Protocol J2A-MC-GZPJ

A Drug-Drug Interaction Study to Assess the Effect of Carbamazepine on the Pharmacokinetics of Orforglipron in Healthy Participants

NCT06370728

Approval Date: 31 Jan 2024

Title Page

Protocol Title: A Drug-Drug Interaction Study to Assess the Effect of Carbamazepine on the Pharmacokinetics of Orforglipron in Healthy Participants

Protocol Number: J2A-MC-GZPJ

Amendment Number: This is the initial protocol.

Compound: Orforglipron (LY3502970)

Brief Title: A drug-drug interaction study of orforglipron with carbamazepine 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: IND: 142842

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

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Medical Monitor Name and Contact Information will be provided separately.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Drug-Drug Interaction Study to Assess the Effect of Carbamazepine on the Pharmacokinetics of Orforglipron in Healthy Participants

Brief Title: A drug-drug interaction study of orforglipron with carbamazepine in healthy participants

Regulatory Agency Identifier Number: IND: 142842

Rationale:

Study J2A-MC-GZPJ, or GZPJ, is a Phase 1, open-label, non-randomized, fixed-sequence, 1-period, single-arm, drug-drug interaction (DDI) study in healthy participants to evaluate the effect of CYP3A induction by use of carbamazepine on a single dose of orforglipron.

Carbamazepine is an inducer of cytochrome P450 (CYP) enzymes, including CYP3A. Considering the increase in orforglipron exposure of approximately 3.5-fold in the presence of a strong CYP3A inhibitor, as shown in Study J2A-MC-GZGM, orforglipron is a moderately sensitive CYP3A substrate and an investigation is needed to study potential DDI between carbamazepine and orforglipron.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effect of carbamazepine on the PK of orforglipron in healthy participants	• AUC(0-∞), AUC(0-t_{last}), and C_{max} of orforglipron
Secondary	
• To describe the safety and tolerability of orforglipron when dosed with carbamazepine in healthy participants	• TEAEs, SAEs, and discontinuations due to AEs

Abbreviations: AE = adverse event; AUC(0-∞) = area under the concentration versus time curve from zero to infinity; AUC(0-t_{last}) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; C_{max} = maximum observed drug concentration;

PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Overall Design:

Study GZPJ is an open-label, non-randomized, fixed-sequence, 1-period, single-arm, DDI study in healthy participants.

Brief Summary:

Screening

All participants will be screened up to 42 days prior to Day 1.

Treatment Period

On Day -1, participants will be admitted to the clinical research unit and remain resident across the treatment period.

On Day 1, participants will receive a single dose of [redacted] mg orforglipron.

On Day 5, safety assessments will be performed.

Participants will receive twice daily carbamazepine doses of

- [redacted] mg on Days 6 to 8
- [redacted] mg on Days 9 to 11, and
- [redacted] mg on Days 12 to 18.

On Day 15, participants will receive a single dose of [redacted] mg orforglipron.

On Day 18, participants will be discharged from the clinical research unit after the second carbamazepine dose following completion of study procedures, provided they are deemed medically fit by the investigator or designee.

Follow-up visit

Participants will attend a follow-up visit between Days 32 to 35.

Study Population:

Participants will

- be overtly healthy individuals assigned male at birth or individuals not of childbearing potential
- be between 21 to 70 years of age, inclusive, 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, inclusive
- not have the HLA-B*1502 or HLA-A*3101 allele, and
- have a hemoglobin level of
    - at least 11.4 g/dL for individuals assigned female at birth, and
    - at least 12.5 g/dL for individuals assigned male at birth.

Number of Participants:

Approximately 30 participants will be enrolled to ensure that approximately 20 evaluable participants will complete the study.

Intervention Groups and Duration:

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

- single doses of [redacted] mg orforglipron, and
- twice-daily doses of [redacted] and [redacted] mg carbamazepine.

Participants will be followed through to Day 35. Total study duration is approximately 77 days.

Ethical Considerations of Benefit/Risk:

To date, orforglipron has been administered up to [redacted] mg as a single dose and titrated using multiple doses of up to a target dose of [redacted] mg for a maximum of 36 weeks. The common safety or tolerability concerns have been

- gastrointestinal-related effects that are consistent with glucagon-like peptide-1 pharmacology, and
- changes in vital signs that have resolved spontaneously over time.

Gastrointestinal adverse events including nausea, vomiting, constipation, abdominal distension, diarrhea, eructation, dyspepsia, and abdominal pain have been the most frequently reported events across all completed and ongoing studies. These adverse events have been mostly mild in severity and the majority resolved without treatment. Studies that used starting doses of 2 and [redacted] mg had an acceptable safety and tolerability profile, but with several participants experiencing nausea and vomiting in each study. The planned single dose of [redacted] mg for the present study is expected to be well tolerated.

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

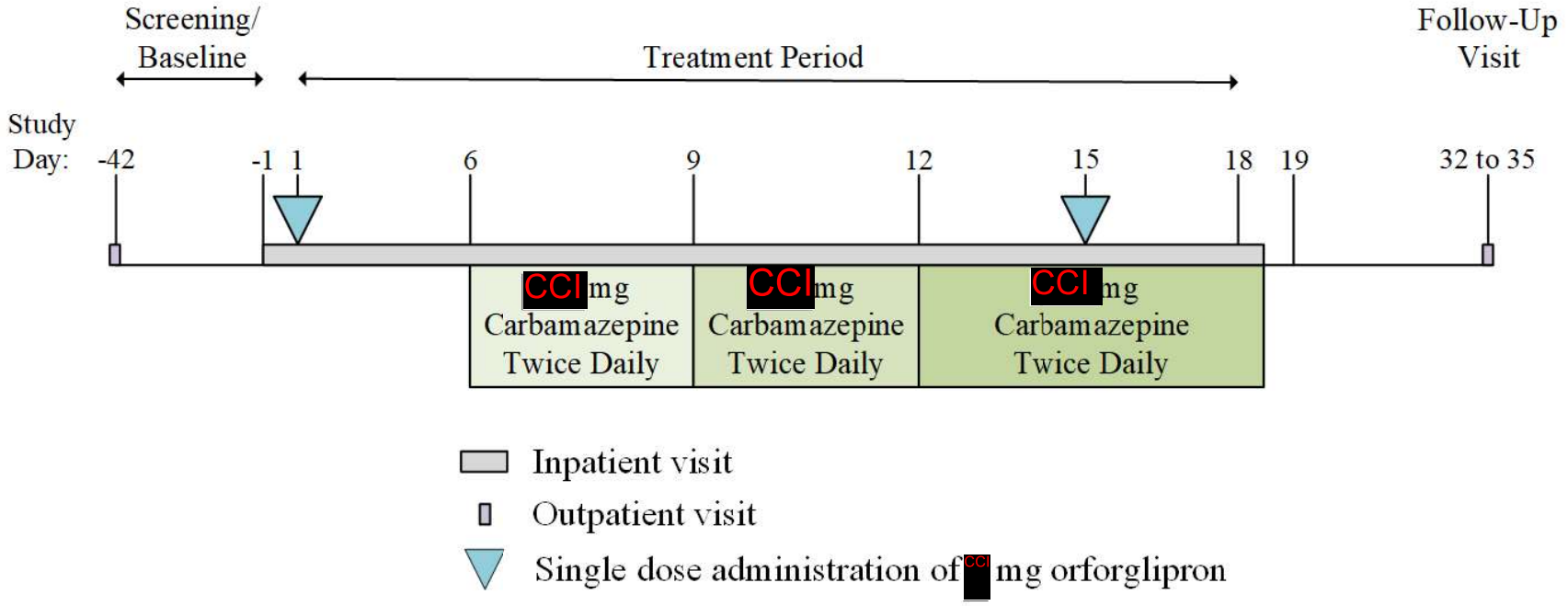
As of 24 November 2023, approximately 268 healthy participants and 674 participants with type 2 diabetes, obesity, or overweight who have received orforglipron in completed Phase 1 and 2 studies have been reviewed, and no safety or tolerability concerns that preclude further investigation of orforglipron have been identified.

Carbamazepine is indicated for the treatment of epilepsy and trigeminal neuralgia. It is known to be a moderate to strong inducer of CYP3A both at the intestinal wall and the liver leading to approximately 80% decrease in area under the concentration versus time curve of drugs metabolized by this enzyme. Significant adverse reactions reported with carbamazepine include serious dermatological reactions; aplastic anemia agranulocytosis and drug-induced immune thrombocytopenia, hypersensitivity reactions, including drug reactions with eosinophilia and systemic symptoms, anaphylactic reactions and angioedema; suicidal behavior and ideation. In DDI studies in which carbamazepine was administrated to healthy participants for less than 1 month in duration, carbamazepine was found to be tolerated with appropriate safety monitoring. However, drug-induced immune thrombocytopenia caused by carbamazepine typically occurs within the first 2 weeks of treatment. If suspected, prompt drug discontinuation is advised.

Data from Phase 1 and 2 studies indicate that orforglipron treatment may result in a decrease in body weight.

Data Monitoring Committee: No.

1.2. Schema


Screening/
Baseline
Treatment Period
Follow-Up
Visit
Study
Day:
-42
-1
1
6
9
12
15
18
19
32 to 35
CCI mg
Carbamazepine
Twice Daily
CCI mg
Carbamazepine
Twice Daily
CCI mg
Carbamazepine
Twice Daily
Inpatient visit
Outpatient visit
Single dose administration of CCI mg orforglipron

1.3. Schedule of Activities

Screening and Baseline Schedule

Procedure	Screening and Baseline		Comments
Days	**-42 to -2**	**-1**	
Outpatient visit	X		
Informed consent	X		
Medical history, , and nicotine, tobacco, and caffeine use	X		
HLA genotyping	X		
Serology	X		See Section 10.2.
Estimated glomerular filtration rate	X		
Follicle-stimulating hormone	X		Individuals AFAB only. See Section 10.4.
Height	X		
Weight	X		
Vital signs	X		
CRU admission		X	
Genetic sample		X	
Single 12-lead ECG	X	X	
Hematology	X	X	See Section 10.2.
Clinical chemistry	X	X	
Calcitonin	X		
Urinalysis	X	X	See Section 10.2.
Physical examination	X	X	Screening: complete exam. Day -1: symptom-directed exam.
Ethanol test and urine drug screen	X	X	Screening: alcohol urine test. Day -1: alcohol breath or urine test.
C-SSRS baseline and screening	X	X	

Abbreviations: AFAB = assigned female at birth; C-SSRS = Columbia-Suicide Severity Rating Scale; CRU = clinical research unit; ECG = electrocardiogram; HLA = human leukocyte antigen.

Treatment Period and Follow—Up Visit

Procedure	Treatment Period																		Follow-Up	ED	Comments
Days	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**32 to 35**		
CRU discharge																		X			
Outpatient visit																			X		
Hematology					X			X			X				X			X	X		See Section 10.2.
Clinical chemistry					X			X			X				X			X	X		
C-SSRS since last assessed																		X	X		
Single 12-lead ECG					X			X			X				X			X	X		
Vital signs	P				X			X			X				X			X		X	
Coproporphyrin 1	X	X													X	X					Time points relative to orforglipron administration: P, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours.
Orforglipron administration	X														X						On Day 15, dosed approximately 2 hours before carbamazepine dosing.
Orforglipron PK sampling	X	X	X	X											X	X	X	X			Time points relative to orforglipron administration: P, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, and 72 hours.
Carbamazepine administration						[redacted] mg BID				[redacted] mg BID					[redacted] mg BID						

Abbreviations: BID = twice daily; C-SSRS = Columbia-Suicide Severity Rating Scale; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; 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-GZPJ, or GZPJ, is a Phase 1, open-label, non-randomized, fixed-sequence, 1-period, single-arm, DDI study in healthy participants to evaluate the effect of CYP3A induction by use of carbamazepine on a single dose of orforglipron.

Carbamazepine is an inducer of CYP enzymes, including CYP3A. Considering the increase in orforglipron exposure of approximately 3.5-fold in the presence of a strong CYP3A inhibitor, as shown in Study J2A-MC-GZGM, orforglipron is a moderately sensitive CYP3A substrate and an investigation is needed to study potential DDI between carbamazepine and orforglipron.

2.2. Background

There is an unmet medical need for efficacious, safe, and well-tolerated oral formulations of GLP—1 Ras for the management of T2D and for 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, no off-target toxicity has 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 non-peptide 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

To date, orforglipron has been administered up to [redacted] mg as a single dose and titrated using multiple doses of up to a target dose of [redacted] mg for a maximum of 36 weeks. The common safety or tolerability concerns have been

- GI-related effects that are consistent with GLP-1 pharmacology, and

- changes in vital signs that have resolved spontaneously over time.

GI AEs including nausea, vomiting, constipation, abdominal distension, diarrhea, eructation, dyspepsia, and abdominal pain have been the most frequently reported events across all completed and ongoing studies. These AEs have been mostly mild in severity and the majority resolved without treatment. Studies that used starting doses of [redacted] mg had an acceptable safety and tolerability profile, but with several participants experiencing nausea and vomiting in each study. The planned single dose of [redacted] mg for the present study is expected to be well tolerated.

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

As of 24 November 2023, approximately 268 healthy participants and 674 participants with T2D, obesity, or overweight who have received orforglipron in completed Phase 1 and 2 studies have been reviewed, and no safety or tolerability concerns that preclude further investigation of orforglipron have been identified.

Carbamazepine (refer to the Tegretol package insert, 2023) is indicated for the treatment of epilepsy and trigeminal neuralgia. It is known to be a moderate to strong inducer of CYP3A both at the intestinal wall and the liver leading to approximately 80% decrease in AUC of drugs metabolized by this enzyme (Lutz et al. 2018). Significant adverse reactions reported with carbamazepine include serious dermatological reactions; aplastic anemia agranulocytosis and drug-induced immune thrombocytopenia, hypersensitivity reactions, including DRESS, anaphylactic reactions and angioedema; suicidal behavior and ideation. In DDI studies in which carbamazepine was administrated to healthy participants for less than 1 month in duration, carbamazepine was found to be tolerated with appropriate safety monitoring (Kanefendt et al. 2023). However, drug-induced immune thrombocytopenia caused by carbamazepine typically occurs within the first 2 weeks of treatment. If suspected, prompt drug discontinuation is advised.

Data from Phase 1 and 2 studies indicate that orforglipron treatment may result in a decrease in body weight.

More information about the known and expected benefits, risks, SAEs, and reasonably expected AEs of orforglipron is to be found in the IB. Detailed information about the known and expected benefits and risks of carbamazepine may be found in the package insert.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of carbamazepine on the PK of orforglipron in healthy participants	• AUC(0-∞), AUC(0-t_{last}), and C_{max} of orforglipron
Secondary	
• To describe the safety and tolerability of orforglipron when dosed with carbamazepine in healthy participants	• TEAEs, SAEs, and discontinuations due to AEs
Exploratory	
• To evaluate the effect of multiple oral doses of carbamazepine on endogenous OATP biomarker in healthy participants	• Concentrations of biomarker coproporphyrin 1

Abbreviations: AE = adverse event; AUC(0-∞) = area under the concentration versus time curve from zero to infinity; AUC(0-t_{last}) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; C_{max} = maximum observed drug concentration; OATP = organic anion transporting polypeptide; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study GZPJ is an open-label, non-randomized, fixed-sequence, 1-period, single-arm, DDI study in healthy participants.

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

Screening

All participants will be screened up to 42 days prior to Day 1.

Treatment Period

On Day -1, participants will be admitted to the CRU and remain resident across the treatment period.

On Day 1, participants will receive a single dose of [redacted] mg orforglipron.

On Day 5, safety assessments will be performed.

Participants will receive BID carbamazepine doses of

- [redacted] mg on Days 6 to 8
- [redacted] mg on Days 9 to 11, and
- [redacted] mg on Days 12 to 18.

On Day 15, participants will receive a single dose of [redacted] mg orforglipron.

On Day 18, participants will be discharged from the CRU after the second carbamazepine dose following completion of study procedures, provided they are deemed medically fit by the investigator or designee.

Follow-up visit

Participants will attend a follow-up visit between Days 32 to 35.

4.2. Scientific Rationale for Study Design

The study will be open-label and non-randomized as all participants will receive the same treatment.

Carbamazepine has been chosen as the probe drug as it is an inducer of several CYP enzymes, including CYP3A. A fixed-sequence design has been selected due to the potential for carryover effects from carbamazepine dosing: the CYP induction caused by carbamazepine can linger for several weeks (Magnusson et al. 2008), which would require an increased study length if a 2-sequence crossover design was selected. In addition, fixed-sequence design is commonly used for DDI studies, and is consistent with FDA guidance.

Hepatic OATP1B transporters are also involved in the disposition of orforglipron, and carbamazepine has been purported to also induce OATP1B activity (Lutz et al. 2018). Therefore,

measurement of OATP1B biomarker coproporphyrin will be included, to selectively assess the effect of carbamazepine on in vivo hepatic OATP1B activity.

4.3. Justification for Dose

Orforglipron

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

An oral dose of [redacted] mg orforglipron was selected as this can be given as a single dose without significant risk of GI AEs, as described in Section 2.3. This dose will still allow adequate characterization of orforglipron PK. Higher doses carry the risk of increased incidence of GI AEs, including vomiting, which can be further exacerbated due to the anticipated increased exposure in participants with impaired hepatic function. This can lead to loss of administered drug, impacting the PK associated with the dose.

Carbamazepine

A course of CCI mg BID for 3 days, followed by CCI mg BID for 3 days, and CCI mg BID for 7 days carbamazepine has been selected based on recommendations from the FDA and are previous reported doses used to investigate DDIs with carbamazepine. The dose of CCI mg BID dosing for carbamazepine has been selected as this dose is within the therapeutic dose range for carbamazepine for the treatment of epilepsy and trigeminal neuralgia (Tegretol package insert, 2023). It is tolerated by healthy participants in various CYP3A induction studies and demonstrated moderate to strong induction of CYP3A (Lutz et al. 2018). A CCI-mg BID dose of carbamazepine is therefore considered to be safe and is anticipated to provide sufficient CYP3A induction to fulfill the primary study objective. Carbamazepine dose will be titrated up to the target dose of CCI mg over 7 days to improve its tolerability according to its label.

A dose regimen of CCI mg carbamazepine BID escalating to CCI mg carbamazepine BID has previously been established as an effective means to investigate CYP3A induction (Kanefendt et al. 2023); therefore, orforglipron will be coadministered with carbamazepine after participants have been on CCI mg BID dose for 3 days. CYP3A activity is reduced after cessation of carbamazepine dosing; therefore, carbamazepine dosing will continue for the duration of orforglipron PK sampling collection to ensure stability of CYP3A activity during the orforglipron PK assessment.

Participants will continue dosing with carbamazepine following orforglipron administration on Day 15 to maintain enzyme induction until the PK sampling period is completed. The planned dose levels of carbamazepine are within the limits of the recommended therapeutic dose range to treat patients with various medical conditions.

Significant adverse reactions reported with carbamazepine include

- serious dermatological reactions, strongly associated with the HLA-B*1502 and HLA-A*3101 alleles more common in East Asian populations
- aplastic anemia and agranulocytosis
- hypersensitivity reactions, including DRESS
- anaphylactic reactions and angioedema, and suicidal behavior and ideation.

The majority of these severe reactions are rarely reported.

Particularly at the start of treatment, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reaction occur very commonly or commonly, such as

- central nervous system adverse reactions, including dizziness, headache, ataxia, drowsiness, fatigue, and diplopia
- GI disturbances, including nausea and vomiting, and
- allergic skin reactions.

The dose-related adverse reactions due to carbamazepine usually abate within a few days, either spontaneously, after a transient dosage reduction, or upon cessation of dosing.

4.4. End of Study Definition

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

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit shown in the SoA in Section 1.3.

5. Study Population

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

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. are 21 to 70 years of age, inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. have 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 BMI within the range of 18.5 to 35.0 kg/m^2, inclusive.

Sex and Contraceptive/Barrier Requirements

5. are individuals AMAB 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 in Section 10.4.

Informed Consent

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

Other Inclusion Criteria

7. are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures including dietary requirements.
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; or of interfering with the interpretation of data.
10. have a 12-lead ECG abnormality that, in the opinion of the investigator, increases the risks associated with participating in the study.
11. have clinically significant cardiovascular diseases, especially history or ECG evidence of clinically significant heart blocks.
12. have the HLA-B*1502 or HLA-A*3101 allele.

    Note: participants with other alleles that demonstrate strong evidence of association with carbamazepine-induced hypersensitivity reaction or hepatic impairment may also be excluded.

13. have an abnormal BP or pulse rate, deemed to be clinically significant by the investigator.
14. have a history of epilepsy or seizures.
15. have a history of benign ethnic neutropenia.
16. have a GI disease or GI 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.
17. 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 1.5 × ULN of the reference range.
18. currently have clinically significant atopy or have a history of clinically significant multiple or severe drug allergies or severe post treatment hypersensitivity reactions including, but not limited to
    a. erythema multiforme major
    b. linear immunoglobulin A dermatosis
    c. toxic epidermal necrolysis, or
    d. exfoliative dermatitis.
19. have known allergies to carbamazepine or to orforglipron, related compounds, or any components of the formulation.
20. have a history of serious dermatological adverse reaction, such as toxic epidermal necrolysis, Stevens-Johnson syndrome, or DRESS, or a history of other significant allergic drug reaction, such as anaphylaxis or angioedema.
21. 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. AST, ALT, or ALP equal to or greater than 1.5 × ULN, or

b. total bilirubin equal to or greater than 1.5 × ULN.

Note: participants with Gilbert syndrome may be enrolled.

22. 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.
23. have laboratory evidence of clinically significant anemia, leukopenia, or renal dysfunction; or hyponatremia.
24. have a history of or current psychiatric disorders that in the opinion of the investigator would adversely affect patient safety or compliance.
25. have any medical conditions, medical history, or are taking any medications that are contraindicated in the carbamazepine prescribing information. See Appendix 7 in Section 10.7 for examples.
26. have
    a. known prolongation of QT/QTc interval
    b. a history of additional risk factors for ventricular arrhythmia, that is torsades de pointes, for example heart failure, hypokalemia or hypomagnesemia, significant bradycardia, or
    c. are receiving Class IA or III antiarrhythmics or receiving drugs known to prolong the QT/QTc interval.

Prior and Concomitant Therapy

27. have used or intend to use any prescription or OTC medications within 14 days prior to Day 1 and throughout the study, with the exception of vitamin or mineral supplements, herbal supplements, vaccination, and prescription medications for the treatment of concurrent medical conditions such as thyroid replacement therapy, unless otherwise specified in Section 6.9. See Appendix 4 in Section 10.4 for permitted contraceptives.
28. have used or intend to use any drugs or substances that are known moderate or strong inducers, inhibitors, or substrates of CYP3A within 14 days prior to Day 1, throughout the study, and for 14 days after the last dose of carbamazepine.
29. have used or intend to use any drugs or substances that are known strong inducers or inhibitors of P-gp within 14 days prior to Day 1, throughout the study, and for 14 days after the last dose of carbamazepine.
30. have used or intend to use monoamine oxidase inhibitors within 14 days prior to Day 1, throughout the study, and for 14 days after the last dose of carbamazepine.
31. have used or intend to use any drugs or substances that are moderate or strong OATP inhibitors or drugs that may be affected by an increase in gastric pH should be separated in dosing from orforglipron by at least 2 to 4 hours within 14 days prior to Day 1 and throughout the study.
32. require the treatment of concurrent medical conditions, use of sensitive CYP3A substrates, CYP3A substrates with a narrow therapeutic index, and other drugs for which carbamazepine causes or is expected to cause a decrease in drug levels, such as listed in

the carbamazepine US prescribing information, within 14 days prior to Day 1, throughout the study, and for 14 days after the last dose of carbamazepine.

Prior and Concurrent Clinical Study Experience

33. 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.
34. have participated, within the last 3 months, in a clinical study involving an IP. If the previous IP has a long $t_{1/2}$, 5 half-lives or 3 months, whichever is longer, should have passed since last dosing, prior to Day -1.

Diagnostic Assessments

35. show evidence of HIV infection or positive HIV antibodies. A negative test within 6 months of screening would not need to be repeated.
36. show evidence of hepatitis C or positive hepatitis C antibody. A negative test within 6 months of screening would not need to be repeated.
37. show evidence of hepatitis B, positive hepatitis B surface antigen, or positive hepatitis B core antibody. A negative test within 6 months of screening would not need to be repeated.
38. have serum calcitonin levels of equal to or greater than 20 ng/L.
39. have history renal impairment with CLcr less than 90 mL/min.

Other Exclusion Criteria

40. regularly use known drugs of abuse.
41. have a positive result following an ethanol test or urine drug screen at screening and Day -1.
42. are women who are lactating.
43. are unwilling to comply with the dietary restrictions required for this study, as described in Section 5.3.1.
44. 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 as detailed in Section 5.3.2.
45. 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.
46. 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.
47. 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.
48. are employees of Eli Lilly and Company or the CRU.
49. are, in the opinion of the investigator or sponsor, unsuitable for inclusion in the study.

50. are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.
51. have answered "yes" to
    a. either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS **and** the ideation occurred within the past month, or
    b. have answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS, **and** the behavior occurred within the past month.

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 will be required to refrain from consumption of

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

Food

On all dosing days for orforglipron, participants must fast for at least 8 hours prior to dosing and will remain fasted for at least 2 hours after dosing.

Carbamazepine should be taken with breakfast and dinner, approximately 12 hours apart. The carbamazepine doses should be taken at approximately the same time of day for a given participant.

On Day 15, the day of orforglipron and carbamazepine coadministration, orforglipron should be administered in the fasted state approximately 2 hours before carbamazepine dosing. Carbamazepine will then be dosed.

On orforglipron dosing days with PK sample collection, participants must fast for at least 2 hours after orforglipron dosing.

Drink

On orforglipron dosing days with PK sample collection, 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. 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.

5.3.3. Activity

Participants will be advised to maintain their regular levels of physical activity and exercise during the study. Participants will abstain from strenuous exercise within 24 hours prior to 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 Interventions and Concomitant Therapy

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

6.1. Study Interventions Administered

Orforglipron

Orforglipron will be administered orally as a single dose with approximately 240 mL of water. Participants will be fasted for at least 8 hours prior to orforglipron dosing and will remain fasted for at least 2 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.

Carbamazepine

Carbamazepine will be administered orally BID, approximately 12 hours apart, with approximately 240 mL of water. The carbamazepine doses should be administered at approximately the same time for a given participant. On Day 15, the day of orforglipron and carbamazepine coadministration, orforglipron should be administered in the fasted state approximately 2 hours before carbamazepine dosing. Carbamazepine will then be dosed with breakfast.

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

Table GZPJ.1. Study Intervention Administered

Intervention Name	Orforglipron	Carbamazepine
Dosage Formulation	Capsule	Tablet (immediate release)
Dosage Levels	[redacted] mg	[redacted] mg BID [redacted] mg BID [redacted] mg BID
Route of Administration	Oral	Oral
Sourcing	Provided centrally by the sponsor	Purchased locally by site

Abbreviation: BID = twice daily.

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 manual or automated monitored area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

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

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

6.3. Assignment to Study Intervention

This is a non-randomized study.

6.4. Blinding

This is an open-label study.

6.5. Study Intervention Compliance

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

Dose modification is not permitted in this study.

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

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

6.8. Treatment of Overdose

Orforglipron

For this study, any dose of orforglipron greater than [redacted] mg will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

Carbamazepine

For this study, any dose of carbamazepine greater than CCI mg within the same day will be considered an overdose.

For additional information, refer to the product label for carbamazepine, as applicable (Tegretol package insert, 2023).

In the event of an orforglipron or carbamazepine 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

Any medication or vaccine, including OTC or prescription medicines, vitamins or mineral supplements, herbal supplements, vaccination, or prescription medications for the treatment of concurrent medical conditions such as thyroid replacement therapy, that the participant is receiving at the time of enrollment or receives during the study must be recorded along with the

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

The clinical pharmacologist or clinical research physician should be contacted if there are any questions regarding concomitant or prior therapy.

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

From 14 days prior to Day 1, throughout the study, and for 14 days after the last dose of carbamazepine, participants are not permitted to use

- moderate or strong CYP3A4 inhibitors
- moderate or strong CYP3A inducers
- monoamine oxidase inhibitors
- CYP3A substrates, and
- strong P-gp inhibitors and strong P-gp inducers.

OATP inhibitors and drugs affected by an increase in gastric pH

From 14 days prior to Day 1, throughout the study, and until discharge from the CRU, participants are not permitted to use

- moderate or strong OATP inhibitors, and

- drugs that may be affected by an increase in gastric pH should be separated in dosing from orforglipron by at least 2 to 4 hours.

Other Concomitant Medications

From 14 days prior to Day 1, throughout the study, and for 14 days after the last dose of carbamazepine, participants are not permitted to use sensitive CYP3A substrates, CYP3A substrates with a narrow therapeutic index, or any medications that are contraindicated or are listed as carbamazepine causing or expecting to cause decreased drug levels, in the carbamazepine prescribing information. See Appendix 7 in Section 10.7 for examples.

Acetaminophen, at doses of up to 3 g per day, is permitted for use during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor, 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 in Section 10.1.

7.1. Discontinuation of Study Intervention

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

A participant should be permanently discontinued from study intervention if

- the participant becomes pregnant during the study
- acute pancreatitis is diagnosed
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons
- answered "yes" to
    - Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, **or**
    - any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

  Note: a psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.
- the investigator determines that a systemic hypersensitivity reaction, or clinically significant drug rash, has occurred related to study intervention administration. The sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor
- the participant has a systemic hypersensitivity reaction or clinically significant drug rash
- the participant has confirmed moderate reduction in hemoglobin or moderate granulocytopenia:
    - hemoglobin levels less than 11 g/dL or a decrease from baseline of equal to or greater than 1.6 g/dL
    - white blood cell count of less 3000/mm^3
    - neutrophil count of less than 1500/mm^3, or
    - other evidence of significant bone marrow suppression or immune-mediated cytopenia, regardless of severity.
- the participant has a platelet count of less than 125,000/mm^3
- the participant has moderate hyponatremia, that is, confirmed moderate hyponatremia (equal to or less than 130 mEq/L × 2) or any symptomatic hyponatremia
- the participant has a clinically significant ECG reading, including

- new onset symptomatic PR interval greater than 220 msec, or second- or third-degree atrioventricular block
- a sustained PR interval greater than 240 msec, or symptomatic first-degree or Mobitz type I second-degree atrioventricular block, or
- occurrence of Mobitz type II second- or third-degree atrioventricular block
- ECG changes considered to be clinically significant by investigators.

7.1.1. Hepatic Criteria for Study Drug Interruption or Discontinuation

See Section 8.3.5.3 for hepatic criteria for study drug interruption or discontinuation.

7.2. Participant Discontinuation/Withdrawal from the Study

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 investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an ED visit, as shown in the SoA in Section 1.3. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

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

7.3. Lost to Follow-Up

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

8. Study Assessments and Procedures

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

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

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

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

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

8.1. Efficacy Assessments

Efficacy is not evaluated in this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

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

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

8.2.2. Vital Signs

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

BP and pulse rate should be measured after at least 5 minutes supine. When possible, measurements of BP and pulse rate should be performed 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 obtained between 2 to 3 minutes after standing.

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

Unscheduled orthostatic vital signs 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

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

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

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

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of study intervention should be reported to the sponsor, or its designee, as an AE via the electronic CRF.

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

8.2.4. Clinical Safety Laboratory Tests

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

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within the designated follow-up period after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or 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 in Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

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

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

Carbamazepine is considered to be a central nervous system active drug.

Participants being treated with carbamazepine should be monitored appropriately and observed closely for SIB or any other unusual changes in behavior, especially at the beginning and end of

the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

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

C-SSRS

The C-SSRS captures the occurrence, severity, and frequency of SIB during the assessment period via a semi-structured interview by a trained rater.

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

Timing of collection and AE monitoring

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

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

Follow standard procedures for reporting SAEs.

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

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

- AEs
- SAEs, and
- PCs.

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs, as defined in Section 8.3.3, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up, as defined in Section 7.3.

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

8.3.1. Timing and Mechanism for Collecting Events

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

Table GZPJ.2. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Pregnancy					
Pregnancy in individuals AFAB and AFAB partners of AMAB participants	After the start of study intervention	At least 45 days after the last dose	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint paper 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 paper form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint paper 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 paper form	N/A

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. Pregnancy

Collection of pregnancy information

AMAB participants with partners who become pregnant

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

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

- will obtain a consent to release information from the pregnant AFAB 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 AFAB partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status, that is, the presence or absence of anomalies, or indication for the procedure.

AFAB participants who become pregnant

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

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

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

A spontaneous abortion, that is, occurring at less than 20 weeks gestational age, or still birth, that is occurring at equal to or greater than 20 weeks gestational age is always considered to be an SAE and will be reported as such.

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

Any 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.

8.3.3. Adverse Events of Special Interest and Other Safety Topics

AESIs and other safety topics for this program include

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

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

8.3.4. Pancreatic Monitoring

Diagnosis of acute pancreatitis

Acute pancreatitis is an AE of interest in all studies with orforglipron, including this study. The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks 2006; Koizumi 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 3 × ULN
- 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
- 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 investigational products.

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 et al. 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 3 × ULN, is not

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

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

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 less than 1.5 × ULN)

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

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

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

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

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation	Interrupt or discontinue study drug
ALT or AST ≥2 × baseline	X		
ALP ≥2 × baseline	X		
TBL ≥2 × ULN[b]	X		
ALT or AST ≥3 × baseline or ≥250 U/L (whichever occurs first)	X	X	
ALP ≥2.5 × baseline	X	X	
ALT or AST ≥2 × baseline or ≥250 U/L	X	X	X

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

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

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

8.3.5.1. Close Hepatic Monitoring

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

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5 × ULN)	Participants with elevated baseline (ALT, AST, or ALP ≥1.5 × ULN)
ALT or AST ≥3 × ULN **or**	ALT or AST ≥2 × baseline **or**
ALP ≥2 × ULN **or**	ALP ≥2 × baseline **or**
TBL ≥2 × ULN[a]	TBL ≥2 × ULN[a]
[a] In participants with Gilbert's syndrome the threshold for TBL may be higher.	

Close hepatic monitoring should include these actions:

- Laboratory tests detailed in Appendix 6 in Section 10.6, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, creatine kinase, and complete blood count with differential, should be checked within 48 to 72 hours of the detection of elevated liver tests to confirm the abnormality and to determine if it is increasing or decreasing.
- If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 2 to 3 times weekly until levels normalize or return to approximate baseline values.
- In addition to laboratory tests, basic evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include
    - physical examination and a thorough medical history, including current symptoms
    - recent illnesses such as heart failure, systemic infection, hypotension, or seizures

- recent travel
- concomitant medications including OTC, herbal and dietary supplements, and
- history of alcohol drinking and other substance abuse.

8.3.5.2. Comprehensive Hepatic Evaluation

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

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

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

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

Comprehensive hepatic evaluation should include these actions:

- At a minimum, comprehensive hepatic evaluation should include physical examination and a thorough medical history, as outlined above, as well as
  - tests for prothrombin time-INR,
  - tests for viral hepatitis A, B, C, and E,
  - tests for autoimmune hepatitis, and
  - an abdominal imaging study, for example, ultrasound or CT scan.
- Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for
  - hepatitis D virus
  - cytomegalovirus
  - Epstein-Barr virus
  - acetaminophen levels
  - acetaminophen protein adducts
  - urine toxicology screen
  - Wilson's disease

  - blood alcohol levels
  - urinary ethyl glucuronide, and
  - blood phosphatidylethanol.
- Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, and additional tests including
  - magnetic resonance cholangiopancreatography
  - endoscopic retrograde cholangiopancreatography
  - cardiac echocardiogram, or
  - a liver biopsy.
- Clinical and laboratory monitoring should continue at a frequency of 1 to 3 times weekly until levels normalize or return to approximate baseline values.
- All the medical information and tests results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.3.5.3. Interruption or Discontinuation of Study Intervention

If a participant develops any one of the following laboratory or clinical changes, interrupt the study intervention and continue close monitoring and comprehensive hepatic evaluation as described in Section 8.3.5.1 and Section 8.3.5.2.

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

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

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

Interruption or discontinuation of study intervention should include these actions:

- While the participant is not receiving the study intervention, clinical and laboratory monitoring should continue at a frequency of 1 to 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 tests results related to the close hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.
- Resumption of the study intervention 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 non-study-intervention etiology is identified. Otherwise, the study intervention should be permanently discontinued.

8.3.6. Hypoglycemia

Participants will be trained by authorized study personnel about signs and symptoms of hypoglycemia and how to treat hypoglycemia.

Investigators should use the following classification of hypoglycemia:

Level 1 hypoglycemia:

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

Level 2 hypoglycemia:

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

Level 3 hypoglycemia:

Severe hypoglycemia, in adults: A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the

assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

- The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.
- If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

Nocturnal hypoglycemia:

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

8.3.7. Hypersensitivity Reactions

Many drugs, including oral agents 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 in Section 10.2.2. Laboratory results are provided to the sponsor via the central laboratory.

8.4. Pharmacokinetics

Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of orforglipron 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 will be taken, 1 sample of sufficient volume 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. Samples collected for analyses of orforglipron plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.5. Pharmacodynamics

PD parameters are not evaluated in this study.

8.6. Genetics

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

See Appendix 5 in Section 10.5 for information regarding genetic research and Appendix 1 in Section 10.1.9 for details about sample retention and custody.

8.7. Biomarkers

At the visits and times specified in the SoA in Section 1.3, venous blood samples of approximately 3 mL will be collected to determine the plasma concentrations of coproporphyrin 1. The actual date and 24-hour clock time of each sampling will be recorded. Concentrations of coproporphyrin 1 will be assayed using a validated liquid chromatography tandem-mass spectrometry method.

8.8. Immunogenicity Assessments

Not applicable.

8.9. Health Economics or Medical Resource Utilization and Health Economics

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

9. Statistical Considerations

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

9.1. Statistical Hypothesis

The primary objective of this study is to evaluate the effect of carbamazepine 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.
Safety analysis set	All participants who are exposed to at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
PK analysis set	All enrolled participants who receive at least 1 dose of study intervention and have evaluable PK data.
Coproporphyrin 1 biomarker Set	All participants who receive at least 1 period of evaluable coproporphyrin 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 × median t_{max}.

9.2.1. Study Participant Disposition

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

9.2.2. Study Participant Characteristics

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

- age
- sex
- weight
- height
- BMI
- ethnicity

- race, and
- other demographic characteristics.

9.2.3. Treatment Compliance

The date and time will be recorded and listed for each dose of orforglipron and carbamazepine.

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 or not they completed all protocol requirements.

Coproporphyrin 1 biomarker analyses will be conducted from all participants who have at least 1 period of evaluable coproporphyrin 1 data.

Additional exploratory analyses of the data may be conducted as appropriate. Study results may be pooled with the results of other studies for safety, PD, and population PK analysis purposes to minimize the limitations of a small size study and to leverage the totality of evidence across multiple studies if data warrants.

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

9.3.2. Pharmacokinetic Analyses

9.3.2.1. Pharmacokinetic Parameter Estimation

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

The primary parameters for analysis will be AUC(0-∞), AUC(0-t_{last}), and C_{max} of orforglipron. Other noncompartmental parameters, such as t_{max}, $t_{1/2}$, apparent clearance, and apparent volume of distribution may be reported. If deemed necessary, additional analysis may be performed. All PK parameters will be listed and summarized using description statistics.

9.3.2.2. Pharmacokinetic Statistical Inference

PK parameter estimates will be evaluated to delineate the effects of carbamazepine's interaction with orforglipron.

The PK parameters C_{max} and AUC for orforglipron when administered alone, that is reference, and in the presence of carbamazepine, that is 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 and will be adjusted for other factors, if needed. The least-squares means for orforglipron and orforglipron + carbamazepine, the difference between least-squares means for test – reference, and the associated 90% CIs will be calculated from the model and back-transformed from the log scale to provide estimates of the GLSMs for orforglipron and orforglipron + carbamazepine, geometric mean ratio between test and reference, and corresponding 90% CIs. A DDI will be assessed by examining the 90% CIs for the geometric mean ratio of GLSMs of orforglipron coadministered with carbamazepine relative to orforglipron alone.

The t_{max} of both test and reference will be analyzed using a Wilcoxon signed-rank test. An estimate of the median difference, that is test – reference, and approximate 90% CI will be reported.

9.3.3. Exploratory Endpoint Analysis

9.3.3.1. Coproporphyrin 1 Biomarker analyses

Plasma concentrations of coproporphyrin 1 will be listed and summarized using standard descriptive statistics. Parameter estimates for coproporphyrin 1 will be calculated by standard noncompartmental methods. Parameters, including concentration predose, C_{max}, t_{max}, AUC(0-$_{tlast}$), and AUC(0-24), will be summarized using descriptive statistics.

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

9.3.3.2. Statistical Methods

The PK parameters C_{max} and AUC for coproporphyrin 1 (test) with the C_{max} and AUC for coproporphyrin 1 (reference) 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 to provide estimates of the geometric means for each treatment, geometric mean ratio between test and reference treatments, and corresponding 90% CIs.

9.3.4. Safety Analyses

9.3.4.1. Clinical Evaluation of Safety

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

The incidence of AEs for each capsule dose level will be presented by severity and by association with IP as perceived by the investigator. AEs reported to occur prior to the first study dose will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities. The number of SAEs will be reported. Details regarding the analysis of AESIs will be described in the SAP.

9.3.4.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include clinical chemistry and vital signs. The parameters and changes from baseline, that is the last observation prior to the first dose, where appropriate, will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

9.3.5. Other Analyses

9.3.5.1. Analysis of C-SSRS data

Suicide-related thoughts and behaviors will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide.

9.4. Interim Analysis

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

9.5. Sample Size Determination

Approximately 30 participants will be enrolled to ensure that approximately 20 evaluable participants will complete the study.

The sample size is calculated to quantify the carbamazepine's effect on each of the PK parameters, that is AUC(0-∞), AUC(0-t_{last}), and C_{max}, of orforglipron. Assuming a maximum intraparticipant coefficient of variation of 40%, a sample size of 20 completers will provide at least 90% chance to ensure that no more than 80% decrease on each of the PK parameters of interest of orforglipron induced by carbamazepine assuming a true effect of 0.3.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following

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

Investigator sites are compensated for participation in the study as detailed in the CTA.

10.1.2. Informed Consent Process

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

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

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

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

A copy of the ICFs must be provided to the participant and is kept on file.

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

10.1.3. Data Protection

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

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

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

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

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

10.1.4. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators, for example, by phone or email, as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing

any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

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

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

Data

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

10.1.5. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

Data Capture System

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

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

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

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

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

10.1.6. Source Documents

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

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

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

10.1.7. Study and Site Start and Closure

First Act of Recruitment

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

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

Study or Site Termination

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

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

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

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

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

10.1.8. Publication Policy

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

10.1.9. Sample Retention

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

Sample Type	Custodian	Retention Period After Last Participant Visit
Pharmacokinetics	Sponsor or designee	1 year
Coproporphyrin 1	Sponsor or designee	1 year
Pharmacogenetics	Sponsor or designee	15 years
HLA genotyping	Sponsor or designee	15 years

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.

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
• Phosphate
• Glucose (fasting)[a]
• Urea
• Total protein
• Albumin
• Amylase
• Lipase
• Creatinine
• Liver panel
  ○ Total bilirubin
  ○ Direct bilirubin
  ○ Indirect bilirubin
  ○ Alkaline phosphatase
  ○ Aspartate aminotransferase
  ○ Alanine aminotransferase
• Lipid panel[b]
	[a] Performed after overnight fast.
	
	[b] Lipid panel to be performed at screening only.

Clinical Laboratory Tests	Comments
○ Total cholesterol ○ Triglycerides ○ Low-density lipoprotein cholesterol ○ High-density lipoprotein cholesterol	
Urinalysis	Assayed by local laboratory.
• Specific gravity • pH • Protein • Glucose • Ketones • Bilirubin • Urobilinogen • Leukocytes • Blood • Nitrite • Microscopic examination of sediment[c]	All urinalysis tests performed only at screening and Day -1. [c] Microscopic examination of sediment only to be performed if dipstick result is abnormal and is further definable by microscopy. Microscopy to be performed at the local safety laboratory, if clinically indicated, at investigator's discretion.
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 RNA 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[d] • Follicle-stimulating hormone[d,f] • Calcitonin[d] • Ethanol test[e] • Urine drug screen • HLA genotyping[d,g] • Coproporphyrin 1[g]	[d] Performed at screening only. [e] Urine test performed at screening, and breath or urine test performed on Day -1. [f] Performed for individuals AFAB only. [g] Assayed by Lilly central laboratory.

Clinical Laboratory Tests	Comments
Pharmacokinetic Samples	Assayed by Lilly central laboratory. Results will not be provided to the investigative sites.
• Orforglipron concentration	
Genetics Sample	Assayed by Lilly central laboratory. Results will not be provided to the investigative sites.

10.2.1. Blood Sampling Summary

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

Protocol J2A-MC-GZPJ Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	20	1	20
Clinical laboratory tests[a]	10	7	70
Coproporphyrin 1	3	18	54
Pharmacokinetics	2	25[b]	50
Genetic sample	10	1	10
Total			204
Total for clinical purposes (rounded up to nearest 10 mL)			210

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

[b] Includes additional 3 samples, if required.

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 tests 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 unfavourable and unintended sign, including an abnormal laboratory finding, symptom, or new or exacerbated disease temporally associated with the use of a medicinal, that is investigational product, or investigational combination product, whether or not related to the medicinal, that is investigational, product or investigational combination product.

Events meeting the AE definition

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

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

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

10.3.2. Definition of SAE

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

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

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

10.3.3. Definition of Product Complaints

Product complaint

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

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

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

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

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

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

AE, SAE, and PC recording

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

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

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

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

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

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

Assessment of intensity

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

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

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

Assessment of causality

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

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

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

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

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

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

The investigator may change their opinion of causality in light of follow-up information and send 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 Global Patient Safety Clinical Trial SAE Transmission Cover Sheet and Form.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

Prompt notification by the investigator to the sponsor of 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 has processes for safety reports for identification, recording, and expedited reporting of suspected unexpected serious adverse reactions according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB or IEC, and investigators.

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
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. 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 HRT.

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

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

[c] The individual should not be taking medications during amenorrhea such as oral contraceptives, 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

IOCBP are excluded from the trial. INOCBP may participate in this trial.

10.5. Appendix 5: Genetics

Use and Analysis of DNA

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

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

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

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

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

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

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

Hepatic Evaluation Testing

See Section 8.3.5 for guidance on appropriate test selection.

Each test in the table below is to be performed at a local laboratory. Based on availability of these tests, multiple local laboratories may be needed. All local laboratories must be qualified in accordance with applicable local regulations.

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	ALP 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:	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 IgM are acceptable substitutes.

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

10.7. Appendix 7: Medications Contraindicated in the Carbamazepine Prescribing Information

Contraindications

Contraindicated drugs for carbamazepine (refer to the Tegretol package insert, 2023) include

- monoamine oxidase inhibitors
- tricyclic compounds to which participants has previously shown sensitivity, such as amitriptyline, desipramine, imipramine, protriptyline, and nortriptyline
- inhibitors of human microsomal epoxide hydrolase, such as loxapine, quetiapine, valproic acid, and brivaracetam.
- moderate and strong CYP3A inhibitors, including aprepitant, cimetidine, ciprofloxacin, danazol, diltiazem, macrolides (for example, erythromycin, clarithromycin), fluoxetine, fluvoxamine, trazodone, omeprazole, oxybutynin, isoniazid, niacinamide (nicotinamide), azoles (for example, ketaconazole, itraconazole, fluconazole, voriconazole), acetazolamide, verapamil, ticlopidine, grapefruit juice, and protease inhibitors.
- moderate and strong CYP3A inducers, including cisplatin, doxorubicin HCl, felbamate, fosphenytoin, rifampin, phenobarbital, phenytoin, primidone, methsuximide, theophylline, and aminophylline.

Effect of Carbamazepine on Plasma Levels of Concomitant Agents

Decreased Levels of Concomitant Medications

Carbamazepine is a potent inducer of hepatic 3A4 and is also known to be an inducer of CYP1A2, 2B6, 2C8/9/19, and may therefore reduce plasma concentrations of comedications mainly metabolized by CYP 1A2, 2B6, 2C8/9/19, and 3A4, through induction of their metabolism. When used concomitantly with carbamazepine, monitoring of concentrations or dosage adjustment of these agents may be necessary:

- When carbamazepine is added to aripiprazole, the aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. If carbamazepine is later withdrawn, the aripiprazole dose should be reduced.
- When carbamazepine is used with tacrolimus, monitoring of tacrolimus blood concentrations and appropriate dosage adjustments are recommended.
- The use of concomitant strong CYP3A4 inducers, such as carbamazepine should be avoided with temsirolimus. If patients must be coadministered carbamazepine with temsirolimus, an adjustment of temsirolimus dosage should be considered.
- The use of carbamazepine with lapatinib should generally be avoided. If carbamazepine is started in a patient already taking lapatinib, the dose of lapatinib should be gradually titrated up. If carbamazepine is discontinued, the lapatinib dose should be reduced.
- Concomitant use of carbamazepine with nefazodone results in plasma concentrations of nefazodone and its active metabolite insufficient to achieve a therapeutic effect. Coadministration of carbamazepine with nefazodone is contraindicated.

- Monitor concentrations of valproate when carbamazepine is introduced or withdrawn in patients using valproic acid.

In addition, carbamazepine causes, or would be expected to cause, decreased levels of the following drugs, for which monitoring of concentrations or dosage adjustment may be necessary: acetaminophen, albendazole, alprazolam, aprepitant, buprenorphone, bupropion, citalopram, clonazepam, clozapine, corticosteroids (for example, prednisolone, dexamethasone), cyclosporine, dicumarol, dihydropyridine calcium channel blockers (for example, felodipine), doxycycline, eslicarbazepine, ethosuximide, everolimus, haloperidol, imatinib, itraconazole, lamotrigine, levothyroxine, methadone, methsuximide, mianserin, midazolam, olanzapine, oral and other hormonal contraceptives, oxcarbazepine, paliperidone, phensuximide, phenytoin, praziquantel, protease inhibitors, risperidone, sertraline, sirolimus, tadalafil, theophylline, tiagabine, topiramate, tramadol, trazodone, tricyclic antidepressants (for example, imipramine, amitriptyline, nortriptyline), valproate, warfarin, ziprasidone, zonisamide.

Other Drug Interactions

- Cyclophosphamide is an inactive prodrug and is converted to its active metabolite in part by CYP3A. The rate of metabolism and the leukopenic activity of cyclophosphamide are reportedly increased by chronic coadministration of CYP3A4 inducers. There is a potential for increased cyclophosphamide toxicity when coadministered with carbamazepine.
- Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.
- Concomitant use of carbamazepine with olanzapine, dantrolene, or ibuprofen may increase plasma carbamazepine levels.
- Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.
- Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.
- Concomitant use of carbamazepine with hormonal contraceptive products (for example, oral, and levonorgestrel subdermal implant contraceptives) may render the contraceptives less effective because the plasma concentrations of the hormones may be decreased. Breakthrough bleeding and unintended pregnancies have been reported. Alternative or back-up methods of contraception should be considered.
- Resistance to the neuromuscular blocking action of the nondepolarizing neuromuscular blocking agents pancuronium, vecuronium, rocuronium and cisatracurium has occurred in patients chronically administered carbamazepine. Whether or not carbamazepine has the same effect on other non-depolarizing agents is unknown. Patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected, and infusion rate requirements may be higher.
- Concomitant use of carbamazepine with rivaroxaban, apixaban, dabigatran, and edoxaban (direct acting oral anticoagulants) is expected to result in decreased plasma concentrations of these anticoagulants that may be insufficient to achieve the intended

therapeutic effect. In general, coadministration of carbamazepine with rivaroxaban, apixaban, dabigatran, and edoxaban should be avoided.

10.8. Appendix 8: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
AESI	adverse event of special event
AFAB	assigned female at birth
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMAB	assigned male at birth
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from zero to infinity
AUC(0-t_{last})	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
BID	twice daily
BMI	body mass index
BP	blood pressure
C-SSRS	Columbia-Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice, and applicable regulatory requirements.
CRF	case report form: a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CRU	clinical research unit

CT	computed tomography
CTA	clinical trial agreement
CYP	cytochrome P450
DDI	drug-drug interaction
DRESS	drug reactions with eosinophilia and systemic symptoms
ECG	electrocardiogram
ED	early discontinuation
EDC	electronic data capture system
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLSM	geometric least squares mean
HbA1c	glycated hemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.

informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INOCBP	individuals not of childbearing potential
INR	international normalized ratio
IOCBP	individuals of childbearing potential
IP	investigational product: a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
IRB	institutional review board
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a PC • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
OATP	organic anion transporting polypeptide
OTC	over-the-counter
P-gp	P-glycoprotein 1
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PK/PD	pharmacokinetic(s)/pharmacodynamic(s)

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.
SIB	suicidal ideation and behavior
SoA	Schedule of Activities
$t_{1/2}$	half-life associated with the terminal rate constant
T2D	type 2 diabetes
TBL	total bilirubin
TEAE	treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
t_{max}	time of maximum observed drug concentration
ULN	upper limit of normal

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