Statistical Analysis Plan J2A-MC-GZPP (1)

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

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Title Page

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

Protocol Number: J2A-MC-GZPP

Compound Number: Orforglipron (LY3502970)

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

Sponsor Name: Eli Lilly and Company

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Version history

This statistical analysis plan (SAP) for Study J2A-MC-GZPP (GZPP) is based on the protocol dated 11 November 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 GZPP.

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

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

1.1. Objectives, Endpoints, and Estimands

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

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

1.2. Study Design

Study GZPP is an open-label, nonrandomized, fixed-sequence, 1 period, single-arm, drug-drug interaction study in healthy participants. The purpose of this study is to measure the PK parameters of orforglipron in the absence or presence of quinidine. Quinidine will be administered in this study to serve as an inhibitor of P-glycoprotein transport. To assess the extent to which quinidine inhibits CYP3A4 metabolism, the PK parameters of midazolam and 1-hydroxymidazolam will be assessed when coadministered with quinidine. To assess the extent to which quinidine inhibits OATP1B transport, the PK parameters of coproporphyrin-1 will be assessed when coadministered with quinidine.

Study details are as follows:

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

Study population

Participants will

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

Number of participants

Approximately 28 participants will be enrolled such that approximately 20 evaluable participants will complete the study.

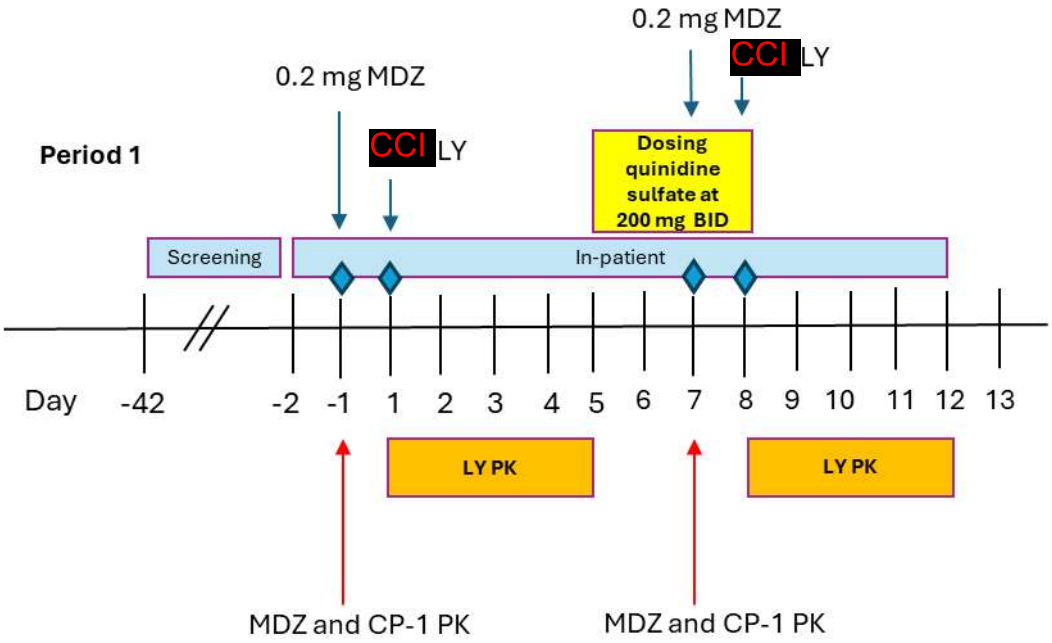
Intervention groups and duration

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

Participants will receive the following study interventions while resident in the clinical research unit:

- Day -1: 0.2-mg midazolam orally alone
- Day 1: CCI orforglipron orally alone
- Days 5 to 8: 200-mg quinidine twice daily orally
- Day 7: 0.2-mg midazolam coadministered with quinidine, and
- Day 8: CCI of orforglipron coadministered with quinidine.

Data monitoring committee: No.



Abbreviations: BID = twice daily; CP-1 = coproporphyrin-1; MDZ = midazolam; PK = pharmacokinetics.

Figure GZPP.1.1. Study schema.

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2. Statistical Hypotheses

The hypothesis is to evaluate the effect of quinidine (200 mg twice daily steady state) on the PK of orforglipron (CCI single dose) in healthy participants.

2.1. Multiplicity Adjustment

There is not multiplicity adjustment in this study.

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 dose of study intervention and have evaluable coproporphyrin 1 data according to the intervention they received.

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

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4. Statistical Analyses

4.1. General Considerations

Statistical analysis of Study GZPP 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 the PK analysis set.

Coproporphyrin analyses will be conducted on the Coproporphyrin 1 biomarker set.

Safety analyses will be conducted on the safety analysis set.

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.

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

Summary statistics and statistical analysis could 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 vs. time curves [AUCs], maximum observed drug concentration [C_{max}], and so on), the geometric mean and geometric coefficient of variation (%CV) will also be presented. For categorical data, frequency counts 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, geometric mean ratio (GMR) will be reported in 3 decimal points, and the 90% CI of the GMR will be reported in 4 decimal points. Observed concentration data, for example, C_{max}, will be reported as received. Observed time data, for example time of maximum observed drug concentration (t_{max}), will be reported as received. N values will be reported as whole numbers and percentages will be reported in 1 decimal point. 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 may not have sufficient number of participants or data for presentation. If this occurs, the blank table, figure, and listing 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, 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, adverse events (AEs) leading to discontinuation, and information on the first and last dose.

4.3. Primary Endpoints Analysis

4.3.1. PK Variables

Concentrations of orforglipron will be determined in plasma. PK parameters of orforglipron concentrations in plasma will be calculated. A full list of and definitions of parameters can be found in Section 4.3.3.

4.3.2. Plasma PK Summaries

4.3.2.1. Plasma Concentrations

Plasma concentrations of orforglipron below the quantification 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 will be set to missing. Descriptive statistics (number of participants, arithmetic mean, geometric mean, arithmetic SD, geometric %CV, median, min, and max) will be used to summarize the plasma concentrations by treatment group at each scheduled time point. Concentrations collected outside +/-10% of the scheduled sampling time will be excluded from summaries and flagged in listings. Any time point with less than 2/3 of the observations quantifiable and within the +/-10% sampling window will not have summary statistics presented. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final CSR.

Linear (+SD) and semilogarithmic plots of the arithmetic mean plasma concentrations by scheduled sampling time will be provided by treatment. 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 the same presentation rules as concentration summary tables.

Linear and semilogarithmic plots of the individual plasma concentrations 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 PK Parameters.” The individual plots on the semilogarithmic scale will indicate the start time (Lz_Start) and 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 orforglipron will be estimated by applying noncompartmental methods using Phoenix WinNonlin®. The version used will be documented in the CSR.

After the oral administration of orforglipron (alone or with quinidine), plasma concentrations of orforglipron will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
$AUC_{(0-\infty)}$	ng.h/mL	Area under the concentration vs. time curve from time zero to infinity
$AUC_{(0-t_{last})}$	ng.h/mL	Area under the concentration vs. time curve from time zero to time t, where t is the last time point with a measurable concentration
$\%AUC_{(t_{last}-\infty)}$	%	Percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
C_{max}	ng/mL	Maximum observed drug concentration
t_{max}	h	Time of maximum observed drug concentration
$t_{1/2}$	h	Half-life associated with the terminal rate constant (λ_Z) in noncompartmental analysis
CL/F	L/h	Apparent total body clearance of drug calculated after extravascular administration
V_{SS}/F	L	Apparent volume of distribution at steady state after extravascular administration
V_Z/F	L	Apparent volume of distribution during the terminal phase after extravascular administration

In estimating the PK parameters, BQL values at the beginning of the profile (prior to the first quantifiable concentration) will be set to zero. Missing predose values will also be set to zero. BQL values that occur after the first quantifiable concentration will be set to missing. If an entire concentration-time profile is BQL, then PK parameters cannot be estimated for that profile.

For parameter estimation, actual sampling times (that is, the duration of time between dosing and sampling), rather than scheduled sampling times, will be used. The actual time for the predose sample will be set to zero. If the actual time is missing, the scheduled time relative to dosing will be substituted and flagged.

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 linear-log trapezoidal method will be used for performing the analysis. The parameters based on predicted last quantifiable drug concentration will be reported.

The terminal elimination rate constant will initially be obtained using the Best Fit option. The PK scientist will review the Best Fit selections and adjust to optimize the selections to ensure that no points from the distribution phase are included. Adjustments will ensure to exclude C_{max} and points from the distribution phase and to include at least 3 time points. The number of points included and start and stop times will be included in the Phoenix WinNonlin output but will not be reported or summarized.

Profiles with 4 or fewer post–dose quantifiable values, with less than 3 values near median t_{max} will be excluded from the summary statistics. Descriptive statistics (n, arithmetic mean, geometric mean, arithmetic SD, geometric %CV, median, min, and max) will be used to summarize the calculated PK parameters. For t_{max}, only n, median, min, and max will be presented.

A scatter plot of individual (including mean and median) PK parameters C_{max}, $AUC_{(0\text{-}t_{last})}$ and $AUC_{(0\text{-}\infty)}$ by treatment will be provided.

The following flags will be applied to parameters that meet the predefined criteria from descriptive statistics and inferential analyses.

Table GZPP.4.1. PK Parameter Flag Criteria

Criteria Name	Criteria	Parameters to be Evaluated Using the Criteria
Extrapolation	AUC%Extrap>20%	$AUC_{(0\text{-}\infty)}$, CL, CL/F, V_z, V_z/F, V_{ss}, V_{ss}/F
Regression	Adj Rsq<0.8	$AUC_{(0\text{-}\infty)}$, $t_{1/2}$, CL, CL/F, V_z, V_z/F, V_{ss}, V_{ss}/F

Abbreviations: Adj = adjusted; $AUC_{(0\text{-}\infty)}$ = 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.

Derived parameters that used a flagged parameter in their derivation will also be flagged.

All parameters will be listed by participant, parameters that meet the criteria in Table GZPP.4.1 will be flagged but included in the summary statistics. Upon evaluation of the output, additional sensitivity analyses may be conducted.

If a participant has an AE of vomiting that occurs at or before 2 times the median t_{max} of their dosing group, the parameters will be flagged, and a sensitivity analysis may be performed to determine the effect on the resulting summary statistics.

An in-text PK summary table will be presented in CSR main body, which should include the number of subjects (included in the summary statistics), geometric mean (geometric %CV) for all PK parameters, except for t_{max} (which will report median (range)), and $t_{1/2}$ (which will report geometric mean (range)).

Additional PK parameters may be calculated, or additional analysis may be performed, if necessary. Exceptions or special handling of data will be clearly documented within the final CSR.

4.3.4. Primary Analysis for Primary Endpoint

PK parameter estimates will be evaluated to delineate the effects of quinidine onorforglipron.

The PK parameters C_{max}, $AUC_{(0\text{-}t_{last})}$, and $AUC_{(0\text{-}\infty)}$ for orforglipron when administered alone (reference), and in the presence of quinidine (test), will be compared using a linear mixed-effect model. The parameters will be log-transformed prior to analysis. The model will include treatment as a fixed effect and participant as a random effect. The least squares mean for reference and test, 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 for reference and test, GMR between test and reference, and corresponding 90% CIs. Quinidine's effect on orforglipron PK will be assessed by examining the 90% CIs for the ratio of geometric least squares means of orforglipron coadministered with quinidine 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. Secondary Endpoints Analysis

4.4.1. Midazolam PK Analysis

Concentrations of midazolam and 1-hydroxymidazolam will be collected in plasma. PK parameters of midazolam and 1-hydroxymidazolam concentrations in plasma will be calculated in the same manner as orforglipron.

After the oral administration of midazolam (alone or with quinidine), plasma concentrations of midazolam and 1′-hydroxymidazolam will be used to determine the following PK parameters where possible.

Parameter	Units	Definition
$AUC_{(0-\infty)}$	ng.h/mL	Area under the concentration vs. time curve from time zero to infinity
$AUC_{(0-t_{last})}$	ng.h/mL	Area under the concentration vs. time curve from time zero to time t, where t is the last time point with a measurable concentration
$\%AUC_{(t_{last}-\infty)}$	%	Percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
C_{max}	ng/mL	Maximum observed drug concentration
t_{max}	h	Time of maximum observed drug concentration
$t_{1/2}$	h	Half-life associated with the terminal rate constant (λ_z) in noncompartmental analysis
CL/F	L/h	Apparent total body clearance of drug calculated after extravascular administration (midazolam only)
V_z/F	L	Apparent volume of distribution during the terminal phase after extravascular administration (midazolam only)
MR(AUC)	NA	Metabolite ratio based upon $AUC_{(0-\infty)}$ (metabolite only)

Abbreviation: NA: Not applicable.

An in-text PK summary table will be presented in CSR main body, which should include the number of subjects (included in the summary statistics), geometric mean (geometric %CV) for all PK parameters, except for t_{max} (which will report median (range)), and $t_{1/2}$ (which will report geometric mean (range)).

4.4.2. Statistical Analyses

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

4.5. Exploratory Endpoint Analysis

4.5.1. 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.

The following PK parameters will be calculated for coproporhyrin 1.

Parameter	Units	Definition
$AUC_{(0\text{-}t_{last})}$	pg.h/mL	Area under the concentration vs. time curve from time zero to time t, where t is the last time point with a measurable concentration
$AUC_{(0\text{-}24)}$	pg.h/mL	Area under the concentration vs. time curve from time zero to 24 hours postdose
C_{max}	pg/mL	Maximum observed drug concentration
t_{max}	h	Time of maximum observed drug concentration

AUC of coproporphyrin 1 will be calculated with linear trapezoidal linear interpolation method. All parameters will be summarized using descriptive statistics.

An in-text PK summary table will be presented in CSR main body, which should include the number of subjects (included in the summary statistics), geometric mean (geometric %CV) for all PK parameters, except for t_{max} (which will report median (range)).

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

4.5.1.1. Coproporphyrin 1 Biomarker Statistical Analyses

The log-transformed 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 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, GMR between test and reference treatments, and corresponding 90% CIs.

4.6. Safety Analyses

4.6.1. Extent of Exposure

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

4.6.2. Protocol Deviation

Important protocol deviations that occur during Study GZPP will be listed if data are available.

4.6.3. Adverse Events

A treatment-emergent AE (TEAE) is defined as an AE, which occurs after the first dose of study intervention, or which is present prior to dosing and increase in severity after the first dose.

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

A non-TEAE is defined as an AE that 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 the severity of former or with lower severity.

Where changes in severity are recorded in the case report form, only the most severe will be used in the summary tables.

TEAEs will be summarized by days (screening to Day -2, Day -1, Day 1-6, Day 7, Day 8 to end of study) severity, and relationship to the study drug. The frequency (the number of TEAEs, serious AEs, the number of participants experiencing an TEAE and serious AE, and the percentage of participants experiencing TEAEs) will be summarized by decreasing frequency within each system organ class and preferred term, as defined by the Medical Dictionary for Regulatory Activities Version 27.1.

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. For events occurring on the day of first taking study medication, the case report form-collected flag will be used to determine whether the event was pre- versus posttreatment. If at any point multiple severity levels are available, the worst level will be taken into consideration.

4.6.3.1. Serious AE and Safety Topics

Serious AEs will be listed.

The following are the AEs of special interest and other safety topics for the study.

- severe or serious gastrointestinal AEs of nausea, constipation, vomiting, and diarrhea
    - Preferred terms of: Diarrhoea (10012735), Nausea (10028813), Vomiting (10047700), Frequent bowel movements (10017367), Vomiting projectile (10047708), Constipation (10010774), Infrequent bowel movement (10059158), and Faeces hard (10016101)
- Pancreatitis
    - Acute pancreatitis standardized MedDRA queries (SMQ) Narrow terms only (20000022)
    - Pancreatitis chronic preferred term (10033649)
    - major adverse cardiovascular events
    - Myocardial infarction (SMQ) Narrow terms only (20000047)
    - Other ischaemic heart disease (SMQ) Narrow terms only (20000168)
    - Cardiac failure (SMQ) Narrow terms only (20000004)
    - Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ) Narrow terms only (20000166)
    - Haemorrhagic central nervous system vascular conditions (SMQ) Narrow terms only (20000064)
    - Ischaemic central nervous system vascular conditions (SMQ) Narrow terms only (20000063), and

    - Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic (SMQ) Narrow terms only (20000165)
- arrhythmias and cardiac conduction disorders
    - Arrhythmia-related investigations, signs and symptoms SMQ Narrow and Broad terms (20000051)
    - Supraventricular tachyarrhythmia SMQ Narrow and Broad terms (20000057)
    - Tachyarrhythmia terms, nonspecific SMQ Narrow terms only (20000164)
    - Ventricular tachyarrhythmia SMQ Narrow terms only (20000058)
    - Conduction defects SMQ Narrow terms only (20000056), and
    - Cardiac conduction disorders HLT (10000032)
- hepatic disorder
    - Liver-related investigations, signs and symptoms SMQ Narrow and Broad terms (20000008)
    - Cholestasis and jaundice of hepatic origin SMQ Narrow and Broad terms (20000009)
    - Hepatitis, non–infectious SMQ Narrow and Broad terms (20000010)
    - Hepatic failure, fibrosis and cirrhosis and other liver damage SMQ Narrow and Broad terms (20000013), and
    - Liver-related coagulation and bleeding disturbances SMQ Narrow terms only (20000015)
- hypoglycemia
    - Hypoglycaemia SMQ Narrow terms only (20000226)
- hypotension, orthostatic hypotension, and syncope
    - Preferred terms of: Diastolic hypotension (10066077), Hypotension (10021097), Hypotensive crisis (10083659), Orthostatic hypotension (10031127), Blood pressure ambulatory decreased (10005731), Blood pressure decreased (10005734), Blood pressure diastolic decreased (10005737), Blood pressure orthostatic decreased (10053356), Blood pressure systolic decreased (10005758), Mean arterial pressure decreased (10026983), Blood pressure orthostatic (10053352), Dizziness (10013573), Presyncope (10036653), Syncope (10042772), Drop attacks (10013643), and Loss of consciousness (10024855)
- acute kidney injury and chronic kidney disease
    - Acute renal failure SMQ Narrow (20000003), and
    - Chronic kidney disease SMQ Narrow (20000213)
- gallbladder and biliary tract disorders
    - Gallbladder-related disorders SMQ Narrow (20000124)
    - Biliary tract disorders SMQ Narrow (20000125), and
    - Gallstone-related disorders SMQ Narrow (20000127)
- hypersensitivity reactions
    - Anaphylactic reaction SMQ Narrow (20000021)
    - Angioedema SMQ Narrow (20000024), and
    - Hypersensitivity SMQ Narrow (20000214).

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

4.6.4. Concomitant Medications

Concomitant medications will be coded using the WHO drug dictionary. Concomitant medications will be included in the patient narrative.

4.6.5. Physical Examinations

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

4.6.6. Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) 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.

4.6.7. Electrocardiograms

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

4.6.8. Clinical Laboratory Parameters

Listings for any clinical chemistry, hematology, serology, and urinalysis including local laboratory, if available, with values outside the reference ranges 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.

4.6.9. Hepatic Monitoring

If a participant experiences elevated laboratory parameters, as detailed in Section 8.2.5. of Protocol GZPP, additional tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in Protocol GZPP. 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 computed 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).

4.6.10. Other Assessments

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

4.7. Other Analyses

4.7.1. Subgroup Analyses

No subgroup analyses are planned.

4.8. Interim Analyses

No interim analyses are planned.

4.9. Changes to Protocol-Planned Analyses

There were no changes to the protocol-planned analyses.

5. Sample Size Determination

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

6. Supporting Documentation

Not applicable.

7. References

Not applicable.

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