Protocol Amendment J2A-MC-GZPP (a)

A Drug-Drug Interaction, Single-arm, Open-label Study to Assess the Effect of Quinidine on the Pharmacokinetics of Orforglipron in Healthy Participants

NCT06704763

Approval Date: 11 Nov 2024

Title Page

Protocol Title:

A Drug-Drug Interaction, Single-arm, Open-label Study to Assess the Effect of Quinidine on the Pharmacokinetics of Orforglipron in Healthy Participants

Protocol Number: J2A-MC-GZPP

Amendment Number: a

Compound: Orforglipron (LY3502970)

Brief Title: A Drug-Drug Interaction Study of Orforglipron with Quinidine in Healthy 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(s): IND: 142842

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

Document ID: VV-CLIN-162180

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	19-Sep-2024

Amendment [a]

This amendment is considered to be nonsubstantial.

Overall rationale for the amendment

The protocol is being amended to provide clarifications and correct identified errors.

Section # and Name	Description of Change	Brief Rationale

1.3. Schedule of Activities (SoA)	• Removed the redundant "Out-patient visit" row
	• Updated "Medical assessment" to "Physical examination" and added additional time points
	• Combined "Hematology" and "Chemistry" rows into 1 row
	• Updated "IOCBP" to "AFAB" for "Urine pregnancy" row
	• Added additional time points for
	  o Hematology, and
	  o Vital signs.
	• Updated text in ECG, Midazolam dosing, and LY dosing rows to make more succinct.
		To provide clarifications and correct identified errors.

1.3. Schedule of Activities (SoA)	Added additional ECG collection time points.	For additional ECG monitoring as quinidine will be administered in this study.
4.4. End of Study Definition	Added additional text to allow flexibility to determine completer status if assessments are missed.	To provide clarifications.
5.1. Inclusion Criteria	• Criterion 2: Updated "cardiac monitoring" to "ECG" • Criterion 4: Added "at screening"	To provide clarifications and correct identified errors.
5.2. Exclusion Criteria	• Criteria 29 to 31: Removed text stating that a negative test within 6 months of screening would not need to be repeated • Criteria 32 and 33: Added "at screening"	To provide clarifications and correct identified errors.

Section # and Name	Description of Change	Brief Rationale
	• Criterion 33: Removed reference to creatine clearance and added description of eGFR calculation • Criterion 35: Updated "Day -1" to "Day -2". • Criterion 36: Updated "women" to "AFAB"	
6.1. Study Intervention(s) Administered	Added text to specify fluid intake during the 4-hour fast after orforglipron dosing.	To provide clarification.
6.9. Prior and Concomitant Therapy	Under subheading "Other concomitant medications", added that hormonal contraception and hormone replacement therapy are permitted for use during the study	To provide clarification.
9.3.5.2. Statistical Evaluation of Safety	Removed sentence regarding clinical chemistry and hematology data outside reference ranges.	To correct an identified error.
10.2. Appendix 2: Clinical Laboratory Tests	• Added magnesium to list of clinical chemistry • Corrected "HBV RNA" to "HBV DNA" • Updated "Day -1" to "Day -2" for ethanol test • Corrected footnote labelling	To provide clarifications and correct identified errors.
10.2.1. Blood Sampling Summary	Updated sampling volumes in summary table	To correct identified errors.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Drug-Drug Interaction, Single-arm, Open-label, Study to Assess the Effect of Quinidine on the Pharmacokinetics of Orforglipron in Healthy Participants

Brief Title: A Drug-Drug Interaction Study of Orforglipron with Quinidine in Healthy Participants

Regulatory Agency Identifier Number(s): IND: 142842

Rationale:

Study J2A-MC-GZPP (GZPP) is a Phase 1, open-label, nonrandomized, fixed-sequence, single-arm, drug-drug interaction study in healthy participants to evaluate the effects of quinidine on a single dose of orforglipron (LY3502970). In vitro data indicate that orforglipron is a substrate of both the P-glycoprotein (P-gp) transporter as well as the CYP3A4 metabolizing enzyme.

Quinidine is a relatively selective inhibitor of P-gp as compared to CYP3A4, and it is being used in this study to understand the role of P-gp transport on the pharmacokinetics (PK) of orforglipron.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effect of quinidine on the PK of orforglipron	• AUC and C_{max} of orforglipron administered alone and in the presence of quinidine
Secondary	
• To evaluate the effect of quinidine on midazolam PK • To evaluate the safety and tolerability of orforglipron when dosed alone and in the presence of quinidine	• PK parameters of midazolam and 1-hydroxymidazolam (AUC and C_{max}) administered alone and in the presence of quinidine • Incidence of TEAEs and SAEs

Abbreviations: AUC = area under the curve; C_{max} = maximum observed drug concentration; PK = pharmacokinetic(s); SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Overall Design:

Study GZPP is an open-label, fixed-sequence, single-arm, drug-drug interaction study in healthy participants, with all participants receiving the same dosing schedule. The goal of this study is to investigate the effect of quinidine on the PK of orforglipron. The study consists of a screening period, a treatment period, and a safety follow-up visit.

Brief Summary:

Study GZPP is an open-label, nonrandomized, fixed-sequence, 1 period, single-arm, drug-drug interaction (DDI) study in healthy participants. The purpose of this study is to measure the PK parameters of orforglipron in the absence or presence of quinidine. Quinidine will be administered in this study to serve as an inhibitor of P-gp transport. To assess the extent to

which quinidine inhibits CYP3A4 metabolism, the PK parameters of midazolam and 1-hydroxymidazolam will be assessed when coadministered with quinidine. To assess the extent to which quinidine inhibits OATP1B transport, the PK parameters of coproporphyrin-1 will be assessed when coadministered with quinidine.

Study details are as follows:

- The study duration will be up to 54 days.
- The treatment duration will be up to 11 days.
- The visit frequency will be
  - 1 out-patient visit during the screening period (<Day -42)
  - clinical admission on Day -2
  - discharge on Day 12, and
  - 1 follow-up visit on Day 20.

Study Population:

Participants will

- be overtly healthy individuals assigned male at birth (AMAB) or female at birth (AFAB)
- be aged from 21 to 70 years at the time of signing the informed consent
- have a body weight equal to or greater than 45 kg and a body mass index within the range of 18.5 to 35.0 kg/m^2
- have blood pressure and pulse rate in normal range, and
- have a hemoglobin level of at least 11.4 g/dL for AFAB and at least 12.5 g/dL for AMAB.

Number of Participants:

Approximately 28 participants will be enrolled such that approximately 20 evaluable participants will complete the study. This is an open-label, single-arm study. No randomization is required.

Intervention Groups and Duration:

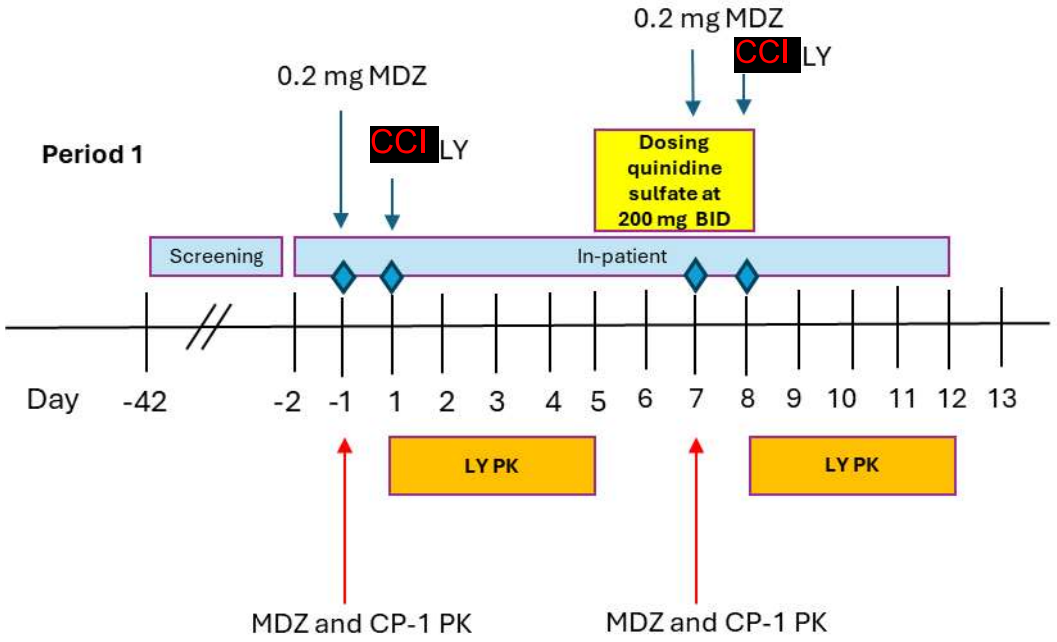
All participants will be screened within 42 days prior to enrollment. Eligible participants will be admitted to the clinical research unit (CRU) on Day -2 and remain resident in the CRU until discharge on Day 12. A follow-up visit will be performed on Day 20.

Participants will receive the following study interventions while resident in the CRU:

- Day -1: 0.2 mg midazolam orally alone
- Day 1: CCI of orforglipron orally alone
- Days 5 to 8: 200 mg of quinidine twice daily (BID) orally
- Day 7: 0.2 mg midazolam coadministered with quinidine
- Day 8: CCI of orforglipron coadministered with quinidine

Data Monitoring Committee: No.

1.2. Schema



- **BID** = twice daily
- **CP-1** = coproporphyrin-1
- **LY** = LY3502970 (orforglipron)
- **MDZ** = midazolam
- **PK** = pharmacokinetics

1.3. Schedule of Activities (SoA)

Procedure	Screening	Baseline		Study Day												Follow-up or ED	Comments
	<42 Days	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	Follow-up Day 20	
Informed consent	X																
Clinic admission		X															
Clinic discharge															X		
Weight	X																
Height	X																
Physical examination	X														X	X	
Chemistry and Hematology	X	X														X	
Serum pregnancy	X																
Urine pregnancy		X														X	For individuals AFAB.
Genetic sample			X														
ECG (single ECG)	X	X					X	X	X	X	X	X			X	X	
Vital signs	X	X					X	X	X	X	X	X			X		
Midazolam dosing			X							X							Fast at least 8 hours before dosing.

Midazolam PK sampling			P, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hr	P*						P, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hr	P*						Time points relative to midazolam administration. "P*" is pre-LY dose.
LY dosing				X							X						Fast at least 8 hours before dosing.
LY PK sampling				P, 0.5, 1, 2, 4, 6, 8, 12, 16 hr	24 hr	48 hr	72 hr	96 hr (P*)			P, 0.5, 1, 2, 4, 6, 8, 12, 16 hr	24 hr	48 hr	72 hr	96 hr		Time points relative to LY dosing time. "P*" is pre-quinidine dose.
Coproporphyrin-1 plasma samples			0, 0.5, 1, 2, 4, 6, 8, 12, 16 hr	P						P, 0.5, 1, 2, 4, 6, 8, 12, 16 hr	P						Predose sample on Days 7 and 8 will be taken prior to quinidine administration.
Quinidine dosing - 200 mg BID								X	X	X	X						Coadministered at the same time as midazolam on Day 7 or LY on Day 8.

Abbreviations: AFAB = assigned female at birth; BID = twice daily; ECG = electrocardiogram; ED = early discontinuation; hr= hour; LY = LY3502970; P = predose; PK = pharmacokinetic.

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-GZPP (GZPP) is a Phase 1, open-label, nonrandomized, fixed-sequence, single-arm, DDI study in healthy participants to evaluate the effects of quinidine on the PK of orforglipron.

In vitro, orforglipron is a substrate of CYP3A4 and P-gp. Quinidine is a relatively selective inhibitor of P-gp as compared to CYP3A4, and it is being used in this study to understand the role of P-gp transport in the PK of orforglipron.

2.2. Background

There is an unmet medical need for efficacious, safe, and well-tolerated oral formulations of GLP-1 receptor agonists (GLP-1 RAs for the management of T2D and the treatment of overweight or obesity.

Orforglipron is being investigated for its potential use as a therapy for chronic weight management and T2D. Orforglipron is a chemically synthesized molecule that shows agonist activity for human GLP-1 receptor. To date, off-target toxicity has not been identified in the clinical studies.

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

Orforglipron is a nonpeptide, chemically synthesized oral GLP-1 RA that can be administered once daily 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

Orforglipron

Detailed information about the known and expected benefits and risks and reasonably expected AEs of orforglipron may be found in the IB.

The potential risks associated with orforglipron are similar to those of marketed GLP-1 RAs. The most reported TEAEs observed in the orforglipron clinical studies, healthy participants, or participants with obesity or T2D were GI effects, including

- nausea
- vomiting
- diarrhea
- constipation, and
- abdominal pain.

Most were mild to moderate in severity and tended to occur during the dose escalation period. To date, there are no recognized AEs from orforglipron other than those related to GLP-1 receptor agonism.

No anticipated therapeutic benefit is reported for the participants in this study. However, participants may benefit from the screening procedures (through detection of unknown health issues) even if they receive no therapeutic benefit from the study.

Refer to Section 6.2 of the IB for detailed description of potential risks for orforglipron.

Quinidine and midazolam

Detailed information about the known and expected benefits and risks of quinidine and midazolam may be found in their respective package inserts.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of quinidine on the PK of orforglipron	• AUC and C_{max} of orforglipron administered alone and in the presence of quinidine.
Secondary	
• To evaluate the effect of quinidine on midazolam PK • To evaluate the safety and tolerability of orforglipron when dosed alone and in the presence of quinidine	• PK of midazolam and 1-hydroxymidazolam (AUC and C_{max}) administered alone and in the presence of quinidine. • Incidence of TEAEs and SAEs.
Exploratory	
• To evaluate the effect of quinidine on endogenous organic anion transporter polypeptide (OATP) biomarker	• Concentrations of biomarker coproporphyrin-1.

Abbreviations: AUC = area under the curve; C_{max} = maximum observed drug concentration; OATP = organic anion transporter polypeptide; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study GZPP is an open-label, fixed-sequence, single-arm, DDI study in healthy participants, with all participants receiving the same dosing schedule.

Section 1.2 illustrates the study design, and Section 1.3 describes the SoA for the study including PK blood sampling and multiple safety assessments, such as

- vital signs
- ECG
- physical examinations, and
- clinical laboratory test.

Screening

All participants will be screened up to 42 days prior to Day -2.

Treatment period

On Day -2, participants will be admitted to the CRU and remain resident across the treatment period. Participants will receive 1 dose of midazolam (0.2 mg) on Day -1 and then receive orforglipron (CCI) on Day 1. PK of midazolam will be collected on Day -1. PK of orforglipron will then be collected from Days 1 to 5. Participants will receive 200 mg BID of quinidine on Day 5 and will receive this 200 mg BID daily until Day 8. Participants will receive a second dose of midazolam (0.2 mg) on Day 7 and then orforglipron (CCI) on Day 8. Midazolam PK (including 1-hydroxymidazolam) will be collected on Days 7 and 8, and orforglipron PK will then be collected on Day 8 through Day 12. Biomarker sampling for CP-1 will be collected on Days -1 and 7, with a 24-hour sampling timepoint on Days 1 and 8. Participants will be discharged from the CRU at Day 12.

Follow-up visit

Participants will attend a follow-up visit on Day 20.

4.2. Scientific Rationale for Study Design

Study GZPP will be open-label, fixed-sequence, single-arm, and nonrandomized study. All participants will receive the same treatment.

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

In vitro, orforglipron is a substrate of CYP3A4 and P-gp. In a clinical DDI study, multiple doses of the CYP3A4 and P-gp inhibitor clarithromycin increased the exposure of orforglipron approximately 3.5-fold. Quinidine is a relatively selective inhibitor of P-gp as compared to CYP3A4, and it is being used in this study to understand the role of P-gp in the PK of orforglipron.

Use of a single dose of orforglipron is sufficient to assess the role of P-gp in orforglipron disposition. The mean $t_{1/2}$ of orforglipron ranges from 24.6 to 35.3 hours. The effect of

quinidine, if any, on orforglipron PK is expected to be primarily in the intestine and therefore not expected to significantly increase orforglipron elimination $t_{1/2}$. PK sampling up to 96 hours following orforglipron dosing is considered sufficient. The t_{max} of orforglipron ranges from 4 to 12 hours. Quinidine and orforglipron are to be administered concomitantly in this study to maximize interaction in the intestine.

While quinidine is a demonstrated clinical P-gp inhibitor, increasing the rate and extent of absorption of clinical P-gp substrates such as digoxin (Pedersen et al. 1983), it is a weak inhibitor of CYP3A4 in vitro. Therefore, a portion of this study will evaluate the effect of quinidine on midazolam to assess the extent to which quinidine is a clinically selective P-gp inhibitor versus CYP3A4 inhibition. Accordingly, the measurement of the endogenous OATP1B biomarker CP-1 is included in this study to assess the effect of quinidine on in vivo OATP1B activity, which has not been evaluated previously. As orforglipron is a substrate of CYP3A4, P-gp, and hepatic OATP1B transporters, these data will be used for the mechanistic interpretation of any effect of quinidine on orforglipron PK.

4.3. Justification for Dose

Orforglipron

In the single and 4-week multiple dose study in healthy participants, Study J2A-MC-GZGA (GZGA), orforglipron doses through CCI were safe and well tolerated with an acceptable safety profile following dose escalation.

An oral dose of CCI orforglipron was selected as this can be given as a single dose without significant risk of GI AEs, and this dose is not associated with severe TEAEs, as described in Section 2.3 of this document and in Section 6.2 of the IB. This dose will still allow adequate characterization of orforglipron PK.

Midazolam

Midazolam is a benzodiazepine medication used for anesthesia, procedural sedation, and severe agitation. It is also an index substrate of CYP3A. To assess gut CYP3A activity that could impact the assessment of P-gp inhibition by quinidine on the PK of orforglipron, a 0.2 mg dose of midazolam was chosen. This subtherapeutic dose is sufficiently measurable in plasma but should avoid the sedative effect of midazolam (Cannady et al. 2015).

Quinidine

Quinidine is an antiarrhythmic and antimalarial agent used to treat and manage arrhythmias and malaria. It is also a known P-gp inhibitor, and single and multiple doses of 200 mg affect the PK of clinical P-gp substrates (for example, digoxin). A dosing regimen of 200 mg BID for 10 days has recently been utilized in a similar DDI study (Imlunestrant Study J2J-MC-JZLI). This dosing regimen is below the therapeutic starting doses for the treatment of arrhythmia (200 to 400 mg every 6 hours) and is therefore subtherapeutic and not expected to reach therapeutic concentration of quinidine in plasma to elicit antiarrhythmic effect. Quinidine is a moderately sensitive CYP3A substrate. However, orforglipron has been demonstrated not to affect CYP3A activity in vivo (Study GZGA) and is therefore unexpected to increase quinidine exposure.

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. If any assessments are missed, the designation of completer can be determined by the sponsor and investigator.

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 the following criteria apply:

Age

1. Participants are 21 to 70 years of age, 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 ECG.
3. Have a hemoglobin level of
    a. at least 11.4 g/dL for individuals AFAB, and
    b. at least 12.5 g/dL for individuals AMAB.

Weight

4. Have a body weight equal to or greater than 45 kg, and a body mass index within the range of 18.5 to 35.0 kg/m^2 at screening.

Sex assigned at birth and contraceptive/barrier requirements

5. Are individuals AMAB or IOCBP or INOCBP.

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

Informed consent

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

Other inclusion criteria

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

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

9. Have significant history of or current cardiovascular, respiratory, hepatic, renal, GI, endocrine, hematological, psychological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting risk when taking orforglipron, midazolam, or quinidine; or interfering with the interpretation of data.
10. Have a 12-lead ECG abnormality, including known prolongation of QT/QTc interval, significant bradycardia, significant heart blocks or a history of any risk factors for ventricular arrhythmia, heart failure, hypokalemia or hypomagnesemia, or other factors that, in the opinion of the investigator, increases the risks associated with participating in the study.
11. Have an abnormal blood pressure or pulse rate, deemed to be clinically significant by the investigator.
12. Have a history of benign ethnic neutropenia.
13. Have a GI disease or disorder, such as relevant esophageal reflux or gall bladder disease, which could be aggravated by GLP-1 analogs or impacts gastric emptying, for example gastric bypass surgery or pyloric stenosis, except for appendectomy.
14. Have
    a. a history or presence of pancreatitis, including chronic pancreatitis or idiopathic acute pancreatitis, or
    b. elevation in serum amylase or lipase greater than 1.5x ULN of the reference range.
15. Have known allergies to
    a. quinidine
    b. midazolam
    c. orforglipron
    d. related compounds, or
    e. any components of the formulation.
16. Have liver disease, obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or laboratory evidence of clinically significant hepatic dysfunction, including
    a. ALT, AST, or ALP equal to or greater than 1.5x ULN, or
    b. total bilirubin equal to or greater than 1.5x ULN.

    Note: participants with Gilbert syndrome may be enrolled.

17. Have had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.

18. Have laboratory evidence of clinically significant
    a. anemia
    b. leukopenia
    c. renal dysfunction, or
    d. hyponatremia.
19. Have a history of or current psychiatric disorders that in the opinion of the investigator would adversely affect patient safety or compliance.
20. Have any medical conditions, medical history, or are taking any medications that are contraindicated in the quinidine or midazolam prescribing information.

Prior/concomitant therapy

21. Have used within 14 days prior to Day 1 or intend to use any drug that prolongs QT interval throughout the study.
22. Have used or intend to use any prescription or over the counter medications within 14 days prior to Day 1 and throughout the study, with the exception of
    a. vitamin or mineral supplements
    b. herbal supplements (cannabis or cannabidiol (CBD)-containing products are not allowed)
    c. vaccination, and
    d. prescription medications for the treatment of concurrent medical conditions such as thyroid replacement therapy, unless otherwise specified in Section 6.9.
23. Have used or intend to use any drugs or substances that are known moderate or strong inducers or inhibitors of CYP3A (for example, clarithromycin, azole antifungals, and certain antiepileptics) within 14 days prior to Day 1 and throughout the study.
24. Have used P-gp substrates with a narrow therapeutic index for which small increases in plasma exposure may result in SAEs (for example, digoxin) throughout the study.
25. Have used or intend to use any drugs or substances that are moderate or strong OATP inhibitors (for example, rifampin and certain antivirals) or inhibitors of P-gp (for example, cyclosporine and verapamil) within 14 days prior to Day 1 and throughout the study.
26. Require
    a. the treatment of concurrent medical conditions
    b. use of sensitive CYP2D6 substrates (for example, dextromethorphan, metoprolol, paroxetine, and venlafaxine)
    c. CYP2D6 substrates for which a small increase in plasma concentrations may result in SAEs (for example, tricyclic antidepressants), and
    d. other drugs for which quinidine causes or is expected to cause a decrease in drug levels, such as listed in the quinidine US prescribing information, within 14 days prior to Day 1 and throughout the end of the study.

Prior/concurrent clinical study experience

27. 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.
28. Have participated, within the last 3 months, in a clinical study involving an IP. If the previous IP has a long t1/2, 5 half-lives or 3 months, whichever is longer, should have passed since last dosing, prior to Day -1.

Diagnostic assessments

29. Show evidence of HIV infection or positive HIV antibodies.
30. Show evidence of hepatitis C or positive hepatitis C antibody.
31. Show evidence of hepatitis B, positive hepatitis B surface antigen, or positive hepatitis B core antibody.
32. Have serum calcitonin levels of equal to or greater than 20 ng/L at screening.
33. Have history of renal impairment with estimated glomerular filtration rate less than 90 mL per minute when calculated using Chronic Kidney Disease Epidemiology Collaboration equation at screening.

Other exclusion criteria

34. Regularly use known drugs of abuse.
35. Have a positive result following an ethanol test or urine drug screen at screening and Day -2.
36. Are participants AFAB who are pregnant or lactating.
37. Are unwilling to comply with the dietary restrictions required for this study.
38. Have alcohol intake that exceeds recommended average weekly alcohol consumption limits per local regulation, or an amount deemed significant by the investigator and are unwilling to comply with the alcohol restrictions for this study.
39. Smoke more than 10 cigarettes, or an equivalent amount of nicotine, per day, and are unable or unwilling to refrain from smoking while resident at the CRU.
40. Have donated plasma or blood of 450 mL or more, or participated in a clinical study that required a blood volume of 400 mL or more since the last study visit, within the past 3 months.
41. Are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
42. Are employees of Eli Lilly and Company (Lilly) or the CRU.
43. Are, in the opinion of the investigator or sponsor, unsuitable for inclusion in the study.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

From 7 days before the start of orforglipron administration until discharge from the study, participants are required to not consume

- red wine
- Seville oranges or Seville orange-containing products
- grapefruit or grapefruit juice
- pomelos
- exotic citrus fruits
- grapefruit hybrids, or
- commercial apple or orange.

Food

On all dosing days for midazolam and orforglipron, participants must fast for at least 8 hours prior to dosing and will remain fasted for at least 4 hours after dosing.

Drink

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

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

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 consume no more than 10 cigarettes or equivalent amount of nicotine per day.

CBD-containing products

No use of CBD-containing products will be permitted from 14 days prior throughout the study.

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 24 hours prior to each CRU admission, 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. Rescreened participants should be assigned a new participant number for every screening or rescreening event.

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

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

Orforglipron

Orforglipron will be administered orally as a single dose with approximately 240 mL of water on Days 1 and 8, as shown in Section 1.2. Participants will be fasted for at least 8 hours prior to orforglipron dosing and will remain fasted for at least 4 hours after dosing. Participants must refrain from drinking fluids from 1 hour prior to and until 1 hour after orforglipron dosing, except for the water required for dose administration.

Quinidine

Quinidine will be administered orally BID on Days 5 through 8. It should be taken at approximately the same time each day and can be taken with food or milk, except for the morning dose on the day of midazolam and with orforglipron dosing when it should be taken in the fasted state. Participants should remain fasted on this dosing day for 4 hours after orforglipron dose. Participants must refrain from drinking fluids until 1 hour after orforglipron dosing.

Midazolam

Midazolam liquid will be administered orally as a single dose on Days -1 and 7. Midazolam should be administered in the fasted state. Participants must refrain from drinking fluids from 1 hour prior to and until 1 hour after midazolam dosing, except for the water required for dose administration.

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

Table GZPP.1. Study GZPP Interventions

Intervention Name	Orforglipron	Quinidine	Midazolam
Dosage Level(s)	CCI	200 mg BID	0.2 mg
Dose Formulation	Capsule	Capsule	Liquid
Route of Administration	Oral	Oral	Oral
Sourcing	Provided centrally by sponsor	Purchased locally by the single site	Purchased locally by the single site

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study 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 monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

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

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Assignment to Study Intervention

This is a nonrandomized study.

6.4. Blinding

This is an open-label study.

6.5. Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee. 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.

6.6. Dose Modification

Does modification is not permitted in this study.

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

Orforglipron, midazolam, and quinidine will not be made available to participants after the conclusion of the study.

6.8. Treatment of Overdose

Orforglipron

For this study, any dose of orforglipron greater than CCI will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

Midazolam

For this study, any dose of midazolam greater than 0.2 mg will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

Quinidine

For this study, any daily dose of quinidine greater than 400 mg (200 mg BID) will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

Overdose event

In the event of an orforglipron, midazolam, or quinidine overdose, the investigator should:

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced
- closely monitor the participant for any AE, 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

CYP3A4 inhibitors, CYP3A inducers, monoamine oxidase inhibitors, and CYP2D6 and P-gp substrates

From 14 days prior to Day 1, continuing throughout the study, participants are not permitted to use other

- moderate or strong CYP3A4 inhibitors
- moderate or strong CYP3A inducers
- monoamine oxidase inhibitors
- CYP2D6 substrates or CYP2D6 substrates with a narrow therapeutic index
- P-gp inhibitors and P-gp inducers, or
- moderate or strong OATP inhibitors.

Other concomitant medications

From 14 days prior to Day 1, throughout the study, participants are not permitted to use any medications that are contraindicated or are listed as quinidine causing or expecting to cause increased drug levels, in the quinidine prescribing information.

Participants must abstain from taking prescription or nonprescription drugs, including vitamins and dietary or herbal supplements, within 7 days, or 14 days if the drug is a potential enzyme inducer, or 5 half-lives, whichever is longer, before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Acetaminophen, at doses of up to 3 g per day, hormonal contraception, and hormone replacement therapy are permitted for use during the study. Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the medical monitor on a case-by-case basis, if required.

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, Section 10.1.7.

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will discontinue the study intervention, thereby discontinuing the treatment period, and will remain in the study to complete procedures for an early discontinuation visit, as shown in the SoA in Section 1.3. If an early discontinuation visit occurs, a follow-up visit is not required.

A participant should be permanently discontinued from study intervention if

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

7.1.1. Liver Chemistry Stopping Criteria

See Section 8.2.5 for hepatic criteria for study drug interruption or discontinuation.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study

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

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit as shown in the SoA 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 Appendix 1, Section 10.1.10, for information 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

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.

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

8.2.2. Vital Signs

For each participant, vital signs should be conducted according to the SoA in Section 1.3. If warranted, additional vital signs may be measured.

Blood pressure and pulse rate should be measured after the participant has been supine for at least 5 minutes. When possible, these measurements should be recorded at approximately the same time of day at each scheduled time point.

If orthostatic measurements are required, participants should be supine for at least 5 minutes, and measurement should be obtained between 2 and 3 minutes after standing.

If the participant feels unable to stand, only supine vital signs will be recorded.

Unscheduled orthostatic vital sign assessments should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured throughout the study per investigator discretion.

8.2.3. Electrocardiograms

A single 12-lead digital ECG will be collected according to the SoA (Section 1.3). All single ECGs recorded should be stored at the investigational site.

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures pulse rate, QRS, QT, and QTc intervals.

ECGs must be recorded before collecting any blood samples. Participants must be supine for at least 5 to 10 minutes before ECG collection, and they must remain supine and awake during the ECG collection.

Any clinically significant findings from ECGs that result in a diagnosis and 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 (a physician or qualified designee) at the site promptly after the time of ECG collection as is practical, to determine whether the participant meets entry criteria.

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2, Section 10.2, for the list of clinical laboratory tests to be performed and the SoA 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 participants' condition.

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

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

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

If laboratory values from nonprotocol 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. 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 <1.5x 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 ≥3x ULN	X		
ALP ≥2x ULN	X		
TBL ≥2x ULN[b]	X		
ALT or AST ≥5x ULN	X	X	
ALP ≥2.5x ULN	X	X	
ALT or AST ≥3x ULN with hepatic signs or symptoms[a]	X	X	X
ALT or AST ≥5x ULN for more than 2 weeks	X	X	X
ALT or AST ≥8x ULN	X	X	X
ALT or AST ≥3x ULN and TBL ≥2x ULN[b] or INR ≥1.5	X	X	X
ALP ≥3x ULN	X	X	X
ALP ≥2.5x ULN and TBL ≥2x ULN[b]	X	X	X
ALP ≥2.5x 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 ≥1.5x 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 ≥2x baseline	X		
ALP ≥2x baseline	X		
TBL ≥2x ULN[b]	X		
ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first)	X	X	
ALP ≥2.5x baseline	X	X	
ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a]	X	X	X
ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks	X	X	X
ALT or AST ≥4x baseline or ≥400 U/L (whichever occurs first)	X	X	X
ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) and TBL ≥2x ULN[b] or INR ≥1.5	X	X	X
ALP ≥3x baseline	X	X	X
ALP ≥2.5x baseline and TBL ≥2x ULN[b]	X	X	X
ALP ≥2.5x 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.

8.2.5.1. Close Hepatic Monitoring

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

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

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

Close hepatic monitoring should include the following actions:

- Laboratory tests (Appendix 6, 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 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. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize.
- In addition to lab 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 (for example, heart failure, systemic infection, hypotension, or seizures)
- recent travel
- concomitant medications (including over the counter)
- herbal and dietary supplements, and
- history of alcohol drinking and other substance abuse.

8.2.5.2. 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 <1.5x ULN)	**Participants with elevated baseline (ALT, AST, or ALP ≥1.5x ULN)**
ALT or AST ≥5x ULN **or**	ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) **or**
ALP ≥2.5x ULN **or**	ALP ≥2.5x baseline **or**
ALT or AST ≥3x ULN with hepatic signs or symptoms[a] **or**	ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a] **or**
ALT or AST ≥3x ULN and TBL ≥2x ULN[b] or INR ≥1.5	ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) and TBL ≥2x 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 the following actions:

- At a minimum, comprehensive hepatic evaluation should include physical examination and a thorough medical history, as outlined above, as well as
  - PT-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).
- Remaining sample collected for hepatic evaluation may be stored as an exploratory biomarker sample. These stored samples will be used for the limited purpose of additional hepatic evaluations for up to 15 years.
- 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 (HDV),
  - cytomegalovirus (CMV),
  - Epstein-Barr virus (EBV),
  - 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 (MRCP),
  - endoscopic retrograde cholangiopancreatography (ERCP),
  - cardiac echocardiogram, or
  - a liver biopsy.
- Clinical and laboratory monitoring should continue at a frequency of 1 to 3 times weekly until levels normalize or return to approximate baseline values.
- All the medical information and test results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.2.5.3. Interruptions or Discontinuation of Study Interventions

If a participant develops any one of the following laboratory or clinical changes, interrupt the study drug and continue close monitoring and comprehensive hepatic evaluation, as described in Sections 8.2.5.1 and 8.2.5.2.

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

- While the participant is not receiving the study drug, clinical and laboratory monitoring should continue at a frequency of 1 to 3 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 test results related to the close hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.
- Resumption of the study drug after interruption for a hepatic reason can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results returned to near baseline and if a self-limited nonstudy-drug etiology is identified. Otherwise, the study drug should be permanently discontinued.

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

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

- AEs
- SAEs, and
- product complaints (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 nonleading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs and AEs of special interest (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 product complaints, 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, Section 10.3.

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, 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	N/A
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	N/A
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 participants AFAB and partners AFAB of participants AMAB	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
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; AFAB = assigned female at birth; AMAB = assigned male at birth; 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. Collection of Pregnancy Information

8.3.2.1. Participants Who Become Pregnant

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

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

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

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

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

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

8.3.2.2. Participants with Partners Who Become Pregnant

When to collect pregnancy information

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

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

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

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

When not to collect pregnancy information

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

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

8.3.3. 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 8.3.5
- major adverse cardiovascular events
- arrhythmias and cardiac conduction disorders
- hepatic disorder, as detailed in Section 8.2.5
- hypoglycemia
- hypotension, orthostatic hypotension, and syncope
- acute kidney injury and chronic kidney disease

- gallbladder and biliary tract disorders, and
- hypersensitivity reactions, as detailed in Section 8.3.4.

If the above events are reported, sites will be prompted to collect additional details and data.

8.3.4. Hypersensitivity Reactions

Many drugs, including oral and biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Appendix 2, Section 10.2.1. Laboratory results are provided to the sponsor via the central laboratory.

8.3.5. Pancreatic Monitoring

Diagnosis of acute pancreatitis

Acute pancreatitis is an AESI 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 (total, pancreatic, or both) and/or lipase equal to or greater than 3x ULN, and
- 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.

Discontinuation for acute pancreatitis

If acute pancreatitis is diagnosed, the participant must discontinue use of the IPs.

Asymptomatic elevation of serum amylase 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, equal to or greater than 3x ULN, is not

mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

8.4. Pharmacokinetics

Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of orforglipron and midazolam (including 1-hydroxymidazolam) as specified in the SoA in Section 1.3.

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.

At visits during which whole blood samples for the determination of PK of orforglipron and midazolam (including 1-hydroxymidazolam) will be taken, 1 sample of sufficient volume per drug can be used.

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

Samples will be used to evaluate the PK of orforglipron and midazolam (including 1-hydroxymidazolam). Samples collected for analyses of orforglipron and midazolam (including 1-hydroxymidazolam) plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.4.1. Bioanalysis Samples

Bioanalysis samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of orforglipron and midazolam (including 1-hydroxymidazolam) will be assayed using a validated liquid chromatography tandem mass spectrometry method (LC MS/MS).

8.5. Pharmacodynamics

PD parameters are not evaluated in this study.

8.6. Biomarkers

8.6.1. Coproporphyrin-1

Blood samples will be collected from participants to determine the plasma concentrations of coproporphyrin-1 (CP-1). The actual date and 24-hour clock time of each sampling will be recorded. Refer to the SoA (Section 1.3) for CP-1 sampling timepoints.

Concentrations of CP-1 will be assayed using a validated LC-MS/MS method.

8.7. Immunogenicity Assessments

Not applicable.

8.8. Health Economics OR Medical Resource Utilization and Health Economics

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

9. Statistical Considerations

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

9.1. Statistical Hypothesis

The primary objective of Study GZPP is to evaluate the effects of quinidine on the PK of orforglipron in healthy participants.

9.2. Analyses Sets

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

Participant Analysis Set	Description
Entered	All participants who sign the ICF.
Enrolled	All participants assigned to study intervention.
PK analysis set	All enrolled participants who receive at least 1 dose of study intervention and have evaluable PK data.
Safety analysis set	All participants who are exposed to 1 dose of study intervention. Participants will be analyzed according to the intervention they received.
CP-1 biomarker set	All participants who receive at least 1 dose of study intervention and have at least 1 period of CP-1 data.

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

9.3. Statistical Analyses

9.3.1. General Considerations

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

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.1, unless otherwise stated, and all CIs will be given at a 2-sided 90% level.

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 study intervention, whether they completed all protocol requirements or not.

Additional exploratory analyses of the data may be conducted as deemed appropriate. PK analyses will be conducted on the Pharmacokinetic Analysis Set. Safety analyses will be conducted on the Safety Analysis Set. CP-1 analysis will be conducted on the CP-1 Biomarker Set.

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 CSR.

9.3.2. Primary Endpoint Analysis

9.3.2.1. PK Parameter Estimation

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

AUC and C_{max} of orforglipron are the primary parameters for analysis. Other noncompartmental parameters, such as

- t_{max}
- $t_{1/2}$
- apparent clearance, and
- apparent volume of distribution may be reported.

Additional analysis may be performed if deemed necessary. All PK parameters will be listed and summarized using description statistics.

9.3.2.2. Statistical Methods

PK parameter estimates will be evaluated to delineate the effects of quinidine's interaction on orforglipron. The PK parameters C_{max} and AUC for orforglipron, when administered alone (reference) and in the presence of quinidine (test), will be compared using a linear mixed-effect model. The parameters will be log-transformed prior to analysis. The model will include treatment as a fixed effect and participant as a random effect. The least-square means for each treatment, the difference between the treatment least-square means (test-reference), and the associated 90% CIs will be estimated from the model and back-transformed from the log scale. This will provide estimates of the geometric means for each treatment, geometric mean ratio between test and reference treatments, and corresponding 90% CIs. Quinidine's effect on orforglipron will be assessed by examining the 90% CIs for the geometric mean ratios of orforglipron coadministered with quinidine relative to orforglipron alone. The t_{max} of orforglipron for both treatments, test and reference, will be analyzed using a Wilcoxon signed-rank test. An estimate of the median difference and approximately 90% CI will be reported.

9.3.3. Secondary Endpoint Analyses

9.3.3.1. PK Parameter Estimation

PK parameter estimates for midazolam and 1-hydroxymidazolam will be calculated using standard noncompartmental methods of analysis. AUC and C_{max} of midazolam and 1-hydroxymidazolam, as well as the metabolite ratio based on AUC, are the primary parameters for analysis.

Other noncompartmental parameters, such as

- t_{max}
- $t_{1/2}$
- apparent clearance, and
- apparent volume of distribution may be reported.

All PK parameters will be listed and summarized using descriptive statistics.

9.3.3.2. Statistical Methods

PK parameter estimates will be evaluated to delineate the effects of quinidine's on midazolam. The PK parameters C_{max}, AUC, and metabolite ratio of midazolam and 1-hydroxymidazolam, when administered alone (reference) and in the presence of quinidine (test), will be compared using a linear mixed-effect model. The parameters will be log-transformed prior to analysis. The model will include treatment as a fixed effect and participant as a random effect. The least-square means for each treatment, the difference between the treatment least-square means of the test and the reference, and the associated 90% CIs will be estimated from the model and back-transformed from the log scale to provide estimates of the geometric means for each treatment, geometric mean ratio between test and reference treatments, and corresponding 90% CIs.

Incidences of TEAEs and SAEs will be reported to evaluate the safety and tolerability of orforglipron when dosed alone or in the presence of quinidine.

9.3.4. Exploratory Endpoint Analysis

9.3.4.1. Coproporphyrin-1 Analyses

Plasma concentrations of CP-1 will be listed and summarized, using standard descriptive statistics. Parameter estimates for CP-1 will be calculated by standard noncompartmental methods. Parameters, including C_{max}, t_{max}, and AUC, will be summarized using descriptive statistics.

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

9.3.5. Safety Analyses

9.3.5.1. Clinical Evaluation of Safety

The incidence of TEAEs for each treatment will be presented by severity and by association with study intervention or study procedure 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 TEAE will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities. The number of IP-related SAEs will be reported.

9.3.5.2. Statistical Evaluation of Safety

All safety analyses will be made on the Safety Analysis Set. Safety parameters that will be assessed include safety laboratory parameters and vital signs. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data. Laboratory measurements will be summarized with respect to

observed values by treatment, at each time point, using descriptive statistics. Vital signs will be summarized with respect to observed values and change from baseline values by treatment at each time point using descriptive statistics.

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

Approximately 28 participants will be enrolled, such that approximately 20 evaluable participants will complete the study. Assuming a maximum intraparticipant CV of 40%, a sample size of 20 completed participants will provide at least a 94% chance to ensure that no more than 80% decrease on each of the PK parameters of interest of orforglipron induced by quinidine, assuming a true effect of 0.3 over orforglipron alone.

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 Good Clinical Practice Guidelines
- Applicable laws and regulations.

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

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

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

The investigator will be responsible for the following

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

Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement.

10.1.2. Informed Consent Process

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

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

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

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

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

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

10.1.3. Data Protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information 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/IEC members, and by inspectors from regulatory authorities.

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

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

10.1.4. Dissemination of Clinical Study Data

Communication of suspended or terminated dosing

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

Reports

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

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

Data

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

10.1.5. Data Quality Assurance

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

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

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

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct or remote 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 Good Clinical Practice, and all applicable regulatory requirements.

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

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

Data capture system

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

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

Data collected via the sponsor-provided data capture system will be stored at a third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. 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/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 product complaint management system.

10.1.6. Source Documents

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

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

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

10.1.7. Study and Site Start and Closure

Study start

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

First act of recruitment

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

Study or site termination

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

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

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

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

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

10.1.8. Publication Policy

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

10.1.9. Investigator Information

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

10.1.10. Sample Retention

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

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

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the local laboratory.

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 of the protocol.

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	

Clinical Chemistry	Assayed by local laboratory.

• Sodium
• Potassium
• Bicarbonate
• Chloride
• Calcium
• Magnesium
• Phosphate
• Glucose (fasting)[a]
• Urea
• Total protein
• Albumin
• Amylase
• Lipase
• Creatinine
• Liver panel
  ○ Total bilirubin
  ○ Direct bilirubin
  ○ Indirect bilirubin
  ○ Alkaline phosphatase
  ○ Aspartate aminotransferase
	[a] Performed after overnight fast.
	[b] To be performed at screening only.

Clinical Laboratory Tests	Comments
○ Alanine aminotransferase • Lipid panel[b] ○ Total cholesterol ○ Triglycerides ○ Low-density lipoprotein cholesterol ○ High-density lipoprotein cholesterol	
HIV and Hepatitis Serology	Assayed by local laboratory, unless otherwise stated.
• 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 HBV DNA and 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 to confirm a positive hepatitis B core antibody test if a hepatitis B surface antigen test is negative.
Other Tests	Assayed by local laboratory unless otherwise stated.
• Estimated glomerular filtration rate[c] • Ethanol test[d] • Urine drug screen • Follicle-stimulating hormone[c,e] • Calcitonin[c] • Coproporphyrin-1[f,g]	[c] Performed at screening only. [d] Urine test performed at screening, and breath or urine test performed on Day -2. [e] Performed for individuals AFAB only. [f] Assayed by Lilly central laboratory. [g] Results will not be provided to the investigative sites.
Pharmacokinetic Samples	Assayed by Lilly central laboratory. Results will not be provided to the investigative sites.
• Orforglipron concentration • Midazolam • 1-hydroxymidazolam	
Genetics Sample	Assayed by Lilly central laboratory. Results will not be provided to the investigative sites.

10.2.1. Blood Sampling Summary

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

Protocol J2A-MC-GZPP Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	25	1	25
Clinical laboratory tests[a]	12.5	2	25
Orforglipron Pharmacokinetics	2	26	52
Blood discard for cannula patency	1	57	57
Coproporphyrin-1 plasma concentrations	2	20	40
Pharmacogenetics	3	1	3
Midazolam Pharmacokinetics[b]	2	22	44
Additional Pharmacokinetics (if needed)	2	3	6
Total			252
Total for clinical purposes			260

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

[b] Includes 1-hydroxymidazolam pharmacokinetics.

10.2.2. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

Purpose of collecting samples after a systemic hypersensitivity event

The samples listed in this Appendix are not collected for acute study participant management. The sponsor will use the laboratory test results from these samples to characterize hypersensitivity events across the clinical development program.

When to collect samples after a systemic hypersensitivity event occurs

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

Obtain follow-up predose samples at the next regularly scheduled laboratory sample collection, ideally prior to the next dose after the event, to assess post-event return-to-baseline values.

Timing	Laboratory Test[a]
Collect from 30 minutes to 4 hours after the start of the event. • Note: The optimal collection time is from 1 to 2 hours after the start of event.	Total tryptase

[a] All samples for hypersensitivity testing will be assayed by Lilly-designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

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

10.3.1. Definition of AE

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments, for example, ECG, radiological scans, and vital 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.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 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 and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma, for example, sprained ankle, which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
  - Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs.
- Other situations:
  - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product complaint

A product complaint 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 product complaints:

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

Product complaints 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.

If the participant identifies a product complaint or a problem with the study intervention, investigators will instruct participants to contact the site as soon as possible so that the situation can be assessed.

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

Device deficiencies are product complaints.

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/product complaint 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/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint form.

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

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

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

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

Assessment of intensity

The investigator will assess 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 a 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/SAE. The investigator will use clinical judgment to determine the relationship.

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

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

The investigator will also consult the IB or product information for marketed products in their assessment.

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

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

The investigator may change their opinion of causality in light of follow-up information and send a 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 SAE Report.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

Prompt notification by the investigator to the sponsor of a 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 will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Individuals assigned female at birth (AFAB)	Individuals assigned the female sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are potentially capable of gestating a fetus and, thus, are capable of exposing an egg, embryo, or fetus to study drug or drug effects.
Individuals assigned male at birth (AMAB)	Individuals assigned the male sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are not capable of gestating a fetus but are capable of exposing a fetus to study drug or drug effects via their semen. Individuals AMAB are considered to be not of reproductive potential if they have had orchiectomy (orchidectomy) with or without penectomy, confirmed by operative note.
Individuals of childbearing potential (IOCBP)[a]	Adult individuals AFAB are considered IOCBP unless they are INOCBP. Individuals AFAB less than 18 years of age are considered IOCBP if they have • had at least 1 cycle of menses, or • Tanner stage 4 breast development (if Tanner staging assessments are required as part of the specific study protocol). Any amount of spotting should be considered menarche. Menarche status and date of menarche should be monitored for every pediatric study participant who is AFAB, starting at 8 years of age until the onset of menses, and therefore, childbearing potential. It is recommended that such monitoring be conducted every 3 to 6 months at a site visit, following evaluation from the provider/investigator. Note: Adolescent or adult individuals AFAB who are receiving hormone therapy as part of gender transition are considered IOCBP unless they meet the conditions outlined below for INOCBP.
Individuals not of childbearing potential (INOCBP)[b]	Individuals AFAB are considered INOCBP if they are not capable of producing ova or embryo and/or are not capable of potentially gestating a fetus. Such individuals include those who • have a congenital anomaly, such as Müllerian agenesis, resulting in confirmed infertility • are infertile due to surgical sterilization, or • are menopausal. Acceptable surgical sterilization methods are hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Menopausal state[c]	The menopausal state is defined as an individual: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[c], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone ≥40 mIU/mL; or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy.

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

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

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

10.4.2. Contraception Guidance

10.4.2.1. Individuals Assigned Male at Birth

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

10.4.2.2. Individuals Assigned Female at Birth

For individuals AFAB, IOCBP and INOCBP may participate in this trial. See Appendix 4, Section 10.4.1, for definitions and additional requirements related to contraception. *Refer to the Pregnancy Testing guidance for pregnancy testing recommendations during the course of a trial.*

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

Must…	Must not…

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

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

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

Examples of different methods of contraception:

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

10.5. Appendix 5: Genetics

Use/analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated.

Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to orforglipron or T2D, obesity, overweight, and related diseases. They may also be used to develop tests and assays including diagnostic tests related to orforglipron or 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 8.2.5 for guidance on appropriate test selection.

Each test in the table below is to be performed at a local laboratory, unless noted otherwise. Multiple local laboratories may be needed due to availability of testing. All local laboratories must be qualified in accordance with applicable local regulations. Testing may not be available in certain regions based on local requirements. If testing is not available based on local requirements, consult with Lilly-designated medical monitor.

Hepatic Hematology Panel	**Hepatic Clinical Chemistry Panel**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts[a]
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Hepatic Coagulation Panel	Copper
Prothrombin time, INR (PT-INR)	Ethyl alcohol (ethanol, EtOH)
Hepatitis A virus (HAV) testing:	Haptoglobin
HAV total antibody[b]	Immunoglobulin IgA (quantitative)
HAV IgM antibody	Immunoglobulin IgG (quantitative)
Hepatitis B virus (HBV) testing:	Immunoglobulin IgM (quantitative)
Hepatitis B surface antigen (HBsAg)	Phosphatidylethanol (PEth)
Hepatitis B surface antibody (anti-HBs)	**Urine Chemistry**
Hepatitis B core total antibody (anti-HBc)	Drug screen
Hepatitis B core IgM antibody	Ethyl glucuronide (EtG)
HBV DNA[c]	**Other Serology**
Hepatitis C virus (HCV) testing:	Anti-nuclear antibody (ANA)
HCV total antibody[b]	Anti-smooth muscle antibody (ASMA) or anti-actin antibody
HCV RNA[c]	Epstein-Barr virus (EBV) testing:
Hepatitis D virus (HDV) testing[d]:	EBV antibody
HDV total antibody[b]	EBV DNA[c]
HDV IgM antibody	Cytomegalovirus (CMV) testing:
HDV RNA[c]	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[c]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[c]	HSV (Type 1 and 2) DNA[c]
Microbiology Culture	Liver kidney microsomal type 1 (LKM-1) antibody
Blood	
Urine	

[a] Availability of acetaminophen protein adducts testing is limited. Testing may be performed at the central lab, if needed.
[b] If lab does not offer total antibody testing, IgG and/ or IgM are acceptable substitutes.
[c] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.
[d] If HDV testing is not available, HBV testing may be sufficient. If HBV testing is positive, consult with the Lilly-designated medical monitor.

10.7. Appendix 7: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence.
AE	adverse event
AESI	adverse event of special interest
AFAB	assigned female at birth
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMAB	assigned male at birth
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
CBD	cannabidiol
CI	confidence interval
C_{max}	maximum observed drug concentration
CP-1	coproporphyrin-1
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
CSR	clinical study report
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction

Term	Definition
DMC	Data Monitoring Committee A Data Monitoring Committee, or Data Monitoring Board is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention and to make recommendations to the sponsor regarding the stopping of a study for efficacy, harm, or futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
ECG	electrocardiogram
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
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 Harmonization
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 informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

Term	Definition
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
INOCBP	individuals not of childbearing potential
INR	internal normalized ratio
IOCBP	individuals of childbearing potential
IP	investigational product
IRB	Institutional Review Board
LC-MS/MS	liquid chromatography tandem mass spectroscopy
MDZ	midazolam
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 involves 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 product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription.
OATP	organic anion transporter polypeptide
P-gp	P-glycoprotein
participant	Equivalent to Clinical Data Interchange Standard Consortium 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

Term	Definition
PK/PD	pharmacokinetics/pharmacodynamics
PT-INR	prothrombin time-international normalized ratio
QTc	corrected QT interval
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.
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

11. References

Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132(6):2131-2157. https://doi.org/10.1053/j.gastro.2007.03.054

Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101(10):2379-2400. https://doi.org/10.1111/j.1572-0241.2006.00856.x

Bayliss WM, Starling EH. The mechanism of pancreatic secretion. *J Physiol*. 1902;28(5):325-353. https://doi.org/10.1113/jphysiol.1902.sp000920

Cannady EA, Wang MD, Friedrich S, et al. Evacetrapib: in vitro and clinical disposition, metabolism, excretion, and assessment of drug interaction potential with strong CYP3A and CYP2C8 inhibitors. *Pharmacol Res Perspect*. 2015;3(5):e00179. https://doi.org/10.1002/prp2.179

Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet*. 2018;392(10160):2180-2193. https://doi.org/10.1016/S0140-6736(18)32260-8

Koizumi M, Takada T, Kawarada Y, et al. JPN guidelines for the management of acute pancreatitis: diagnostic criteria for acute pancreatitis. *J Hepatobiliary Pancreat Surg*. 2006;13(1):25-32. https://doi.org/10.1007/s00534-005-1048-2

Lau J, Bloch P, Schäffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem*. 2015;58(18):7370-7380. https://doi.org/10.1021/acs.jmedchem.5b00726

Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Diabetes Obes Metab*. 2016;18(3):203-216. https://doi.org/10.1111/dom.12591

Nauck MA, Niedereichholz U, Ettler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol*. 1997;273(5):E981-E988. https://doi.org/10.1152/ajpendo.1997.273.5.E981

Newsome P, Francque S, Harrison S, et al. Effect of semaglutide on liver enzymes and markers of inflammation in subjects with type 2 diabetes and/or obesity. *Aliment Pharmacol Ther*. 2019;50(2):193-203. https://doi.org/10.1111/apt.15316

Pedersen KE, Christiansen BD, Klitgaard NA, Nielsen-Kudsk F. Effect of quinidine on digoxin bioavailability. *Eur J Clin Pharmacol*. 1983;24(1):41-47. https://doi.org/10.1007/BF00613925

Scheen AJ. Dulaglutide for the treatment of type 2 diabetes. *Expert Opin Biol Ther*. 2017;17(4):485-496. https://doi.org/10.1080/14712598.2017.1296131

Steinberg WM, Buse JB, Ghorbani MLM, et al. LEADER Steering Committee; LEADER Trial Investigators. Amylase, lipase, and acute pancreatitis in people with type 2 diabetes treated with liraglutide: results from the LEADER randomized trial. *Diabetes Care*. 2017a;40(7):966-972. https://doi.org/10.2337/dc16-2747. [Erratum in: *Diabetes Care*. 2018;41(7):1538**. Fig. 1*C* and *D* omitted the data points from visit 1 (week 2) and were erroneously shifted leftwards.**]

Steinberg WM, Rosenstock J, Wadden TA, et al. Impact of liraglutide on amylase, lipase, and acute pancreatitis in participants with overweight/obesity and normoglycemia, prediabetes, or type 2 diabetes: secondary analyses of pooled data from the SCALE clinical development program. *Diabetes Care*. 2017b;40(7):839-848. https://doi.org/10.2337/dc16-2684

Werner U, Haschke G, Herling AW, Werner K. Pharmacological profile of lixisenatide: a new GLP-1 receptor agonist for the treatment of type 2 diabetes. *Regul Pept*. 2010;164(2-3):58-64. https://doi.org/10.1016/j.regpep.2010.05.008

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