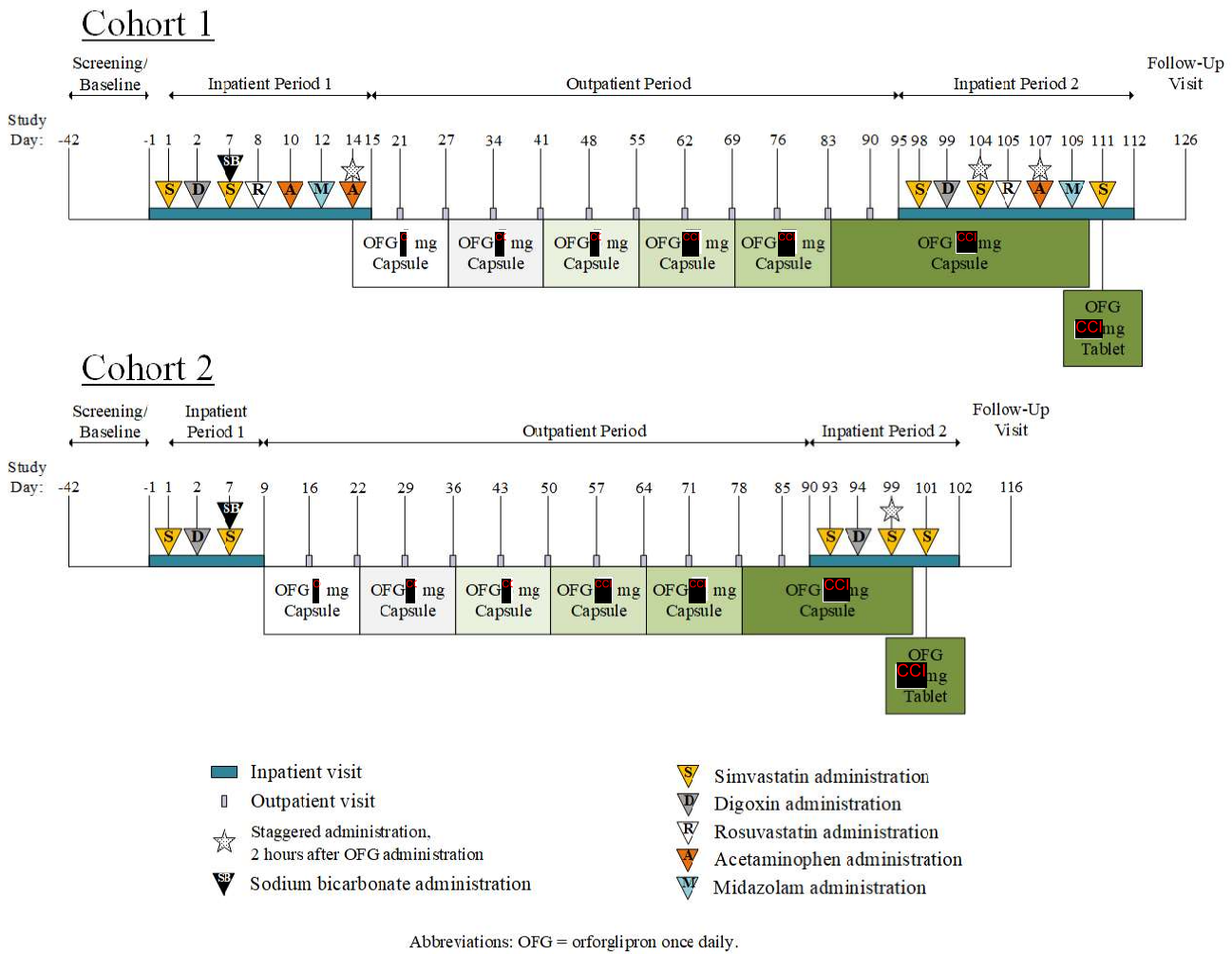
To date, approximately 362 healthy participants and 613 participants with type 2 diabetes, obesity, or overweight have received orforglipron and no safety or tolerability concerns that preclude further investigation of orforglipron have been identified.

Data from Phase 1 and 2 studies indicate that orforglipron treatment may result in a decrease in body weight. These data support improved weight management in healthy overweight and obese participants.

In addition, detailed information about the known and expected benefits and risks of simvastatin, digoxin, rosuvastatin, acetaminophen, and midazolam may be found in their respective package inserts.

Data Monitoring Committee: No.

1.2. Schema



Abbreviations: OFG = orforglipron once daily.

1.3. Schedule of Activities

Screening and Baseline Schedule for Cohorts 1 and 2

Procedure	Screening/Baseline		Comments
Weeks	**-6 to -1**		
Days	**-42 to -2**	**-1**	
CRU admission		X	
Informed consent	X		
Medical history and demographics	X		
BCRP and OATP1B1 genotyping	X		
Serology	X		
Height	X		
Weight	X	X	
Sitting vital signs	X	X	
Clinical laboratory evaluations	X	X	See Section 10.2.
Pregnancy test	X	X	Screening: serum test. Day -1: urine test.
Physical examination	X	X	Screening: complete exam. Day -1: symptom-directed exam.
Ethanol test and urine drug screen	X	X	Screening: alcohol urine test. Day -1: alcohol urine or breath test.
Single 12-lead ECG	X		
C-SSRS baseline and screening	X	X	
PHQ-9	X	X	
Hypoglycemia training		X	
AE and CM review	X		

Abbreviations: AE = adverse event; BCRP = breast cancer resistance protein; C-SSRS = Columbia-Suicide Severity Rating Scale; CM = concomitant medication; CRU = clinical research unit; ECG = electrocardiogram; OATP = organic anion transporting polypeptide; PHQ-9 = Patient Health Questionnaire-9.

Cohort 1

Procedure	Inpatient Period 1												ED	Comments
Weeks	**1**				**2**							**3**		
Days	**1**	**2**	**3 to 6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**		
CRU discharge												X		
Weight											X	X		
Sitting vital signs	P	P		P	P		P		P		P			
Clinical laboratory evaluations												P	X	See Section 10.2.
Pregnancy test													X	Urine test.
Single 12-lead ECG		P, 2, 4h	24h									X		Day 2 time points relative to digoxin administration.
C-SSRS since last assessed												X	X	
PHQ-9												X		
Genetics sample	X													
AE and CM review	X												X	
Study intervention administration and PK sampling – PK sampling time points relative to relevant study intervention administration.														
Simvastatin administration	X													
Simvastatin and simvastatin acid PK sampling	X	X												P, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24h.
Digoxin administration		X												
Digoxin PK sampling		X	X	X										P, 0.5, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, and 120h.
Simvastatin and sodium bicarbonate coadministration				X										Coadministration or simvastatin administration immediately after sodium bicarbonate.
Simvastatin and simvastatin acid PK sampling (after sodium bicarbonate coadministration)				X	X									Relative to simvastatin administration. P, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24h.
Rosuvastatin administration					X									

Procedure	Inpatient Period 1												ED	Comments
Weeks	**1**				**2**							**3**		
Days	**1**	**2**	**3 to 6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**		
Rosuvastatin PK sampling					X	X	X	X						P, 0.5, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, and 72h.
Acetaminophen administration (fed state)							X				X (2h)			On Day 14, administration 2 hours ± 10 min after OFG capsule.
Acetaminophen PK sampling							X	X			X	X		Relative to acetaminophen administration: P, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24h.
Midazolam administration									X					
Midazolam and 1-OH-MDZ PK sampling									X	X				P, 0.5, 0.75, 1, 2, 3, 4, 6, 9, 12, and 24h.
OFG capsule administration											X	X		QD self-administration from Day 15. See Section 4.1.
Plasma OFG PK sampling											X	X		For Day 14 OFG dose. P, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24h.

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; CM = concomitant medication; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; OFG = orforglipron; P = predose; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetic; QD = once daily.

Cohort 1, continued.

Procedure	Outpatient Period											ED	Comments
Weeks	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
Days	**21 ±1**	**27 ±1**	**34 ±1**	**41 ±1**	**48 ±1**	**55 ±1**	**62 ±1**	**69 ±1**	**76 ±1**	**83 ±1**	**90 ±1**		
Outpatient visit	X	X	X	X	X	X	X	X	X	X	X		
Compliance (diary review) and dose escalation	X	X	X	X	X	X	X	X	X	X	X		See Section 4.1 for dose escalation times.
Weight	X	X	X	X	X	X	X	X	X	X	X		
Sitting vital signs	X	X	X	X	X	X	X	X	X	X	X		
Clinical laboratory evaluations		X		X		X		X		X		X	Clinical chemistry tests only. See Section 10.2.
PHQ-9		X		X		X		X		X			
Pregnancy test												X	Urine test.
OFG capsule administration	X												QD self-administration. See Section 4.1.
AE and CM review	X											X	

Abbreviations: AE = adverse event; CM = concomitant medication; ED = early discontinuation; OFG = orforglipron; P = predose; PHQ-9 = Patient Health Questionnaire-9; QD = once daily.

Cohort 1, concluded.

Procedure	**Inpatient Period 2**														**FU/ED**	**Comments**
Weeks	**14**			**15**				**16**							**18**	
Days	**95**	**96 to 97**	**98**	**99**	**100 to 103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**126 ± 3d**	
CRU admission	X															
CRU discharge														X		
Outpatient visit															X	
Weight	X															
Sitting vital signs			P	P		P	P		P		P		P		X	Not required at ED.
Clinical laboratory evaluations		P D96 only												X	X	On Days 96 and 112, clinical chemistry tests only. See Section 10.2.
Pregnancy test	X														X	Urine test.
Physical examination	X															Symptom-directed exam.
Ethanol test and urine drug screen	X															Alcohol urine or breath test.
Single 12-lead ECG	X			P, 2, 4h	24h									X		Day 99 time points relative to digoxin administration.
C-SSRS since last assessed	X														X	
PHQ-9	X									X				X		
AE and CM review	X														X	
Study intervention administration and PK sampling – PK sampling time points relative to relevant study intervention administration.																
OFG capsule administration	X															QD administration until Day 110. On Day 95, participant will self-administer dose prior to CRU admission.

Procedure	**Inpatient Period 2**														**FU/ED**	**Comments**
Weeks	**14**			**15**				**16**							**18**	
Days	**95**	**96 to 97**	**98**	**99**	**100 to 103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**126 ± 3d**	
OFG tablet administration													X			
Plasma OFG PK sampling		X											X	X		For Day 96 and 111 OFG doses. P, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24h.
Simvastatin administration			X			X (2h)							X			Coadministration with OFG on Days 98 and 111. Administration 2 hours ± 10 min after OFG capsule on Day 104.
Simvastatin and SA PK sampling			X	X		X	X						X	X		P, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24h.
Digoxin administration				X												Coadministration with OFG
Digoxin PK sampling				X	X	X										P, 0.5, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, and 120h.
Rosuvastatin administration							X									
Rosuvastatin PK sampling							X	X	X	X						P, 0.5, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, and 72h.
Acetaminophen administration (fed state)									X (2h)							Administration 2 hours ± 10 min after OFG capsule.
Acetaminophen PK sampling									X	X						P, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24h.

Procedure	**Inpatient Period 2**													**FU/ED**	**Comments**
Weeks	**14**			**15**				**16**						**18**	
Days	**95**	**96 to 97**	**98**	**99**	**100 to 103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**126 ± 3d**	
Midazolam administration											X					
Midazolam and 1-OH-MDZ PK sampling											X	X				P, 0.5, 0.75, 1, 2, 3, 4, 6, 9, 12, and 24h.

Abbreviations: 1-OH-MDZ = 1-hydroxymidazolam; AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; CM = concomitant medication; CRU = clinical research unit; D = Day; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; OFG = orforglipron; P = predose; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetic; QD = once daily.

Cohort 2

Procedure	Inpatient Period 1						Outpatient Period											ED	Comments
Weeks	1				2		3	4	5	6	7	8	9	10	11	12	13		
Days	1	2	3 to 6	7	8	9	16 ±1	22 ±1	29 ±1	36 ±1	43 ±1	50 ±1	57 ±1	64 ±1	71 ±1	78 ±1	85 ±1		
CRU discharge						X													
Outpatient visit							X	X	X	X	X	X	X	X	X	X	X		
Compliance (diary review) and dose escalation							X	X	X	X	X	X	X	X	X	X	X		See Section 4.1 for dose escalation times.
Weight							X	X	X	X	X	X	X	X	X	X	X		
Sitting vital signs	P	P		P		P	X	X	X	X	X	X	X	X	X	X	X		
Clinical laboratory evaluations						P		X		X		X		X		X		X	Only clinical chemistry tests performed during Outpatient Period. See Section 10.2.
Pregnancy test																		X	Urine test.
Single 12-lead ECG		P, 2, 4h	24h			X													Day 2 time points relative to digoxin administration.
C-SSRS since last assessed						X												X	
PHQ-9						X		X		X		X		X		X			
Genetics sample	X																		
AE and CM review	X																	X	
Study intervention administration and PK sampling – PK sampling time points relative to relevant study intervention administration.																			
Simvastatin administration	X																		
Simvastatin and simvastatin acid PK sampling	X	X																	P, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24h.
Digoxin administration		X																	
Digoxin PK sampling		X	X	X															P, 0.5, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, and 120h.

Procedure	Inpatient Period 1						Outpatient Period											ED	Comments
Weeks	1				2		3	4	5	6	7	8	9	10	11	12	13		
Days	**1**	**2**	**3 to 6**	**7**	**8**	**9**	**16 ±1**	**22 ±1**	**29 ±1**	**36 ±1**	**43 ±1**	**50 ±1**	**57 ±1**	**64 ±1**	**71 ±1**	**78 ±1**	**85 ±1**		
Simvastatin and sodium bicarbonate coadministration				X															Coadministration or simvastatin administration immediately after sodium bicarbonate.
Simvastatin and simvastatin acid PK sampling (after sodium bicarbonate coadministration)				X	X														P, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24h.
OFG capsule administration						X													QD self-administration. See Section 4.1.

Abbreviations: AE = adverse event; BCRP = breast cancer resistance protein; C-SSRS = Columbia-Suicide Severity Rating Scale; CM = concomitant medication; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; OFG = orforglipron; P = predose; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetic; QD = once daily.

Cohort 2, concluded.

Procedure	**Inpatient Period 2**									**FU/ED**	**Comments**
Weeks	**13**		**14**			**15**				**17**	
Days	**90**	**91 to 92**	**93**	**94**	**95 to 98**	**99**	**100**	**101**	**102**	**116 ± 3d**	
CRU admission	X										
CRU discharge									X		
Outpatient visit										X	
Weight	X										
Sitting vital signs			P	P		P		P		X	Not required at ED.
Clinical laboratory evaluations		P D91 only							X	X	On Days 91 and 102, clinical chemistry tests only. See Section 10.2.
Pregnancy test	X									X	Urine test.
Physical examination	X										Symptom-directed exam.
Ethanol test and urine drug screen	X										Alcohol urine or breath test.
Single 12-lead ECG	X			P, 2, 4h	24h				X		Day 94 time points relative to digoxin administration.
C-SSRS since last assessed	X									X	
PHQ-9	X								X		
AE and CM review	X									X	
Study intervention administration and PK sampling – PK sampling time points relative to relevant study intervention administration.											
OFG capsule administration	X										QD administration until Day 100. On Day 90, participant will self-administer dose prior to CRU admission.
OFG tablet administration								X			
Plasma OFG PK sampling		X						X	X		For Day 91 and 101 OFG doses. P, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24h.

Procedure	**Inpatient Period 2**									**FU/ED**	**Comments**
Weeks	**13**		**14**			**15**				**17**	
Days	**90**	**91 to 92**	**93**	**94**	**95 to 98**	**99**	**100**	**101**	**102**	**116 ± 3d**	
Simvastatin administration			X			X (2h)		X			Coadministration with OFG on Days 93 and 101. Administration 2 hours ± 10 min after OFG capsule on Day 99.
Simvastatin and simvastatin acid PK sampling			X	X		X	X	X	X		P, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24h.
Digoxin administration				X							Coadministration with OFG.
Digoxin PK sampling				X	X	X					P, 0.5, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, and 120h.

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; CM = concomitant medication; CRU = clinical research unit; D = Day; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; OFG = orforglipron; P = predose; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetic; QD = once daily.

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 T2D 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-GZPG, or GZPG, is a Phase 1, open-label, non-randomized, dose escalation, DDI study in healthy overweight or obese participants designed to evaluate the effect of multiple QD doses of orforglipron on the PK of digoxin, simvastatin, rosuvastatin, acetaminophen, and midazolam.

The potential for orforglipron to affect CYP3A, P-gp, or BCRP activity cannot be ruled out using in vitro data; therefore, midazolam, digoxin, and rosuvastatin are being assessed as clinical substrates of CYP3A, P-gp, and BCRP, respectively. Additionally, as a GLP-1 RA, orforglipron delays gastric emptying and acetaminophen is being assessed as a marker substrate to characterize this effect. Finally, sodium bicarbonate in orforglipron capsules is expected to transiently elevate gastric pH. Elevated gastric pH is hypothesized to underlie the increase in simvastatin acid observed with orforglipron capsule coadministration during exploratory clinical assessment, as investigated in Study J2A-MC-GZGA. To assess the gastric pH effect on simvastatin, simvastatin will be administered under a variety of conditions.

An additional objective of the study includes assessment of the effect of the orforglipron tablet on the PK of simvastatin.

2.2. Background

Glucose-lowering therapies that encompass weight loss may have a potential to improve treatment of T2D, slow its progression, and reduce the risk of chronic complications.

There is an unmet medical need for efficacious, safe, and well-tolerated oral formulations of GLP-1 RAs for the management of T2D and for the treatment of overweight or obesity. Oral formulations with fewer restrictions related to administration would allow for further tailoring of therapy to meet individual patient preferences and needs.

Orforglipron is a non-peptide chemically synthesized oral GLP-1 RA that can be administered QD without any food or water restrictions.

A detailed description of the chemistry, pharmacology, efficacy, and safety of orforglipron is provided in the IB.

2.3. Benefit/Risk Assessment

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 to date, the only safety or tolerability concerns have been:

- GI-related effects that are consistent with GLP-1 pharmacology, and
- changes in vital signs that have resolved spontaneously over time.

Elevations in serum bilirubin, transaminase, ALP, and gamma-glutamyl transferase levels have been reported in patients receiving orforglipron.

To date, approximately 362 healthy participants and 613 participants with T2D, obesity, or overweight have received orforglipron and no safety or tolerability concerns that preclude further investigation of orforglipron have been identified.

Data from Phase 1 and 2 studies indicate that orforglipron treatment may result in a decrease in body weight. These data support improved weight management in healthy overweight and obese participants.

In addition, detailed information about the known and expected benefits and risks of simvastatin, digoxin, rosuvastatin, acetaminophen, and midazolam may be found in their respective package inserts.

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 effect, in healthy overweight or obese participants, of: o orforglipron capsule on the PK of digoxin, rosuvastatin, acetaminophen, and midazolam o orforglipron capsule on the PK of simvastatin, following simultaneous or staggered administration, and o sodium bicarbonate on the PK of simvastatin	• $AUC_{(0-\infty)}$ and C_{max} of simvastatin, simvastatin acid, digoxin, rosuvastatin, acetaminophen, and midazolam, and 1'-hydroxymidazolam
Secondary	
• To evaluate the effect of orforglipron tablet on the PK of simvastatin in healthy overweight or obese participants • To describe the safety and tolerability of orforglipron in healthy overweight or obese participants	• $AUC_{(0-\infty)}$ and C_{max} of simvastatin and simvastatin acid • TEAEs, SAEs, and discontinuations due to AEs
Exploratory	
• To evaluate the effect of multiple oral doses of orforglipron on endogenous OATP1B biomarker in healthy participants.	• $AUC_{(0-24)}$ and C_{max} of biomarker coproporphyrin 1, as appropriate

Abbreviations: AE = adverse event; $AUC_{(0-\infty)}$ = area under the concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; OATP = organic anion transporting polypeptide; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

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

The schema in Section 1.2 illustrates the study design. PK blood sampling and safety assessments, including vital signs measurements, physical examinations, clinical laboratory tests, ECGs, and AE recording, will be performed according to the SoA in Section 1.3.

Screening

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

Inpatient Period 1

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

Cohort 1

In Cohort 1, participants will receive:

- CCI mg simvastatin on Day 1
- CCI mg digoxin on Day 2
- CCI mg simvastatin and CCI mg sodium bicarbonate* on Day 7
- CCI mg rosuvastatin on Day 8
- CCI mg acetaminophen on Day 10
- CCI mg midazolam on Day 12, and
- CCI mg orforglipron capsule and CCI mg acetaminophen, 2 hours ± 10 minutes after orforglipron administration, on Day 14.

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

Cohort 2

In Cohort 2, participants will receive:

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

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

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

Outpatient Period and Dose Escalation

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

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

Participants will attend an outpatient visit every week to be dispensed orforglipron capsule and for compliance assessment. Participants will be required to complete a diary daily to ensure that they have been compliant in taking orforglipron capsules daily. Outpatient visits will occur on the days listed in the SoA in Section 1.3.

Inpatient Period 2

Cohort 1

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

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

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

Cohort 2

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

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

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

Follow-up Period

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

4.2. Scientific Rationale for Study Design

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable response in safety, efficacy, or both based on race or ethnicity. This question can be answered only if all the relevant data are collected.

Participants will receive each dose of orforglipron for 14 days. The $t_{1/2}$ of orforglipron is 24.6 to 67.5 hours across the dose levels used in Phase 1 studies. These 14-day escalation steps are designed to enable participants to be able to safely escalate to the [redacted]-mg dose with minimum GI adverse effects that are characteristic of the GLP-1 RA class. This design also allows each individual participant to be used as their own control to limit the number of healthy participants needed for the assessment.

In vitro testing indicates that orforglipron may be a clinical inhibitor of P-gp or BCRP transport, as detailed in the IB. To investigate this, orforglipron will be coadministered with digoxin, a P-gp substrate, and rosuvastatin, a BCRP substrate. Midazolam, a CYP3A substrate, will be coadministered to test for clinical CYP3A inhibition by a [redacted]-mg dose of orforglipron, as in silico modelling does not rule out the possibility of intestinal CYP3A4 at that dose. To increase the solubility of the orforglipron in the drug product, orforglipron capsules contain sodium bicarbonate to increase the pH of the local environment. Elevated gastric pH is hypothesized to underlie the increase in simvastatin acid observed with orforglipron capsule coadministration during exploratory clinical assessment, as investigated in Study J2A-MC-GZGA. Therefore, the current study will assess simvastatin PK following both simultaneous and staggered dosing of orforglipron capsules, as well as in the presence of sodium bicarbonate alone. An additional objective includes assessment of the effect of the orforglipron tablet on the PK of simvastatin, considering the fact that the tablet contains a different pH modifier in a lower amount compared to the capsule. This difference is anticipated to reduce the impact on gastric pH and therefore potentially reduce any pH-related DDI that may be observed with the capsule. Finally, while the effect of orforglipron on gastric emptying has been assessed in Studies GZGA and GZGC using acetaminophen, the effect at [redacted]-mg single dose of orforglipron has not been assessed. The possible delay in gastric emptying will also be assessed following repeated daily [redacted]-mg dosing of orforglipron, to refine in the mechanistic characterization of effects on concomitant medication PK through gastric emptying versus enzymes and transporters.

Healthy overweight and obese participants 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. Additionally, as obesity and overweight are some of the intended indications of orforglipron, participants who are overweight or have obesity will be more representative of the target population than healthy participants. Participants without a history of alcohol or drug abuse or regular comedication are proposed to avoid interaction on drug metabolism and to avoid noncompliance. The 16-week treatment duration will provide sufficient data to assess the PK, safety, and tolerability of orforglipron.

OATP1B1 and BCRP are transporters involved in rosuvastatin disposition. Participants with full function for both transporters will be enrolled in Cohort 1 and receive rosuvastatin. Since 16 to 20 completers are necessary to assess effect on rosuvastatin, midazolam, and acetaminophen, these are only included in Cohort 1. An increased number of completers is required to assess effect on digoxin and simvastatin, which will be achieved by dosing in Cohort 2.

Orforglipron inhibits hepatic transporters OATP1B1 and OATP1B3 in vitro. Measurement of the endogenous OATP1B biomarker, coproporphyrin 1, may be performed to selectively assess in vivo hepatic OATP1B inhibition by orforglipron.

4.3. Justification for Dose

Orforglipron

Orforglipron doses of [redacted] to [redacted] mg in the capsule formulation administered orally QD, and of [redacted] mg in the tablet formulation, were selected based on the following:

- In the single and a 4-week multiple dose study in healthy participants, GZGA, orforglipron doses through [redacted] mg were safe and well tolerated following dose escalation.
- In the 12-week study GZGC, in participants with T2D, orforglipron doses between 3 and [redacted] mg were safe and well tolerated following dose escalation.
- The Phase 2b studies assessed safety, tolerability, PK, and PD in participants with T2D, in Study GZGE, and individuals who are overweight or have obesity, in Study GZGI, at doses starting at [redacted] or [redacted] mg and escalating up to a maximum dose of [redacted] mg. In these studies, orforglipron has been found to be safe and well tolerated in this dose range, with GI AEs being the most common AEs.
- The [redacted]-mg capsule dose is the highest dose to be tested in Phase 3 studies. This dose was selected based on robust body weight change and HbA1c improvement observed in Phase 2 studies .
- The selected dose of the tablet formulation of orforglipron will be [redacted] mg as it is anticipated to have an equivalent or slightly higher exposure than the [redacted] mg capsule, thus providing an appropriate comparison of the effect of orforglipron capsule and tablet on simvastatin exposure.

High acute doses of GLP-1 RAs, including orforglipron, are often poorly tolerated due to GI symptoms, whereas a more gradual dose escalation scheme to reach a high dose has been shown to improve GLP-1 RA tolerability. Dosing algorithms starting at a low dose of [redacted] mg accompanied by dose escalation every 14 days would permit adequate time for development of tolerance to GI events and are predicted to minimize GI tolerability concerns. The selected dose

and escalation scheme would enable further evaluation of benefit and risk considerations of orforglipron.

Midazolam

The [redacted]-mg dose of midazolam was chosen as it is lower than the therapeutic dose, in order to minimize the risk for sedation and respiratory suppression, and is within a range that enables reliable detection of perpetrator DDI risk (Eap et al. 2004).

Rosuvastatin

The [redacted]-mg dose of rosuvastatin was chosen as this is the clinically relevant dose considered safe to administer and has been used concomitantly in previous clinical DDI studies.

Digoxin

The [redacted]-mg dose of digoxin was chosen as this is the clinically relevant dose considered safe to administer and has been used concomitantly in previous clinical DDI studies. A single [redacted]-mg dose is expected to result in C_{max} levels within the therapeutic range for digoxin, therefore producing minimal risk.

Simvastatin

A [redacted]-mg dose of simvastatin was chosen as this is a clinically relevant dose considered safe to administer and has been used concomitantly in previous clinical studies.

Acetaminophen

Acetaminophen is a well-established marker for the rate and extent of gastric emptying (Young 2005). It is rapidly absorbed from the duodenum upon release from the stomach. A delay in gastric emptying is reflected in the alterations to the concentration versus time profile of acetaminophen, specifically, decreasing its C_{max} and increasing t_{max} without altering the extent, that is total drug amount, absorbed. A dose of approximately [redacted] mg acetaminophen is considered to be sufficient for bioanalytical detection.

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 visit shown in the SoA in Section 1.3.

5. Study Population

Participant eligibility for enrollment in the study is based on the criteria listed in this section. The inclusion and exclusion criteria used to determine eligibility should only apply at screening or other specified visits, and not continuously throughout the study.

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply. Participants who meet these criteria will be assigned to Cohort 1 or 2 depending on their genotype. Participants with the specified BCRP, that is *ABCG2,* and OATP1B1, that is *SLCO1B1*, genotype will be assigned to Cohort 1. Participants of any genotype can be assigned to Cohort 2.

Age

1. are 18, or the legal age of consent in the jurisdiction in which the study is taking place, to 70 years of age, inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. have an estimated glomerular filtration rate equal to or greater than 60 mL/min, to determine normal renal function.

Weight

4. have a stable body weight, that is equal to or less than 5% body weight change, for 1 month prior to screening.
5. have a BMI equal to or greater than 27 kg/m^2.

Sex and Contraceptive and Barrier Requirements

6. are male or female.

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

   Note: hormone replacement therapy in post-menopausal women is allowed, but women must be on stable therapy for 90 days prior to screening.

Informed Consent

7. 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

8. have venous access sufficient to allow for blood sampling as per the protocol.
9. 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:

Medical Conditions

10. have any type of diabetes with HbA1c levels equal to or greater than 6.5%.
11. have a history of significant active or unstable MDD or other severe psychiatric disorder, for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder within 2 years of screening, or in the investigator's opinion, have any significant mental health or psychiatric disorder that may put the individual at higher risk of study participation.

    Note: participants with MDD or generalized anxiety disorder whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.

12. have a PHQ-9 score of 15 or more at screening and Day -1.
13. are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide or have a lifetime history of suicide attempt.
14. have answered "yes" on the "Suicidal Ideation" portion of the C-SSRS to:
    a. Question 4 **and** the ideation occurred within the past month
    b. Question 5 **and** the behavior occurred within the past month, or
    c. 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 month prior to screening or Day -1.
15. have any other conditions, including known drug or alcohol abuse, that may preclude the participant from following and completing the protocol in the opinion of the investigator.
16. have:
    a. a history or presence of acute or chronic pancreatitis, or
    b. an elevation in serum lipase or amylase greater than 3 × ULN of the reference range.

    Note: 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.

17. have obesity induced by other endocrine disorders, such as Cushing's syndrome or Prader-Willi syndrome.
18. have:
    a. known clinically significant gastric emptying abnormality, for example, severe gastroparesis or gastric outlet obstruction

   b. undergone gastric bypass, bariatric surgery, or restrictive bariatric surgery, for example Lap-Band®, or
   c. chronically take medications that directly affect GI motility.
19. have a known self or family history, at the first-degree relative level, of multiple endocrine neoplasia type 2A or 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma.
20. have evidence of hypothyroidism or hyperthyroidism based on clinical evaluation that, in the opinion of the investigator, would pose a risk to participant safety. Testing of thyroid-stimulating hormone is not required.

    Note: participants who are on a stable dose of thyroid replacement therapy for at least 90 days prior to screening and who are anticipated to remain on this dose throughout the study period may be included in the study.

21. have, in 6 months prior to screening, had:
    a. myocardial infarction
    b. unstable angina
    c. coronary artery bypass graft
    d. percutaneous coronary intervention (diagnostic angiograms are permitted)
    e. transient ischemic attack
    f. cerebrovascular accident (stroke) or decompensated congestive heart failure, or
    g. currently have New York Health Association Class III or IV heart failure.
22. have a 12-lead ECG abnormality at screening that, in the opinion of the investigator, increases the risks associated with participating in the study.
23. have an active or untreated malignancy or have been in remission from a clinically significant malignancy for less than 5 years prior to screening, other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer.
24. have:
    a. donated more than 500 mL of blood within 8 weeks prior to screening
    b. had a blood transfusion or severe blood loss within 90 days prior to screening
    c. known hemoglobinopathy, for example, hemolytic anemia or sickle cell anemia
    d. a hemoglobin value less than 11 g/dL for males, or less than 10 g/dL for females, or
    e. any other condition known to interfere with HbA1c measurements.
25. have evidence of a significant, active autoimmune abnormality, for example lupus or rheumatoid arthritis, that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next 6 months.
26. have evidence of significant active, uncontrolled medical condition or history of any medical problem capable of constituting a risk when taking the study medication or interfering with the interpretation of data, as judged by the investigator.

Prior and Concomitant Therapy

27. have had a dose change to concomitant medications within a period of 1 month prior to Day 1, unless otherwise specified (see exclusion criteria 20 and 37).

28. have a known allergy or hypersensitivity to midazolam, simvastatin, rosuvastatin, or digoxin that would pose an unacceptable risk to the patient.
29. are receiving medications intended to promote weight loss, including prescribed, OTC, or alternative remedies, within 30 days prior to Day 1. See Section 10.7.1 for more details.
30. are receiving or have received chronic, that is greater than 2 weeks, systemic glucocorticoid therapy within 90 days prior to screening, excluding the following unless the participant has received such therapy within 4 weeks prior to screening:
    a. topical
    b. intraocular
    c. intranasal
    d. single intraarticular injection, or
    e. inhaled preparations.
31. have a positive result following an ethanol test and urine drug screen at screening and Day -1.
32. have known or suspected hypersensitivity to study medication, to selective GLP-1 RAs or glucose-dependent insulinotropic polypeptide/GLP-1 or GLP-1/glucagon dual RAs.

    Note: participants who previously took GLP-1 analogs or related compounds and who discontinued those medications for intolerability should not be enrolled.

33. have any exposure to GLP-1 analogs or other related compounds within 90 days prior to Day 1. See Section 10.7 for examples of excluded medications.
34. are receiving metformin or any other glucose-lowering medication, regardless of the indication for use, within 90 days prior to Day 1. See Section 10.7 for examples of excluded medications.
35. are currently receiving a central nervous system stimulant, for example, Ritalin-SR with the exception of caffeinated beverages.
36. have used or intend to use any prescription or OTC medications within 30 days prior to screening and throughout the study, with the exception of vitamin or mineral supplements, vaccination, and prescription medications for the treatment of concurrent medical conditions such as thyroid replacement therapy, unless otherwise specified (see exclusion criteria 20 and 37). See Appendix 7 in Section 10.7 for examples of excluded medications and Appendix 4 in Section 10.4 for permitted contraceptives.
37. are receiving or have received the following medicines in the list below, from 14 days prior to screening and throughout the study, during both inpatient and outpatient periods. This is to avoid altering the PK of orforglipron which is a CYP3A4, P-gp, and OATP substrate. See Section 6.9 for further details.
    a. strong CYP3A4 inhibitors
    b. strong CYP3A inducers
    c. moderate CYP3A4 inhibitors
    d. moderate CYP3A inducers
    e. drugs that are sensitive P-gp or BCRP substrates with narrow therapeutic index, or
    f. strong OATP inhibitors.

38. are unable to hold therapy during and for 7 days, or 5 half-lives, whichever is longer, prior to inpatient periods if taking the following medicines. This list overlaps that of the prior exclusion criteria, but the list of excluded medicines is more restrictive, immediately before and during the inpatient periods, to avoid confounding the DDI assessment.
    a. midazolam
    b. digoxin
    c. simvastatin
    d. rosuvastatin
    e. any medications that are contraindicated in the midazolam, simvastatin, rosuvastatin, or digoxin prescribing information
    f. OTC or prescription medication that maintains elevated gastric pH
    g. any medications that transiently affect gastric pH, or
    h. statins for hypercholesterolemia. See Section 6.9 for more details.

    Note: caution should be used when prescribing other fibrates with simvastatin, as these agents can cause rhabdomyolysis when given alone and the risk is increased when they are coadministered.

Prior and Concurrent Clinical Study Experience

39. 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.
40. have participated in a clinical study and received treatment, whether active or placebo, within 90 days from the last dose of that study, prior to Day -1 of the current study. If the study involved an IP, at least 5 elimination half-lives or 90 days, whichever is longer, should have passed before dosing with orforglipron.
41. have previously completed or withdrawn from this study.

Diagnostic Assessments

42. have fasting serum triglyceride levels greater than 500 mg/dL.
43. have an abnormal BP, including:
    a. seated systolic BP equal to or greater than 160 mmHg, or
    b. seated diastolic BP equal to or greater than 100 mmHg.
44. have acute or chronic hepatitis including a history of autoimmune hepatitis, signs and symptoms of any other liver disease, or any of the following at screening:
    a. ALT or AST levels greater than 3.0 × ULN for the reference range
    b. ALP levels greater than 1.5 × ULN for the reference range
    c. TBL levels greater than 1.5 × ULN for the reference range, except for cases of known Gilbert's Syndrome, or
    d. hepatitis B infection, defined as:
        i. positive hepatitis B core total antibody and positive HBV DNA, or
        ii. positive hepatitis B surface antigen.
    e. positive hepatitis C antibody and positive HCV RNA.

Note: participants treated for hepatitis C and diagnosed as cured must have an RNA test at screening and also be HCV RNA negative for at least 3 years prior to screening in order to be eligible for the study. Participants who are positive for hepatitis C antibody but negative for HCV RNA may be enrolled.

45. have serum calcitonin levels equal to or greater than 20 ng/L.
46. have evidence of HIV infection, positive HIV antibodies, or both, historically or at screening.

Other Exclusion Criteria

47. are women who are:
    a. currently pregnant or breastfeeding, or
    b. who intend to become pregnant or to breastfeed at any time during the study or within 20 weeks after receiving the last dose of orforglipron.
48. have difficulty swallowing capsules.
49. have alcohol intake that exceeds recommended average weekly alcohol consumption limits per local regulation, or an amount deemed significant by the investigator. .
50. smoke more than 10 cigarettes or equivalent per day.
51. show evidence of regular use of known drugs of abuse in the opinion of the investigator.
52. are investigative 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.
53. are Lilly employees or are employees of a third-party organization involved in the study which requires exclusion of their employees.
54. are unsuitable for inclusion in the study, in the opinion of the investigator or sponsor.
55. for Cohort 1 only:
    a. have c.34AA, c.421AA, or the diplotype combination of c.34GA/421CA genotypes of ABCG2 as determined through genotyping.
    b. have c.521CC genotypes of SLCO1B1 as determined through genotyping.

Note: participants of any genotype may participate in Cohort 2.

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

From 7 days before the start of study intervention until discharge from the study, participants will be required to refrain from consumption of:

- red wine
- grapefruit and grapefruit-containing products
- Seville oranges and Seville orange-containing products
- star fruits and star fruit-containing products
- pomelo, or

- commercial apple juice or orange juice.

Food

On all dosing days for all study interventions except acetaminophen, participants must fast for at least 8 hours prior dosing.

On acetaminophen dosing days, participants will complete consumption of a meal 5 to 10 minutes prior to acetaminophen administration. The participant must consume as much of the meal as possible within 15 to 20 minutes. The meal should consist of a solid nutrition bar and a liquid nutrition shake that has a total caloric content of approximately 500 kcal. The macronutrient composition of the meals should be targeted to provide approximately 50% of the calories from carbohydrate, 30% of the calories from fat, and 20% of the calories from protein.

On PK sample collection days other than acetaminophen dosing days, participants must fast for at least 4 hours after dosing. On all other days, participants may consume their meal 30 minutes after dosing.

Drink

On PK sample collection days, participants must refrain from drinking fluids from 1 hour prior to and until 1 hour after 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

Caffeine

Participants will be allowed to maintain their regular caffeine consumption throughout the study.

Alcohol

No alcohol will be allowed at least 24 hours prior to each CRU admission and outpatient visit, and throughout the duration of each CRU visit. Between CRU visits, alcohol consumption should not exceed recommended average weekly alcohol consumption limits per local regulation.

Tobacco

No use of tobacco- or nicotine-containing products will be permitted while at the CRU. Between CRU visits, participants must not consume 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. Participants will abstain from strenuous exercise within 24 hours prior to all visits if possible.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study, known as a screen failure, may be rescreened once at least 2 weeks after the initial screen. Rescreened participants should

be assigned a new participant number for every screening or rescreening event. Rescreened participants are not required to repeat screening genotyping assessments.

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

Not applicable.

6. Study Interventions 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 Interventions Administered

While inpatient at the CRU, orforglipron capsules and tablet, sodium bicarbonate, rosuvastatin, digoxin, simvastatin, acetaminophen, and midazolam 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. Where study interventions are coadministered, there is no required order in which they must be taken.

Orforglipron capsules and tablet, sodium bicarbonate, rosuvastatin, digoxin, simvastatin, and midazolam will be administered following an overnight fast of at least 8 hours. Acetaminophen will be administered 5 to 10 minutes after completion of a meal.

When coadministered with sodium bicarbonate, simvastatin will be coadministered or administered immediately after sodium bicarbonate administration.

During Inpatient Periods 1 and 2, 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 8 hours, but if they forget or miss a dose, 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.

Following initial administration of orforglipron on Day 14 for Cohort 1 or Day 9 for Cohort 2, all participants will be dose escalated for orforglipron once every 2 weeks. Participants who are unable to continue with the dose escalation regime before Day 23 will need to be replaced in the trial.

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

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.

Table GZPG.1. Study Intervention Administered

Intervention Name	Orforglipron[a]		Sodium Bicarbonate (Placebo to Match Orforglipron Capsule)[a]	Midazolam	Rosuvastatin	Digoxin	Simvastatin	Acetaminophen
Dose Formulation	Capsule	Tablet	Capsule	Syrup ([redacted] mg/mL)	Tablet	Tablet	Tablet	Liquid
Dosage Level(s)	[redacted] mg [redacted] mg [redacted] mg [redacted] mg [redacted] mg [redacted] mg	[redacted] mg	[redacted] mg	[redacted] mg	[redacted] mg	[redacted] mg	[redacted] mg	[redacted] mg
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral
Sourcing	Provided centrally by the sponsor			Purchased locally by site				

[a] Orforglipron capsules also contain [redacted] mg of sodium bicarbonate in each strength. The sodium bicarbonate capsules are manufactured as the placebo to match the active capsules, that is, the 'placebo to match LY3502970 C3 capsules' in the IND. The orforglipron tablet contains a lower amount of a different pH modifier.

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention 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.

All study intervention must be stored in a secure, environmentally controlled, and manual or automated monitored 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 in the Pharmacy Manual.

Participant Responsibilities

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

6.3. Assignment to Study Intervention

This is a non-randomized study.

6.4. Blinding

This is an open-label study.

6.5. Study Intervention Compliance

During inpatient visits, study intervention will be administered under medical supervision by the investigator or designee. 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 interventions at home, compliance with study intervention will be assessed at each 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. Intervention start and stop dates will also be recorded in the CRF.

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 modification is not permitted in 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 time period will be considered a potential overdose. However, any dose greater than the dose assigned according to the dose escalation regimen within a 24-hour time period will be considered noncompliant per protocol, and should also be reported to the investigator for management of any AEs and for appropriate documentation.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- contact the clinical pharmacologist or clinical research physician immediately
- evaluate the participant to determine, in consultation with the clinical pharmacologist or clinical research physician, whether study intervention should be interrupted or whether the dose should be reduced
- closely monitor the participant for any AE or SAE and laboratory abnormalities as medically appropriate for the duration of the study, and
- document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.9. Prior and Concomitant Therapy

Any medication or vaccine, including OTC or prescription medicines, vitamins, and herbal supplements, 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 for concomitant therapy of special interest.

Ginger candy, ginger ale, and ondansetron are allowed for nausea.

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.

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 CYP3A4, P-gp, and an OATP substrate, participants must abstain from taking:

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

Additionally, until the results of this study are available, 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 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. The use of moderate CYP3A4 inhibitors or CYP3A inducers is strongly discouraged for initiation during the study, and alternative medications should be considered whenever possible.

Drugs that may be affected by an increase in gastric pH should be separated from study drug administration by at least 2 to 4 hours.

GLP-1 Analogs and Glucose-lowering Medications

Throughout the study, participants must also abstain from taking:

- GLP-1 analogs or other related compounds, and
- glucose lowering medications.

These drugs must be washed out for at least 90 days prior to Day 1.

Weight Loss Medication

Throughout the study, participants must abstain from taking medications intended to promote weight loss, including prescribed, OTC, or alternative remedies. These drugs must be washed out for at least 30 days prior to Day 1.

Acetaminophen

Acetaminophen, at doses of up to 2 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. However, concomitant treatment with acetaminophen should not be allowed after midnight prior to acetaminophen PK assessment and throughout the day of acetaminophen PK sampling. As with all concomitant medications used during the study, any acetaminophen

use will be recorded in the CRF. Acetaminophen use during the Outpatient Period will be recorded in participant diaries.

Other Concomitant Medications

To not interfere in the PK assessment of CYP and transporter substrates, while resident at the CRU and from 7 days prior to inpatient visits, or 5 half-lives, whichever is longer, participants must abstain from taking:

- midazolam
- digoxin
- simvastatin
- rosuvastatin
- any medications that are contraindicated in the midazolam, simvastatin, rosuvastatin, or digoxin prescribing information
- OTC or prescription medication that maintains elevated gastric pH, such as H2-receptor blockers and proton pump inhibitors
- on days of simvastatin dosing only, any medications that transiently affect gastric pH, such as antacids and milk of magnesia
- statins for hypercholesterolemia, and
- **any** inhibitors or inducers of CYP3A, OATP, P-gp, or BCRP.

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.

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

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will remain in the study to complete procedures for an ED visit, as shown in the SoA in Section 1.3.

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
- acute pancreatitis is diagnosed, or
- the participant has a PHQ-9 score of 15 or more, has answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, or has answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

  Note: 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 8.3.5.3 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 ED visit, as shown in the SoA in Section 1.3. 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 site 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 study site. Site 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 site.

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 10.1.9 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 will include, 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 signs 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 orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, participants should be sitting for at least 5 minutes and measurement obtained between 2 to 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 investigational site.

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 site as soon after the time of ECG collection as practical, to determine whether the participant meets entry criteria.

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2 in 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 which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 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 clinical pharmacologist or clinical research physician.

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 in 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.

Serum pregnancy testing will be performed at screening. Urine pregnancy testing will be performed at all other time points, and ED if applicable. See Section 8.3.2 for details.

8.2.6. Depression, Suicidal Ideation and Behavior Risk Monitoring

Participants who have obesity or are overweight are at increased risk for depression (Luppino et al. 2010). Depression can increase the risk for SIB. Therefore, study participants will be screened at trial 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 questionnaire. 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.

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.

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 changes.

Baseline assessment of depression will be monitored during the study using PHQ-9.

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, 5th 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 for details.

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading 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 each participant at subsequent visits/contacts. All SAEs and AESIs as defined in Section 8.3.3 will be followed 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 GZPG.2 describes the timing, deadlines, and mechanism for collecting events.

Table GZPG.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 ICF	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 ICF	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
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 8.3.2)	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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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; ICF = informed consent 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. Pregnancy

Collection of Pregnancy Information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive orforglipron.

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

- will obtain a consent to release information from the pregnant female 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 female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up

will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status, that is presence or absence of anomalies, or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female 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 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 that is 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 less than 20 weeks gestational age, or still birth, occurring at equal to or more than 20 weeks gestational age, is always considered to be an SAE and will be reported as such.

Any post-study 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, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study should 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. Adverse Events of Special Interest and Other Safety Topics

AESIs and other safety topics for this program include:

- severe or serious GI AEs of Nausea, Vomiting, and Diarrhea
- pancreatitis, as detailed in Section 8.3.4
- major adverse cardiovascular events
- arrhythmias and cardiac conduction disorders
- hepatic disorder, as detailed in Section 8.3.5
- hypoglycemia, as detailed in Section 8.3.6
- hypotension, orthostatic hypotension, and syncope
- acute kidney injury and chronic kidney disease
- gallbladder and biliary tract disorders
- hypersensitivity reactions
- depression and SIB, as detailed in Section 8.2.6, and

- abuse potential.

8.3.4. 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 CT 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 CT 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.

8.3.5. Hepatic Safety Monitoring, Evaluation, and Criteria for Study Drug 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 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 drug
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.

8.3.5.1. 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 tests 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 tests 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.

8.3.5.2. 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 CT 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 tests results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.3.5.3. Study Drug 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 8.3.5.1 and comprehensive hepatic evaluation as described in Section 8.3.5.2.

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 drug should include these actions:

- While the participant is not receiving the study drug, clinical and laboratory monitoring should continue at a frequency of 1 to 2 times weekly until liver tests 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 tests 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 drug 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 non-study-drug etiology is identified. Otherwise, the study drug should be permanently discontinued.

8.3.6. 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

As specified in the SoA in Section 1.3, whole blood samples will be collected for various analytes for PK assessment. One 2-mL whole blood sample each will be collected for:

- orforglipron
- simvastatin and simvastatin acid
- digoxin
- rosuvastatin
- acetaminophen, and
- midazolam and 1-hydroxymidazolam.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data, for example to obtain data closer to the time of peak plasma concentrations, to ensure appropriate monitoring.

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

Samples will be used to evaluate the PK of all study interventions. Each 2 mL whole blood sample will be divided into aliquots, 1 each for PK of the relevant study intervention. Samples collected for analyses of study intervention plasma concentration may also be used to evaluate biomarkers, efficacy aspects, or safety related to concerns arising during or after the study due to parent compounds or their metabolites.

Genetic analyses will not be performed on these whole blood samples. Participant confidentiality will be maintained. At visits during which whole blood samples for the determination of PK of study interventions will be taken, one sample of sufficient volume can be used.

8.5. Pharmacodynamics

PD 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 and Appendix 1 in Section 10.1.9 for details about sample retention and custody.

8.7. Biomarkers

From samples collected for rosuvastatin PK analysis, concentrations of plasma coproporphyrin 1 may be assayed using a validated liquid chromatography tandem mass spectrometry method. Coproporphyrin 1 may also be measured from other PK samples. Other biomarkers may also be examined in plasma in an exploratory manner.

Samples collected for PK analysis or used in exploratory biomarker analysis will not be retained longer than 1 year after last participant visit.

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 SAP 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 Hypotheses

The primary objectives of this study are to evaluate the effect of the following in healthy overweight or obese participants of:

- orforglipron capsule on the PK of digoxin, rosuvastatin, acetaminophen, and midazolam
- orforglipron capsule on the PK of simvastatin, following simultaneous or staggered administration, and
- sodium bicarbonate on the PK of simvastatin.

The secondary objectives of this study are:

- to evaluate the effect of orforglipron tablet on the PK of simvastatin in healthy overweight or obese participants, and
- to describe the safety and tolerability of orforglipron in healthy overweight or obese participants.

The exploratory objective of this study is:

- to evaluate the effect of multiple oral doses of orforglipron on endogenous OATP1B biomarker in healthy participants.

The exploratory objective will be evaluated only if data is available and deemed appropriate.

9.2. Analyses Sets

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

Participant Analysis Set	**Description**
Enrolled	All participants 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 receive at least 1 dose of study intervention and have evaluable PK data.
Coproporphyrin 1 biomarker set (if applicable)	All participants in Cohort 1 who have at least 1 period of evaluable coproporphyrin 1 data.

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

Demographic characteristics will be recorded and summarized using descriptive statistics, including the participant's:

- age
- sex
- weight
- height
- BMI
- race, and
- other demographic characteristics.

9.2.3. Treatment Compliance

The date and time will be recorded and listed for each dose of:

- orforglipron
- simvastatin
- sodium bicarbonate
- digoxin
- rosuvastatin
- acetaminophen, and
- midazolam.

The orforglipron capsule doses will also be recorded for self-administered doses.

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 on data from all participants who receive at least 1 dose of the study intervention and have evaluable PK.

Safety analyses will be conducted for all enrolled participants who received at least 1 dose of study intervention, whether or not they completed all protocol requirements.

Coproporphyrin 1 biomarker analyses may be conducted on the coproporphyrin 1 biomarker set on all participants in Cohort 1 who have at least 1 period of evaluable coproporphyrin 1 data.

Additional exploratory analyses of the data will be conducted as appropriate. Study results may be pooled with the results of other studies for safety, PD, and population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final clinical study report.

9.3.2. Primary Endpoints Analysis

9.3.2.1. Pharmacokinetic Parameter Estimation of Primary Endpoints

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

- orforglipron
- simvastatin
- simvastatin acid
- digoxin
- rosuvastatin
- acetaminophen
- midazolam
- 1-hydroxymidazolam, and
- any other metabolites of study intervention, if applicable.

The primary parameters for analysis will include C_{max} and AUC. Other parameters, such as t_{max}, half-life, apparent clearance, and apparent volume of distribution, may be reported. If deemed necessary, additional analysis may be performed. All PK parameters will be listed and summarized using descriptive statistics.

9.3.2.2. Pharmacokinetic Statistical Inference of Primary Endpoints

9.3.3. Secondary Endpoint Analysis

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 capsule dose level will be presented by severity and by association with IP as perceived by the investigator. AEs reported to occur prior to the first study dose 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 SAEs will be reported. Details regarding the analysis of AESIs will be described in the SAP.

9.3.3.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include clinical chemistry and vital signs. The parameters and changes from baseline, that is 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.

9.3.3.3. Pharmacokinetic Statistical Inference of Secondary Endpoints

9.3.4. Exploratory Analyses

9.3.4.1. Parameter Estimation of Exploratory Endpoint

If data is available and deemed appropriate, plasma concentrations of coproporphyrin 1 may be listed and summarized using standard descriptive statistics. Parameter estimates for coproporphyrin 1 may be calculated by standard noncompartmental methods. Parameters, including C_{max}, t_{max}, and $AUC_{(0-24)}$, may be summarized using descriptive statistics.

Additional analysis may be performed, if warranted, upon review of the data.

9.3.4.2. Statistical Inference of Exploratory Endpoint

If data is available and deemed appropriate, a statistical comparison of coproporphyrin 1 PK parameters may be performed.

9.3.5. Other Analyses

9.3.5.1. 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.

9.4. Interim Analysis

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

9.5. Sample Size Determination

CCI

[redacted]

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 or IEC by the investigator and reviewed and approved by the IRB or IEC before the study is initiated.

Any amendments to the protocol will require IRB or 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 or IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB or IEC
- notifying the IRB or IEC of SAEs or other significant safety findings as required by IRB or IEC procedures
- providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB or 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 CTA.

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 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB or 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 ethical review board consenting guidance.

A copy of the ICFs 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 which 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 or 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 plans 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 EU 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 by phone, email, or both, 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, that is 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 or 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 CTA 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 EDC 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 EDC 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 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.

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 or 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 or IRBs, the regulatory authorities, and any contract research organizations 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 by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.1.9. 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 (and coproporphyrin 1 if applicable)	Sponsor or designee	1 year
Pharmacogenetics	Sponsor or designee	15 years

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the central or local laboratory, as specified in the table below.

In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing, in the table below, 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.

• 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:
  ○ Neutrophils
  ○ Lymphocytes
  ○ Monocytes
  ○ Eosinophils
  ○ Basophils
	All hematology tests performed only at screening, Day -1, follow-up, and ED visit, if applicable.

Clinical Chemistry	Assayed by local laboratory.

• Sodium
• Potassium
• Bicarbonate
• Chloride
• Calcium
• Phosphate
• Glucose (fasting)
• Urea
• Total protein
• Albumin
• Amylase
• Lipase
• Creatinine
• Creatine kinase
• Liver panel
  ○ Total bilirubin
  ○ Direct bilirubin
  ○ Indirect bilirubin
  ○ Alkaline phosphatase
  ○ Aspartate aminotransferase
	Clinical chemistry tests to be performed at all clinically laboratory evaluation time points.
	
	[a] Lipid panel to be performed at screening only.

○ Alanine aminotransferase ○ Gamma-glutamyl transferase • Lipid panel[a] ○ Total cholesterol ○ Triglycerides ○ Low-density lipoprotein cholesterol ○ High-density lipoprotein cholesterol	
Urinalysis	Assayed by local laboratory.
• Specific gravity • pH • Protein • Glucose • Ketones • Bilirubin • Urobilinogen • Leukocytes • Blood • Nitrite • Microscopic examination of sediment[c]	All urinalysis tests performed only at screening, Day -1, follow-up, and ED visit, if applicable. [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 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) • HBV DNA • 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, C, and HIV. HCV RNA test only performed to confirm a positive hepatitis C antibody test. HBV DNA test only performed if hepatitis B core total antibody test is positive.
Other Tests	Assayed by local laboratory.
• Estimated glomerular filtration rate[d] • Follicle-stimulating hormone[d,g] • Calcitonin[d] • Glycated hemoglobin (HbA1c)[d] • Ethanol test[e] • Urine drug screen[f]	[d] Performed at screening only. [e] Urine test performed at screening, and urine or breath test performed on Day -1, Day 95 of Cohort 1, and Day 90 of Cohort 2. [f] Performed at screening, Day -1, Day 95 of Cohort 1, and Day 90 of Cohort 2. [g] Performed for females only.

Pharmacokinetic Samples	Assayed by Lilly central laboratory. Results will not be provided to the investigative sites.
• Orforglipron concentration • Simvastatin and simvastatin acid concentration • Digoxin concentration • Rosuvastatin concentration • Acetaminophen concentration • Midazolam and 1-hydroxymidazolam concentration	
Genotyping Sample	Assayed by a Lilly central laboratory.
Genetics Sample	Assayed by Lilly central laboratory. Results will not be provided to the investigative sites.
Coproporphyrin 1 Samples (if applicable)	Assayed by Lilly central laboratory for exploratory analysis if deemed appropriate. Results will not be provided to the investigative sites. Concentrations of plasma coproporphyrin 1 may be assayed using samples collected for rosuvastatin PK analysis, or other PK samples if necessary.

10.2.1. Blood Sampling Summary

These tables summarize the approximate number of venipunctures and blood volumes for all blood sampling, including screening, safety laboratories, and bioanalytical assays, during the study.

Protocol J2A-MC-GZPG Sampling Summary – Cohort 1

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	20	1	20
Clinical laboratory tests[a]	10	10	100
Pharmacokinetics	2	215[b]	430
Pharmacogenetics	10	1	10
Total			560
Total for clinical purposes (rounded up to nearest 10 mL)			560

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

[b] Includes additional 3 samples, if required.

Protocol J2A-MC-GZPG Sampling Summary – Cohort 2

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	20	1	20
Clinical laboratory tests[a]	10	10	100
Pharmacokinetics	2	109[b]	218
Pharmacogenetics	10	1	10
Total			348
Total for clinical purposes (rounded up to nearest 10 mL)			350

[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, that is investigational, product, or investigational combination product, whether or not related to the medicinal, that is investigational, product or investigational combination product.

Events meeting the AE definition

- Any abnormal laboratory test results, that is hematology, clinical chemistry, or urinalysis, or other safety assessments, for example, ECG, radiological scans, and vital signs 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 pre-existing 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 DDI.
- Medication error, misuse, or abuse of IMP, 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, such as social, convenience admission to a hospital, or both.
- Anticipated day-to-day fluctuations of pre-existing diseases or conditions 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 one 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, treatment, or both, 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 pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability or 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 or 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 or SAE. In such cases, it should be reported as both a PC and as an AE or SAE.

10.3.4. Recording and Follow-up of AE and/or SAE and Product Complaints

AE, SAE, and product complaint recording

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

The investigator will then record all relevant AE, SAE, or PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE or 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 or SAE. In such cases, it should be reported as both a PC and as an AE or 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 or 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 or symptoms, will be documented as the AE or SAE.

Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one 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 one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

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

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

Alternative causes, such as underlying diseases, 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 or 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 one 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, IRB or IEC, 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 or IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they • have a congenital anomaly such as Müllerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], 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] Women **should not** be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

10.4.2.1. Male Participants

No male contraception is required except in compliance with specific local government study requirements.

10.4.2.2. Female Participants

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

Must…	Must not…

agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males, 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

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Contraception	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)	• female sterilization[a] (including fallopian tube ligation, hysteroscopic sterilization) • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (for men in clinical trials and for female partner if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges, or
	• barrier method with use of a spermicide
	  ○ condom with spermicide
	  ○ diaphragm with spermicide, or
	  ○ female condom with spermicide
	Note: male and female 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

[a] Hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy are the only types of permanent female sterilization that allow a participant to be a WNOCBP.

10.5. Appendix 5: Genetics

Use or 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 or 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 T2D, obesity, overweight, and related diseases. They may also be used to develop tests or assays including diagnostic tests related to orforglipron and T2D, obesity, overweight, and related diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome, as appropriate.

The samples may be analyzed as part of a multi-study 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 8.3.5 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]	

a If lab does not offer total antibody testing, IgG and IgM are acceptable substitutes

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

c Availability of acetaminophen protein adducts testing is limited, so testing may be performed at central labs, 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

Participants must abstain from taking 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
- lorcaserin
- mazindol
- naltrexone/bupropion
- orlistat
- OTC medications, for example, allī®
- phentermine
- phentermine/topiramate
- phenylpropanolamine
- semaglutide
- sibutramine, and
- other incretin-based therapies.

10.7.2. Strong CYP3A4 Inhibitors and Strong CYP3A Inducers

Participants must abstain from taking strong CYP3A4 inhibitors and strong CYP3A inducers, including:

- boceprevir
- cobicistat
- danoprevir and ritonavir
- elvitegravir and ritonavir
- grapefruit juice
- indinavir and ritonavir
- itraconazole
- ketoconazole
- lopinavir and ritonavir
- paritaprevir and ritonavir and ombitasvir and/or dasabuvir
- posaconazole
- ritonavir
- saquinavir and ritonavir
- telaprevir
- tipranavir and ritonavir
- telithromycin
- troleandomycin

- voriconazole
- clarithromycin
- nefazodone
- nelfinavir
- apalutamide
- carbamazepine
- enzalutamide
- mitotane
- phenytoin
- rifampin, and
- St John's wort.

10.7.3. Strong OATP Inhibitors

Participants must abstain from taking strong OATP inhibitors, including:

- rifampin
- cyclosporine
- faldaprevir
- tipranavir/ritonavir
- glecaprevir/pibrentasvir
- telaprevir
- sofobuvir/velpatsasvir/voxilaprevir
- lopinavir/ritonavir
- darunavir/ritonavir, and
- elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.

10.7.4. Drugs that are Sensitive P-gp Substrates with a Narrow Therapeutic Index

Participants must abstain from taking 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.

10.7.5. Drugs that are Sensitive BCRP Substrates with a Narrow Therapeutic Index

Participants must abstain from taking drugs that are sensitive BCRP substrates with a narrow therapeutic index, including prazosin.

10.7.6. Moderate CYP3A4 Inhibitors and Moderate CYP3A Inducers

Participants must abstain from taking 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.

10.7.7. 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 least 2 to 4 hours, including:

- simvastatin
- levothyroxine
- ferrous sulfate

- bisphosphonates, and
- other narrow therapeutic index substrates with potential pH-dependent solubility or stability.

10.7.8. GLP-1 Analogs or Other Related Compounds

Participants must abstain from taking GLP-1 analogs or other related compounds, including:

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

10.7.9. Glucose-lowering Medications

Participants must abstain from taking glucose-lowering medications, including:

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

10.8. Appendix 8: 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 event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{(0-24)}$	area under the concentration versus time curve from time zero to 24 hours postdose
BCRP	breast cancer resistant protein
BMI	body mass index
BP	blood pressure
C-SSRS	Columbia Suicide-Severity Rating Scale
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed drug concentration
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
CT	computed tomography
CTA	clinical trial agreement
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction

ECG	electrocardiogram
ED	early discontinuation
EDC	electronic data capture system
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 ICF directly or through their legally acceptable representatives.
GCP	good clinical practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
HbA1c	glycated hemoglobin
HBV	hepatitis B virus
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
IMP	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.
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 ICF.
INR	international normalized ratio
IP	nvestigational 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 "IMP."
IRB	institutional review board

MDD	major depressive disorder
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 one 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 PC • 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 1
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/PD	Pharmacokinetic(s)/pharmacodynamic(s)
QD	once daily
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
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 and behavior
SoA	Schedule of Activities

$t_{1/2}$	half-life associated with the terminal rate constant
T2D	type 2 diabetes
TBL	total bilirubin
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 of maximum observed drug concentration
ULN	upper limit of normal
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

10.9. Appendix 9: Protocol Amendment History

Amendment [a]

Overall Rationale for the Amendment:

This amendment is considered to be non-substantial and is provided to clarify procedures and ensure consistency within the protocol.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 SoA	Moved genetics sample from Day -1 to Day 1 in Cohorts 1 and 2.	For logistical purposes at the trial site
	Updated days in which predose vital signs assessments are performed.	To correct errors in the initial protocol
	Updated Day 15 (Cohort 1) and Day 9 (Cohort 2) clinical laboratory evaluations to be predose.	To correct errors in the initial protocol
	Added description of OFG PK sampling in relation to Day 14 OFG dose during inpatient period of Cohort 1.	To clarify the procedure
	Moved the clinical laboratory evaluations occurring on Day 95 (Cohort 1) and Day 90 (Cohort 2) to predose on Day 96 (Cohort 1) and predose on Day 91 (Cohort 2).	For logistical purposes at the trial site
	Clarified Day 95 (Cohort 1) and Day 90 (Cohort 2) OFG dose will be self-administered prior to CRU admission.	To clarify the procedure
Section 4.3 Justification for Dose	The rationale for the tablet dose selection was updated.	For clarity and consistency within the protocol
	Added detail that acetaminophen will be provided as [redacted] × [redacted] mg tablets.	For clarity and consistency within the protocol
Section 5.2 Exclusion Criteria	Updated exclusion 27 to refer reader to exclusion criteria 20 and 37.	For clarity and consistency within the protocol
	Updated exclusion 36 to remove incorrect concomitant medication stable dosing period, and refer reader to exclusion criteria 20 and 37.	For clarity and consistency within the protocol
	Updated exclusion 37 to state OFG is a CYP3A4 substrate.	For clarity and consistency within the protocol

Section # and Name	Description of Change	Brief Rationale
	Updated exclusion 40 to include that the 90 day period starts from the last dose of a previous study.	To clarify the time period for exclusion
	Clarified weekly alcohol intake limits in exclusion 49.	Updated to be aligned with local regulations
	Added exclusion 55 to identify the genotypes excluded from Cohort 1.	For clarity and consistency within the protocol
Section 5.3.2 Substance Use: Caffeine, Alcohol, and Tobacco	Clarified weekly alcohol intake limits.	Updated to be aligned with local regulations
Section 6.9 Prior and Concomitant Therapy	Clarified that OFG is a CYP3A4 substrate.	For clarity and consistency within the protocol

Abbreviations: CYP = cytochrome P450; OFG = orforglipron; PK = pharmacokinetic; SoA = schedule of activities.

Amendment [b]

Overall Rationale for the Amendment:

This amendment is considered to be non-substantial and is provided to address regulatory feedback, clarify procedures, and ensure consistency within the protocol. Minor editorial and grammatical changes were also made.

Section # and Name	Description of Change	Brief Rationale
Synopsis 4.1. Study Design	Clarified that Days 14 and 15 OFG dosing in Cohort 1 and Day 9 dosing in Cohort 2 will take place within the CRU.	Updated for consistency within protocol.
Synopsis 4.1. Study Design 4.3. Justification for Dose 6.1. Study Intervention Administered	The OFG tablet strength was changed from CCI mg to CCI mg.	The CCI mg tablet is anticipated to have an equivalent or slightly higher exposure than the CCI mg capsule, thus providing an appropriate comparison of the effect of orforglipron capsule and tablet on simvastatin exposure.
Synopsis 1.2. Schema 1.3. Schedule of Activities 4.1. Study Design	The Day 99 digoxin dose in Cohort 1 and the Day 94 digoxin dose in Cohort 2 was updated from being administered approximately 2 hours after OFG dosing to be coadministered with OFG.	Updated based on regulatory feedback.
Synopsis 4.3. Justification for Dose 6.1. Study Interventions Administered	The formulation of acetaminophen was changed from tablet to liquid.	Preferred dosage form for assessing gastric emptying delay.
1.3. Schedule of Activities 10.2. Clinical Laboratory Tests	The alcohol testing was updated to be breath or urine.	Updated based on site feedback.
1.3. Schedule of Activities	Clarified that all scheduled and unscheduled vital signs will be assessed while participant is sitting.	Updated based on site feedback.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	Clarified that acetaminophen PK sampling is relative to acetaminophen administration.	To provide more clarity for sites.
1.3. Schedule of Activities	A window of ±1 day has been added to each outpatient visit.	To allow more flexibility for sites.
5.1. Inclusion Criteria	The units for eGFR were corrected from mL/m^2 to mL/min.	Corrected the units to reflect the correct units for eGFR.
5.2. Exclusion Criteria	Clarified that TSH is not required for clinical evaluation of hypothyroidism or hyperthyroidism in exclusion criterion 20.	Clarified based on site feedback.
5.3.1. Meals and Dietary Requirements	Further details of the conditions for meal consumption were provided.	Clarified based on site feedback.
5.3.1. Meals and Dietary Requirements	It was clarified that the 4 hours of continued fast post-OFG dosing does not apply to acetaminophen dosing days.	Clarified based on site feedback.
5.4. Screen Failures	It was clarified that participants may be rescreened once and that genotyping was not required to be repeated.	Clarified based on site feedback.
6.1 Study Interventions Administered	Clarified that where study interventions are coadministered, there is no required order in which they must be taken.	Clarified based on site feedback.
6.1 Study Interventions Administered	Clarification was provided for participants who miss a dose of OFG.	Clarified based on site feedback.
6.9. Prior and Concomitant Therapy	Ginger candy, ginger ale, and ondansetron were allowed for treatment of nausea.	Clarified based on site feedback.
10.2. Clinical Laboratory Tests	Gamma-glutamyl transferase was added to the clinical chemistry parameters.	Added to further monitor participant safety.
10.2. Clinical Laboratory Tests	It was clarified when HBV DNA test would be performed.	Clarified based on site feedback.
10.2. Clinical Laboratory Tests	It was clarified that a central laboratory would be used for the genotyping sample.	Clarified based on site feedback.
10.6. Liver Safety: Suggested Actions and Follow-up Assessments	Hepatitis D virus immunoglobulin M antibody was removed from the list of hepatic evaluation tests.	This test is no longer available.

Abbreviations BSA = body surface area; CRU = clinical research unit; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; OFG = orforglipron; PK = pharmacokinetic; TSH = thyroid-stimulating hormone.

Amendment [c]

Overall Rationale for the Amendment:

This amendment is considered to be non-substantial and is provided to include coproporphyrin 1 biomarker evaluation.

The overall changes and rationale for the changes made to the protocol are described in the following table. Note that minor edits have been made throughout the protocol which are not captured in the amendment summary table.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Metabolites simvastatin acid and 1'-hydroxymidazolam added to relevant primary and secondary PK endpoints.	To clarify the PK parameters that will be evaluated.
3. Objectives and Endpoints		
3. Objectives and Endpoints	Coproporphyrin 1 biomarker evaluations added for Cohort 1.	Coproporphyrin 1 levels will be evaluated using the rosuvastatin PK samples to evaluate the effect of multiple oral doses of orforglipron on endogenous OATP1B biomarker.
4.2. Scientific Rationale for Study Design		
8.7. Biomarkers		
9.1. Statistical Hypotheses		
9.2. Analyses Sets		
9.3.1. General Considerations		
9.3.4. Exploratory Endpoint Analysis		
10.1.9. Sample Retention		
10.2. Appendix 2: Clinical Laboratory Tests		
6.8. Treatment of Overdose	Definition of overdose changed from 'any dose of orforglipron greater than the dose assigned' to 'any dose of orforglipron greater than CCI mg within a 24-hour time period', with extra instructions for any dose greater than the dose assigned.	Wording changed to be consistent with other orforglipron studies.

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