Statistical Analysis Plan J2A-MC-GZPJ

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

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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

Compound Number: LY3502970

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

Acronym: GZPJ
Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

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Version History

This statistical analysis plan (SAP) for Study J2A-MC-GZPJ (GZPJ) is based on the protocol dated 31 January 2024.

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	See date on Page 1	Not Applicable	Original version

1. Introduction

This document is the SAP for Study GZPJ.

Study 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.

This SAP supersedes all statistical considerations and analyses described in Protocol GZPJ.

1.1. Objectives, Endpoints, and Estimands

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

1.2. Study Design

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

Pharmacokinetic (PK) blood sampling and safety assessments, including vital signs measurements, physical examinations, clinical laboratory tests, electrocardiograms (ECGs), and adverse event (AE) recording, will be performed according to the Schedule of Activities described in the protocol (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 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.

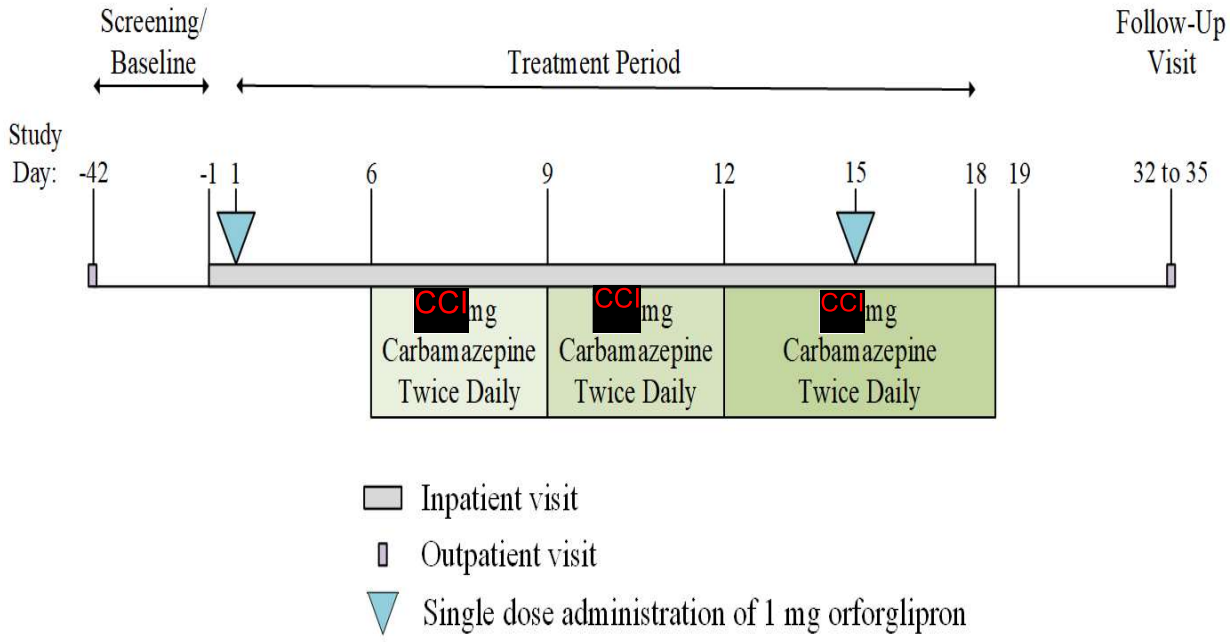

Figure GZPJ.1.1. Illustration of study design for clinical protocol J2A-MC-GZPJ.

2. Statistical Hypotheses

The hypothesis is to evaluate the effect of carbamazepine on the PK of orforglipron in healthy participants.

3. Analysis 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 enrolled 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 according to the intervention they received.
Coproporphyrin 1 biomarker set	All enrolled participants who receive at least 1 period of evaluable coproporphyrin 1 data.

Abbreviations: ICF = informed consent form; PK = pharmacokinetic.

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 time of maximum observed drug concentration (t_{max}) of orforglipron.

4. Statistical Analyses

4.1. General Considerations

Statistical analysis of Study GZPJ will be the responsibility of Eli Lilly and Company 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 confidence intervals (CIs) will be presented at a 2-sided 90% level.

PK analyses will be conducted on data from all enrolled 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 enrolled participants who have evaluable coproporphyrin 1 data.

Additional exploratory or sensitivity analyses of the data may be conducted as appropriate. These additional analyses can be documented in the clinical study report (CSR) without revising the approved SAP. Study results may be pooled with the results of other studies for safety, pharmacodynamics, 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.

Data analysis will be performed using SAS® version 9.4 or greater.

Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum (min), maximum (max), total number of participants in the analysis population (N), and total number of participants in N who have reported data (n); for log-normal data (for example, the PK parameters: area under the concentration versus time curves [AUCs] and maximum observed drug concentration [C_{max}]), the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all participants up to the point of withdrawal including both scheduled and/or unscheduled visit records, with any participants excluded from the relevant population highlighted or flagged. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis set with scheduled visit records only. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Individual derived parameters (for example, PK parameters) and appropriate summary statistics will be reported to 3 significant figures. Observed concentration data, for example C_{max}, will be reported as received. Observed time data, for example t_{max}, will be reported as received. N and percentage values will be reported as whole numbers. Median values will be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

Missing data will not be displayed in listings.

Some of the tables, figures, and listings (TFLs) may not have sufficient numbers of participants or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, "No serious adverse events occurred for this study."

4.2. Demography and Participant Dispositions

The demographic variables age, sex, race, ethnicity, site ID, country of enrollment, body weight, height, and body mass index will be summarized and listed. All other demographic variables may be listed only.

Participant disposition will be listed including participant ID, date of study discontinuation, reason for discontinuation, AEs leading to discontinuation, first and last dose information.

4.3. Primary Endpoint(s) Analysis

4.3.1. PK Variables

Concentrations of orforglipron and coproporphyrin 1 will be collected in plasma. PK parameters of orforglipron and coproporphyrin 1 will be calculated for plasma.

4.3.2. Plasma PK Summaries

4.3.2.1. Plasma Concentrations

For nonendogenous analyte, plasma concentrations analyte below the quantifiable limit (BQL) at the beginning of the profile (prior to the first quantifiable concentration) will be set to zero in the computation of descriptive statistics. BQL values that occur after the first quantifiable point or from endogenous analytes will be considered missing. Descriptive statistics (number of participants, arithmetic mean, arithmetic SD, geometric mean, CV%, median, min, and max) will be used to summarize the plasma concentrations by treatment at each scheduled timepoint. Concentrations collected outside +/- 10% of the scheduled sampling time will be excluded from summaries and flagged in listings. Any timepoint with less than 2/3 of the observations quantifiable and within the +/- 10% sampling window will not have summary statistics presented.

Summary of excluded concentrations will be reported in the CSR.

Linear (+SD) and semi-logarithmic plots of the arithmetic mean plasma concentration by scheduled sampling time will be provided by treatment. Predose average concentration for single-dose data from nonendogenous analytes will be set to zero. Otherwise, only quantifiable concentrations will be included in the average plots. These plots will show time in hours. The plots will present all calculated means and will include a reference line for the lower limit of quantification. Mean plots will follow same presentation rules as concentration summary tables. Predose average concentration for single-dose data from nonendogenous analytes will be set to zero. Otherwise, only quantifiable concentrations will be included in the average plots.

Linear and semi-logarithmic plots of the individual plasma concentration by actual sampling time will be provided by participant (1 participant per page). These plots will show time in hours. Individual plots will use the BQL handling procedure described below for "Plasma Pharmacokinetic Parameters." The individual plots on the semi-logarithmic scale will indicate the start time (Lz_Start) to end time (Lz_End) of the WinNonlin® regression for the determination of the terminal phase rate constant.

4.3.3. Plasma PK Parameters

4.3.3.1. Calculation and Summary of PK Parameters

Plasma PK parameters for analyte will be estimated using noncompartmental methods with Phoenix WinNonlin® (8.1.3). The PK parameters will be estimated from the concentration-time profiles, and AUCs will be calculated using linear up / log down method. In estimating the PK parameters, BQL values at the beginning of the profile, for single-dose, nonendogenous compounds, will be set to zero (if missing, predose concentrations will be set to zero). BQL values that occur after the first quantifiable point will be considered missing. If an entire concentration-time profile is BQL then the profile will be excluded from PK analysis. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time is missing, the scheduled time will be substituted and flagged. Profiles with 3 or fewer quantifiable concentrations will be flagged for exclusion.

The points to be included in the λz range for the terminal elimination phase will be determined by the pharmacokineticist after inspection of the semi-log concentration-time profiles. At least 3 points will be required to be used. The C_{max} data point will not be included.

C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than 1 time point, t_{max} will be assigned to the first occurrence of C_{max}.

The parameters based on predicted last quantifiable drug concentration will be reported.

Descriptive statistics (number of participants, arithmetic mean, geometric mean, arithmetic SD, geometric CV%, median, min, and max) will be used to summarize the calculated PK parameters by treatment. For t_{max}, only median, min, and max will be presented.

A scatter plot of individual (plus mean and median) PK parameters C_{max}, area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration ($AUC(0\text{-}t_{last})$), and area under the concentration versus time curve from zero to infinity ($AUC(0\text{-}\infty)$) by treatment for each analyte will be provided.

The following flags will be used to exclude parameters that meet the predefined criteria for summary and analysis. Update the "Parameters to be Evaluated using the Exclusion Criteria" column per the study design.

Criteria Name	Exclusion Criteria	Parameters to be Evaluated using the Exclusion Criteria
Extrapolation	AUC%Extrap >20%	AUC(0-∞), $T_{1/2}$, CL, CL/F, Vz, Vz/F, Vss, Vss/F
Regression	Adj Rsq <0.8	AUC(0-∞), $T_{1/2}$, CL, CL/F, Vz, Vz/F, Vss, Vss/F
Span	Span ≤2	$T_{1/2}$

Abbreviations: Adj = adjusted; AUC = area under the concentration versus time curve; AUC(0-∞) = area under the concentration versus time curve from zero to infinity; CL = clearance of the analyte in plasma after intravascular administration; CL/F = apparent total body clearance of drug calculated after extravascular administration; Extrap = extrapolated; Rsq = r-squared; $T_{1/2}$ = half-life associated with the terminal rate constant λz in noncompartmental analysis; Vss = volume of distribution at steady state following IV administration; Vss/F = apparent volume of distribution at steady state after extravascular administration; Vz = apparent volume of distribution during the terminal phase after intravascular administration; Vz/F = apparent volume of distribution during the terminal phase after extravascular administration.

Note: flags will be applied to parameters prior to derivation of additional parameters in SAS and will be used to exclude derived parameters as well.

All parameters will be listed by participant, parameters that meet the exclusion criteria will be accompanied by an indication of criteria met.

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

Additional PK parameters may be calculated, or additional analysis may be performed, if necessary. The software and version used for the final analysis will be specified in the CSR. All exceptions or special handling of data will be clearly documented within the final CSR.

Diagnostic PK parameters are listed but not summarized.

4.3.4. Primary Analysis for the Primary Endpoint

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

The PK parameters C_{max}, AUC(0-t_{last}), and AUC(0-∞) for orforglipron when administered alone (Day 1), that is reference, and in the presence of carbamazepine (Day 15), 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 mean for orforglipron and orforglipron + carbamazepine, the difference between least squares mean 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 geometric least squares mean (GLSM) 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 ratio of GLSMs of orforglipron co-administered with carbamazepine relative to orforglipron alone.

Sensitivity analysis may be conducted as deemed necessary.

Example SAS code for primary endpoint analysis:

```
PROC MIXED DATA=TEST COVTEST ALPHA=0.1;
   CLASS TREATMENT SUBJID;
   MODEL LOG_PK=TREATMENT / DDFM=KR2 ALPHA=0.1;
   RANDOM SUBJID;
   LSMEANS TREATMENT / PDIFF CL ALPHA=0.1;
   ODS OUTPUT LSMEANS=LSMEANS DIFFS=DIFFS COVPARMS=COV;
RUN;
```

The t_{max} of the difference between test and reference treatment 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.

4.4. Exploratory Endpoint Analysis

4.4.1. 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}, and AUC from time zero to the end of the dosing interval ($AUC(0\text{-}_{tau})$) will be summarized using descriptive statistics.

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

4.4.1.1. Coproporphyrin 1 Biomarker Statistical analyses

The log-transformed PK parameters C_{max} and $AUC(0\text{-}_{tau})$ for coproporphyrin 1 (test, for example, after orforglipron and carbamazepine treatment) with the C_{max} and $AUC(0\text{-}_{tau})$ for coproporphyrin 1 (reference, for example, after orforglipron treatment) will be compared using a linear mixed-effect model. The model will include treatment as a fixed effect and participant as a random effect. The least squares mean for each treatment, the difference between the treatment least squares mean (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.

4.5. Safety Analyses

4.5.1. Extent of Exposure

A listing of drug exposure will be given for all participants. The listing will consist of the information on participant ID, study day, dose, lot number, fasting information of the participant, dosing date and time, and water intake information.

4.5.2. Protocol Deviation

Important protocol deviations that occur during Study GZPJ will be listed if data is available.

4.5.3. Adverse Events

A treatment-emergent AE is defined as an AE which occurs after the first dose of study intervention, or which is present prior to dosing and becomes more severe post first dose.

A pre-existing condition is defined as a condition that starts before the participant has provided written informed consent and is ongoing at consent.

A nontreatment-emergent AE is defined as an AE which starts after informed consent but prior to dosing, and an AE occurring (with a certain level of severity) after informed consent but stopping prior to the first dose, and this event occurring again after the first dose, with severity of former or with lower severity.

Where changes in severity are recorded in the case report form (CRF), each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables.

Treatment-emergent AEs will be summarized by treatment (orforglipron alone, carbamazepine alone, and orforglipron + carbamazepine), severity, and relationship to the study drug. The frequency (the number of AEs, the number of participants experiencing an AE, and the percentage of participants experiencing an AE) of treatment-emergent AEs will be summarized by decreasing frequency within each system organ class, and preferred term, as defined by the Medical Dictionary for Regulatory Activities version 26.1.

It is possible to have a missing severity for events. For events with a missing severity during the baseline period, the event will be treated as mild in severity for determining treatment emergence. Events with a missing severity during the postbaseline period will be treated as severe, and treatment emergence will be determined by comparing with baseline severity. For events occurring on the day of first taking study medication, the CRF-collected flag will be used to determine whether the event was pre versus posttreatment. If at any point, 2 severity levels are available, the worst level will be taken into consideration.

Serious AEs and discontinuations due to AEs will be listed.

The following are the adverse events of special interest and other safety topics for the study

- severe or serious gastrointestinal (GI) AEs of nausea, vomiting, and diarrhea
- pancreatitis
- major adverse cardiovascular events
- arrhythmias and cardiac conduction disorders
- hepatic disorder
- hypoglycemia
- hypotension, orthostatic hypotension, and syncope
- acute kidney injury and chronic kidney disease
- gallbladder and biliary tract disorders
- hypersensitivity reactions, and
- abuse potential.

If any of the above events are observed, a listing will be presented.

4.5.4. Concomitant Medications

Concomitant medications will be coded using the World Health Organization drug dictionary. Concomitant medications will be included in the patient narrative.

4.5.5. Physical Examinations

Physical examination assessments such as cardiovascular, respiratory, GI, and neurological systems will be performed for safety monitoring purposes and will not be presented.

4.5.6. Vital Signs

Vital signs data will be summarized at each scheduled visit using standard descriptive statistics (n, mean, SD, median, min, max) together with changes from baseline, where baseline is defined as the last nonmissing data up to the first dose.

4.5.7. Electrocardiograms

ECGs will be performed for safety monitoring purposes only and will not be presented. Any clinically significant findings from ECGs will be reported as an AE.

4.5.8. Clinical Laboratory Parameters

Listings for any clinical chemistry, hematology, serology, and urinalysis including local laboratory, if available, with values outside the reference ranges with the flags for individual participant will be presented.

All clinical chemistry and hematology data will be summarized in original value and change from baseline by parameter at each scheduled visit.

4.5.9. Hypoglycemic Events/Glucose Monitoring

Hypoglycemic events will be recorded in the CRF. Hypoglycemic events are defined as follows:

Category	Glucose
Level 1 hypoglycemia	<70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L)
Level 2 hypoglycemia	<54 mg/dL (3.0 mmol/L)
Level 3 (severe) hypoglycemia	N/A
Nocturnal hypoglycemia	N/A

Abbreviation: N/A = not applicable.

Severe hypoglycemia is characterized by altered mental and/or physical status requiring assistance for the treatment of hypoglycemia. Details are given in the protocol.

Nocturnal hypoglycemia is a hypoglycemic event (including severe event) that occurs at night and presumably during sleep – between bedtime and waking. Hypoglycemic events will be listed and summarized according to each category of hypoglycemia.

4.5.10. Hypersensitivity Reactions

Hypersensitivity reactions will be listed only if data are available.

4.5.11. Hepatic Monitoring

If a participant experiences elevated laboratory parameters, as detailed in Section 8.3.5. of Protocol GZPJ, additional tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in Protocol GZPJ. If the abnormality persists or worsens, the following will be presented, where applicable.

The participant's physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over the counter), herbal and dietary supplements, history of alcohol drinking, and other substance abuse will be listed.

Tests for prothrombin time and international normalized ratio, viral hepatitis (A, B, C, or E), and autoimmune hepatitis may be done, and the results will be listed. If an abdominal imaging study is done (for example, ultrasound or computer tomography scan), it will be listed.

Based on the patient'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, a urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, magnetic resonance cholangiopancreatography, biopsy assessments, and blood phosphatidyl ethanol. The results of all these tests will be listed as well (if performed).

4.5.12. Suicidal Ideation and Behavior Risk Monitoring

Suicide-related thoughts and behaviors will be monitored during the study using the Columbia Suicide Severity Rating Scale (C-SSRS). Suicide-related thoughts and behaviors occurring during treatment may be listed for each response to the C-SSRS, consistent with the C-SSRS Scoring and Data Analysis Guide.

4.5.13. Other Assessments

All other safety assessments not detailed in this section may be listed but not summarized or statistically analyzed.

4.6. Other Analyses

4.6.1. Subgroup Analyses

No subgroup analyses are planned.

4.7. Interim Analyses

No interim analyses are planned.

4.8. Changes to Protocol-planned Analyses

There were no changes to the protocol-planned analyses.

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 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.

Approved on 29 Apr 2024 GMT

6. Supporting Documentation

Not applicable.

7. References

Not applicable.

Signature Page for VV-CLIN-147061 v1.0

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