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The GlaxoSmithKline group of companies 206224

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for 206224: An open-label, single sequence crossover, drug interaction study to investigate the effect of linerixibat (GSK2330672) on plasma concentrations of obeticholic acid and conjugates in healthy participants
Compound Number	:	GSK2330672
Effective Date	:	07-FEB-2020

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for original protocol of 206224 (GSK Document Number 2019N406556_00).
- This RAP is intended to describe the analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

Author's Name and Functional Area:

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RAP Team Approvals:

Approver	Date	Approval Method
PPD Clinical Development Director, Clinical Science (Respiratory & Speciality)		
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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

Revision Chronology:		
2019N406556_00	05-JUN-2019	Original

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There have been no changes or deviations to the originally planned statistical analysis specified in the protocol.

2.2. Study Objective(s) and Endpoint(s)

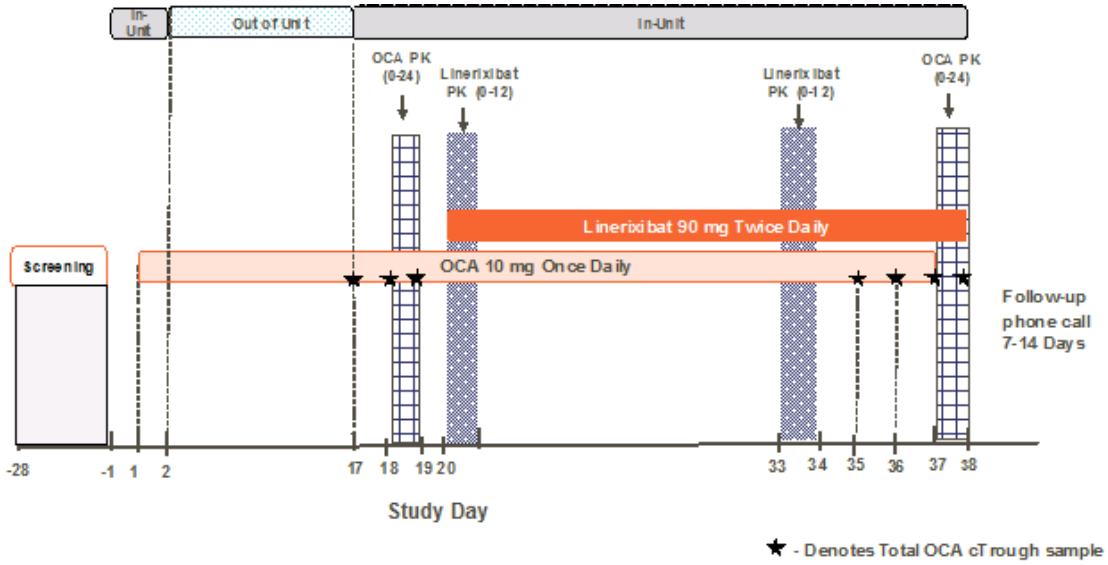
Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
Part A: To assess the effect of oral Linerixibat on the plasma pharmacokinetics of total-OCA (summation of OCA and taurine (tauro-OCA) and glycine (glyco-OCA) conjugates) [Part A Regimen]	• Steady state AUC(0-t), AUC(0-24), Cmax, and Ctrough for total-OCA plasma concentrations
Part B (optional): To assess the effect of oral Linerixibat on the plasma pharmacokinetics of total-OCA (summation of OCA and taurine (tauro-OCA) and glycine (glyco-OCA) conjugates) when Linerixibat and OCA administration is separated by 12 hours or an alternative dose or dosing regimen	• Same as Part A
Secondary Objectives	**Secondary Endpoints**
Part A: To assess the effect of oral Linerixibat on the additional measures of plasma pharmacokinetics of total-OCA (summation of OCA and taurine (tauro-OCA) and glycine (glyco-OCA) conjugates) [Part A Regimen]	• Tmax for total-OCA and assessment of steady state using Ctrough of total-OCA, AUC(0-t), AUC(0-24), Cmax, Ctrough, and Tmax for OCA, tauro-OCA, and glyco-OCA plasma concentrations

Objectives	Endpoints
Part B (optional): To assess the effect of oral Linerixibat on the additional measures of plasma pharmacokinetics of total-OCA (summation of OCA and taurine (tauro-OCA) and glycine (glyco-OCA) conjugates) when Linerixibat and OCA administration is separated by 12 hours or an alternative dose or dosing regimen	• Same as Part A
Part A & Part B (optional): To evaluate the safety and tolerability of Linerixibat and OCA administered according to the dosing schedule in healthy participants To assess repeat dose Linerixibat plasma pharmacokinetics after Day 1 (Study Day 20) and Day 14 (Study Day 33)	• Adverse events, Electrocardiogram, vital signs, and clinical laboratory tests • AUC(0-t), AUC(0-12), Cmax, Tmax, and accumulation (Linerixibat Day 1 (Study Day 20) and Day 14 (Study Day 33))

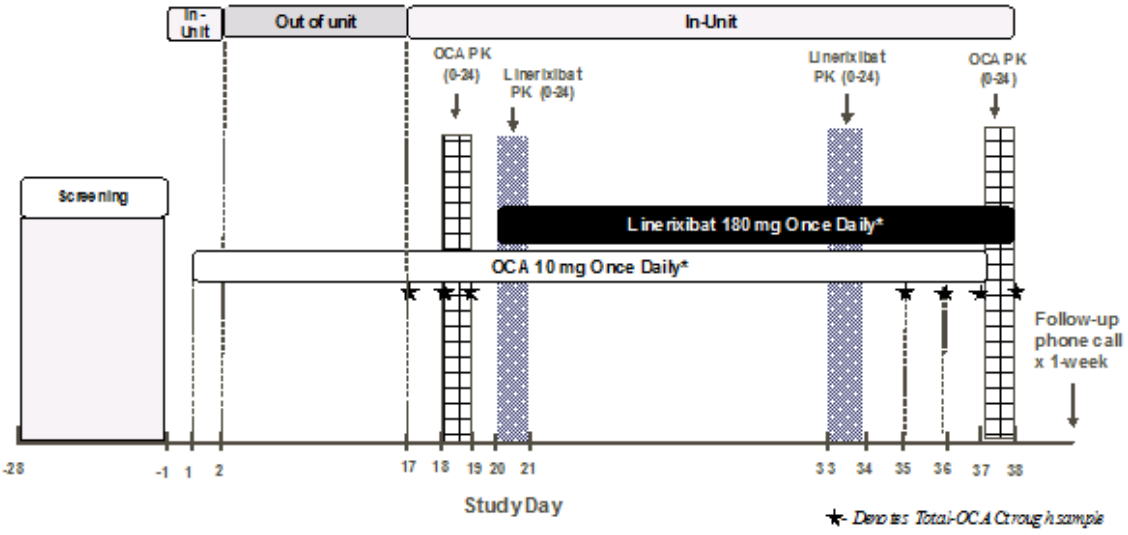
2.3. Study Design

Overview of Study Design and Key Features

Part A Study Design



Part B (Optional) Study Design



Design Features	• This will be a one part (with optional second part) open-label, single sequence, crossover, drug interaction study to investigate the effect of Linerixibat (GSK2330672) on plasma concentrations of Obeticholic acid (OCA) and OCA conjugates in healthy participants.

Overview of Study Design and Key Features	
	• The study will be conducted in a single research centre specialized in the conduct of Phase 1 clinical trials. • No washout period is required between dosing in each session. • A maximum of 19 participants in Part A and a planned 19 participants in Part B (contingent upon analysis of Part A) will be enrolled to study intervention such that approximately 15 participants complete Part A and approximately 15 participants complete Part B of the study (if it is conducted). • The total duration of study participation in Part A would be up to 52 days exclusive of the screening visit (up to 28-35 days). If Part B is conducted, the total study participation would be up to 52 days. • Participants will stay in the clinical unit for 2 nights (Day -1 to Day 2) before being discharged for 15 days of home dosing (Day 2 to Day 16). Participants will then return to the clinical unit for a further 21 overnight stays (Day 17 to Day 38). • If a clinically important OCA/Linerixibat drug-drug interaction (DDI) (average Ctrough of total-OCA < 20 ng/mL) is detected using this definition, the sponsor may consider the merit of conducting a follow-up study (Part B) investigating an alternative 180 mg once daily morning dosing of Linerixibat separated by 12 hours from OCA (once daily) dosed in the evening. • The dose of Linerixibat and/or OCA in the contingent Part B may be adjusted, prior to the initiation, should the Part A analysis suggest different doses of either study drug would be useful to further characterize any potential DDI.
Dosing	Part A: • OCA will be dosed at 10 mg once-daily (QD) for a total of 37 continuous days (Study Day 1 through to the afternoon of Day 37). • Linerixibat will be dosed at 90 mg twice-daily (BID) for total of 18.5 days (Study Day 20 to the morning of Day 38). • The morning dose of Linerixibat and the afternoon dose of OCA should be separated by approximately 4 hours. Part B: • OCA will be dosed at 10 mg once-daily (QD) for a total of 37 continuous days (Study Day 1 through to the afternoon of Day 37).

Overview of Study Design and Key Features	
	• Linerixibat will be dosed at 180 mg once-daily (QD) for total of 18.5 days (Study Day 20 to the morning of Day 38). • Separation of OCA and Linerixibat dosing to be determined.
Treatment Assignment	• This is an open label, single sequence study. All participants will receive the same treatment assignment in Part A and all participants will receive the same treatment assignment in Part B (depending on the analysis of Part A).
Interim Analysis	• No interim analysis is planned for this study.

2.4. Statistical Hypotheses / Statistical Analyses

No formal statistical hypothesis will be tested.

This study is designed to assess the effect of Linerixibat (GSK2330672) on plasma concentrations of OCA and conjugates. The effect will be determined by assessing the primary endpoints (steady state AUC (0-t), AUC(0-24), Cmax, and Ctrough on Day 38 for total-OCA plasma concentrations) and secondary endpoints (Ctrough for assessing steady state of total-OCA, steady state Tmax of total-OCA and steady state AUC(0-t), AUC(0-24), Cmax, Ctrough, and Tmax of OCA, tauro-OCA, and glyco-OCA) during dosing of OCA with and without Linerixibat.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis is planned for this study.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.

Analyses outlined in this RAP are for Part A only and may be updated if Part B is performed.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who sign the ICF. This will be the population for reporting screened population data.	• Study Population
All Participants	• All participants who take at least 1 dose of study intervention. Participants will be analyzed according to the treatment they received. This will be the population for reporting safety and study population data.	• Safety and Study Population
Pharmacokinetic Concentrations	• All participants for whom pharmacokinetic concentrations are reported.	• PK Concentration
Pharmacokinetic Parameters	• All participants for whom pharmacokinetic parameters are derivable.	• PK Analysis

Refer to Appendix 12: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (05-AUG-2019, V1).

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.

- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

The primary focus of the statistical analysis is to estimate the effect of repeat oral doses of Linerixibat on the pharmacokinetics of repeat oral doses of OCA. Thus, the primary comparison of interest is OCA 10 mg QD + Linerixibat 90 mg BID relative to OCA 10 mg QD for each of the pharmacokinetic endpoints summarized on day 38.

Treatment Description	
Code [Use for treatment in displays]	**Description**
OCA	Ocaliva 10 mg QD
OCA+Linerixibat	Ocaliva 10 mg QD + Linerixibat 90 mg BID

Note: Period 1 is defined as dosing of OCA alone.
Period 2 is defined as dosing of OCA and Linerixibat together.
This note will be used in displays where applicable.

5.2. Baseline Definitions

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening	Day -1	
Safety			
Vital Signs	X [1]	X [1]	Day -1 [2]
Laboratory safety tests	X	X	Day -1 [2]
12-lead ECG	X[1]	X[1]	Day -1 [2]

[1] Taken in triplicate.
[2] If Day-1 is missing then Screening will be used as baseline.
If Day-1 and Screening are both missing, then Baseline will be considered missing.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. Multicentre Studies

This is a single centre study.

5.3.1. Covariates and Other Strata

There are no other strata planned.

5.3.2. Examination of Subgroups

There are no subgroups planned for analysis.

5.4. Multiple Comparisons and Multiplicity

No adjustment for pre-planned multiple comparisons are planned.

5.5. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
14.3	Appendix 3: Assessment Windows
14.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
14.5	Appendix 5: Data Display Standards & Handling Conventions
14.5	Appendix 6: Derived and Transformed Data
14.7	Appendix 7: Reporting Standards for Missing Data
14.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the "Screened" and "All Participants" population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, pharmacokinetics, and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 12: List of Data Displays.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

Not applicable.

7.1.2. Summary Measure

Not applicable.

7.1.3. Population of Interest

Not applicable.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

Not applicable.

7.1.5. Statistical Analyses / Methods

Not applicable.

7.1.5.1. Statistical Methodology Specification

Not applicable.

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

Not applicable.

7.2.2. Summary Measure

Not applicable.

7.2.3. Population of Interest

Not applicable.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

Not applicable.

7.2.5. Statistical Analyses / Methods

Not applicable.

7.2.5.1. Statistical Methodology Specification

Not applicable.

7.3. Exploratory Efficacy Analyses

Not applicable.

8. SAFETY ANALYSES

No formal statistical analysis of safety data is planned.

8.1. Adverse Events Analyses

Adverse events including adverse events (AEs), Serious (SAEs) and other significant AEs will be listed and summarized by study phase (Pre-study/screening, OCA alone, OCA+Linerixibat, and follow up) based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 12: List of Data Displays.

8.2. Adverse Events of Special Interest Analyses

No adverse events of special interest specified in the protocol. Not applicable.

8.3. Clinical Laboratory Analyses

Clinical laboratory evaluations will be summarized, and any values of potential clinical concern will be listed. The details of the planned displays are in Appendix 12: List of Data Displays.

8.4. Other Safety Analyses

Other safety measures will be listed and summarized. The details of the planned displays are presented in Appendix 12: List of Data Displays.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

9.1.1. Endpoint / Variables

Steady state AUC (0-t), AUC (0-24), Cmax, and average Ctrough for total-OCA plasma concentrations.

Total-OCA is calculated by summing OCA and the adjusted concentrations of its two metabolites using the following formula:

Total-OCA = OCA + (0.8805 x glyco-OCA) + (0.7969 x tauro-OCA)

9.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 14.5.3 Reporting Standards for Pharmacokinetic)

9.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of *Phoenix® WinNonlin®*. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. Will be calculated for total-OCA.
AUC(0-24)	Area under the concentration-time curve from time zero to the end of the dosing interval (24 hours), using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. Will be calculated for total-OCA.
Cmax	Maximum observed concentration, determined directly from the concentration-time data. Will be calculated for total-OCA.
Average Ctrough	Average concentration at the end of a dosing interval (i.e., average for Days 16, 17, and 18, and average for 34, 35, 36, and 37). Will be determined by the average of Ctrough of total-OCA from Days 17, 18 and 19 for dosing of OCA alone and by the average Ctrough of total-OCA from Days 35, 36, 37, and 38 for dosing of OCA+Linerixibat.

NOTES:

- Additional parameters may be included as required.

9.1.2. Summary Measure

See section 9.1.5 for summary measures.

9.1.3. Population of Interest

The primary pharmacokinetic analyses will be based on the Pharmacokinetic Parameters population, unless otherwise specified.

9.1.4. Strategy for Intercurrent (Post-Randomization) Events

PK parameters will not be imputed if data is missing.

9.1.5. Statistical Analyses / Methods

After log transforming PK parameters AUC(0-t), AUC(0-24), and Cmax for total-OCA, they will be analyzed by a mixed effect model by fitting a fixed effect term for treatment regimen (OCA or OCA+Linerixibat) and treating participant as a random effect. Point estimates for each treatment regimen, the difference between the treatment regimens, and 90% confidence interval (CI) for the difference between the treatment regimens will be constructed. These point estimates, difference, and CI will then be back-transformed exponentially to obtain point estimates, a ratio, and 90% CI for the ratio of OCA+Linerixibat: OCA.

The underlying distributional assumptions involved in the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. If the assumptions are seriously violated, then alternative statistical methods will be considered.

Estimates of within-subject variability (CVw) for the PK parameters will also be calculated using the following equation:

$$CVw(\%) = SQRT (\exp (MSE) - 1) \times 100$$

where MSE is the residual mean squared error from the model.

Descriptive statistics (n, arithmetic mean, associated 95% CI, standard deviation, minimum, median, maximum) will be calculated for all PK parameters by OCA and OCA+Linerixibat. Geometric means, associated 95% CI, and between-subject variability (CVb) for AUC(0-t), AUC(0-24), Cmax, and average Ctrough will be calculated for each treatment regimen where:

$$\text{Geometric mean} = \exp(\text{mean on } \log_e \text{ scale})$$

and

$$CVb(\%) = SQRT (\exp (SD^2) - 1) \times 100$$

where SD is the standard deviation on the log scale.

In addition to this assessment, the average Ctrough parameter for total-OCA of the OCA+Linerixibat treatment regimen will be log transformed and the mean and 90% CI will be calculated. This mean and 90% CI will then be back-transformed and will be compared to the clinically important threshold of 20 ng/mL. If the lower bound of the 90% CI is < 20 ng/mL then this will be considered a clinically important DDI. If there is no DDI shown in the PK parameters in OCA or its metabolites but there is still a reduction at steady state in the mean of average Ctrough for total-OCA so that the lower bound of the 90% CI is < 20 ng/mL this will also be considered a clinically important DDI.

If there is a DDI shown among the PK parameters for OCA and its metabolites but the lower bound of the 90% CI of the mean of average Ctrough of total-OCA ≥ 20 ng/mL then it will be concluded that there is a DDI, but the findings are not clinically important.

In the unexpected and unlikely event that total-OCA, in the absence of Linerixibat, falls below 20 ng/mL, the threshold of 20 ng/mL will be re-evaluated, and the results will be reviewed by the study team for compliance issues and AEs.

If a clinically important OCA/Linerixibat DDI is detected using this definition the sponsor may consider the merit of conducting a follow-up study (**Part B**) investigating an alternative 180 mg once daily morning dosing of Linerixibat separated by 12 hours from OCA once daily, dosed in the evening. Importantly, the dose of Linerixibat and/or OCA in the contingent Part B may also be adjusted, prior to the initiation, should the Part A analysis suggest different doses of either study drug would be useful to further characterize any potential DDI. The decision to conduct **Part B** will require careful assessment of PK parameters measured and analyzed in Part A. Based on the full analysis of the results from Part A the conclusion must be reached that alternative once-daily Linerixibat dosing separated by 12 hours and/or adjustment of study drug doses(s) in Part B has the potential to reduce the DDI observed or otherwise further characterize any potential DDI observed in Part A.

9.1.5.1. Statistical Methodology Specification

The following pharmacokinetic statistical analyses will only be performed if sufficient data is available (i.e. if participants have well defined plasma profiles).

Endpoint / Variables
• Log transformed AUC(0-t), AUC(0-24), and Cmax for total-OCA plasma concentrations. • Log transformed average Ctrough for total-OCA plasma concentration.
Model Specification
• PK parameters will be analyzed for the Pharmacokinetic Parameters Population using a mixed effect model.

• The following covariates will be in the model: treatment regimen (OCA or OCA+Linerixibat) as a fixed effect and subject as a random effect. • Models will be fitted for log(AUC(0-t)), log(AUC(0-24)), and log(Cmax). • The variance-covariance matrix will be assumed unstructured. • Kenward Roger (KR) method will be used for calculating degrees of freedom. If the analysis cannot converge using the KR method, then the residual method will be used instead. • 90% CI will be calculated for the difference between OCA+Linerixibat and OCA. • The point estimates, the difference, and associated 90% CI will then be back-transformed to provide point estimates, a ratio, and 90% CI for the ratio on the original scale. • Model will not include log(average Ctrough) as a dependent variable. Rather, a 90% CI will be calculated for mean log(average Ctrough) for OCA+Linerixibat, which will then be back-transformed and compared to the threshold of 20 ng/mL.
Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
Model Results Presentation
• The N, the mean of each treatment regimen, the estimate of the ratio between treatment regimens, the 90% CI, and the CVw(%) will be presented for AUC(0-t), AUC(0-24), and Cmax. • The mean of average Ctrough and the associated 90% CI will be presented for the OCA+Linerixibat treatment regimen to compare to 20 ng/mL.
Subgroup Analyses
• Not applicable.
Sensitivity and Supportive Analyses
• Not applicable.

9.2. Secondary Pharmacokinetic Analyses

9.2.1. Endpoint / Variables

Tmax, Tlast, Ctrough, and average Ctrough of total-OCA; AUC(0-t), Tlast, AUC(0-24), Cmax, average Ctrough, and Tmax for OCA, tauro-OCA, and glyco-OCA plasma concentrations; AUC(0-t), Tlast, AUC(0-12), Cmax, Tmax, and accumulation ratios RAUC and RCmax for Linerixibat.

9.2.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 14.5.3 Reporting Standards for Pharmacokinetic)

9.2.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of *Phoenix® WinNonlin®*. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. Will be calculated for OCA, tauro-OCA, glyco-OCA, and Linerixibat.
AUC(0-24)	Area under the concentration-time curve from time zero to the end of the dosing interval (24 hours), using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. Will be calculated for OCA, tauro-OCA, and glyco-OCA.
AUC(0-12)	Area under the concentration-time curve from time zero to the end of the dosing interval (12 hours), using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. Will be calculated for Linerixibat.
Cmax	Maximum observed concentration, determined directly from the concentration-time data. Will be calculated for OCA, tauro-OCA, glyco-OCA, and Linerixibat.
Ctrough	Concentration at the end of a dosing interval. Will be calculated for total-OCA.
Average Ctrough	Average concentration at the end of a dosing interval (i.e., average for Days 16, 17, and 18, and average for 34, 35, 36, and 37). Will be determined by the average Ctrough from Days 17, 18 and 19 for dosing of OCA alone and by the average Ctrough from Days 35, 36, 37, and 38 for dosing of

Parameter	Parameter Description
	OCA+Linerixibat. Will be calculated for total-OCA, OCA, tauro-OCA, and glyco-OCA.
Tmax	Time to reach Cmax, determined directly from the concentration-time data. Will be calculated for total-OCA, OCA, tauro-OCA, glyco-OCA, and Linerixibat.
Tlast	Time of the last measurable concentration in the dosing interval. Will be calculated for total-OCA, OCA, tauro-OCA, glyco-OCA, and Linerixibat.
RAUC	The area under the curve AUC(0-12) on Day 14 of Linerixibat dosing divided by the area under the curve over the initial dosing interval on Day 1 of Linerixibat dosing. Will be calculated for Linerixibat.
RCmax	The maximum concentration in the dosing on Day 14 of Linerixibat dosing divided by the maximum concentration during the initial dosing interval on Day 1 of Linerixibat dosing. Will be calculated for Linerixibat.

NOTES:

- Additional parameters may be included as required.

9.2.2. Summary Measure

See section 9.2.5 for summary measures.

9.2.3. Population of Interest

The secondary pharmacokinetic analyses will be based on the Pharmacokinetic Parameters population, unless otherwise specified.

9.2.4. Strategy for Intercurrent (Post-Randomization) Events

PK parameters will not be imputed if data is missing.

9.2.5. Statistical Analyses / Methods

After log transforming PK parameters average Ctrough for total-OCA, and AUC(0-t), AUC(0-24), Cmax, and average Ctrough for OCA, tauro-OCA, and glyco-OCA, they will be analyzed by a mixed effect model by fitting a fixed effect term for treatment regimen (OCA or OCA+Linerixibat) and treating participant as a random effect. Point estimates for each treatment regimen, the difference between the treatment regimens, and 90% CI for the difference between the regimens will be constructed. These point estimates, differences, and CI will then be back-transformed exponentially to obtain point estimates, a ratio, and 90% CI for the ratio of OCA+Linerixibat: OCA for OCA, tauro-OCA, and glyco-OCA.

The underlying distributional assumptions involved in the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. If the assumptions are seriously violated, then alternative statistical methods will be considered.

Estimates of CVw(%) for the PK parameters will also be calculated.

Steady state of the OCA and OCA+Linerixibat treatment regimens will be summarized and assessed graphically using pre-dose Ctrough from Days 17, 18, and 19 and Days 35, 36, 37, and 38 for total-OCA, OCA, glyco-OCA, and tauro-OCA.

Descriptive statistics (n, arithmetic mean and associated 95% CI, standard deviation, minimum, median, maximum) will be calculated for all PK parameters by OCA, tauro-OCA, and glyco-OCA for each treatment regimen. Geometric means, associated 95% CI, and CVb(%) for AUC(0-t), AUC(0-24), Cmax, and average Ctrough of OCA and its metabolites will be calculated for each treatment regimen.

Tmax and Tlast will be summarized using descriptive statistics by total-OCA, OCA, glyco-OCA, and tauro-OCA for each treatment regimen.

The PK parameters, including AUC(0-t), Tlast, AUC(0-12), Cmax, and Tmax for Linerixibat will be summarized using descriptive statistics for Day 20 and Day 33. The PK parameters RAUC and RCmax for Linerixibat will be summarized using descriptive statistics.

9.2.5.1. Statistical Methodology Specification

Endpoint / Variables
• Tmax and Tlast for total-OCA plasma concentrations. • Ctrough of total-OCA plasma concentrations for assessment of steady state and log transformed average Ctrough of total-OCA for analysis. • Tmax, Tlast, and log transformed AUC(0-t), AUC(0-24), Cmax, and average Ctrough for OCA, tauro-OCA, and glyco-OCA plasma concentrations.
Model Specification
• PK parameters will be analyzed for the Pharmacokinetic Parameters Population using a mixed effect model. • The following covariates will be in the model: regimen (OCA or OCA+Linerixibat) as a fixed effect and subject as a random effect. • Models will be fitted for log(average Ctrough) for total-OCA and log(AUC(0-t)), log(AUC(0-24)), log(Cmax), and log(average Ctrough) for OCA and its metabolites by treatment regimen. • The variance-covariance matrix will be assumed unstructured.

• Kenward Roger (KR) method will be used for calculating degrees of freedom. If the analysis cannot converge using the KR method, then the residual method will be used instead. • 90% CI will be calculated for the difference between OCA+Linerixibat and OCA. • The point estimates, the difference, and associated 90% CI will then be back-transformed to provide point estimates, a ratio, and 90% CI for the ratio on the original scale.
Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
Model Results Presentation
• The N, the mean of each treatment regimen, the estimate of the ratio between treatment regimens, the 90% CI, and the CVw(%) will be presented for average Ctrough of total-OCA. • Ctrough of total-OCA for each time point will be presented by each treatment regimen by visual display. • The N, the mean of each treatment regimen, the estimate of the ratio between treatment regimens, the 90% CI, and the CVw(%) will be presented for AUC(0-t), AUC(0-24), Cmax, and average Ctrough by OCA, tauro-OCA, and glyco-OCA.
Subgroup Analyses
• Not applicable.
Sensitivity and Supportive Analyses
• Not applicable.

9.3. Exploratory Pharmacokinetic Analyses

Not applicable.

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

Linerixibat concentration time data may be used and reported in a separate analysis under a separate POPPK RAP and report.

10.1. Statistical Analyses / Methods

Not applicable.

11. PHARMACODYNAMIC AND BIOMARKER ANALYSES

11.1. Primary Pharmacodynamic and Biomarker Analyses

11.1.1. Endpoint / Variables

Not applicable.

11.1.2. Summary Measure

Not applicable.

11.1.3. Population of Interest

Not applicable.

11.1.4. Strategy for Intercurrent (Post-Randomization) Events

Not applicable.

11.1.5. Statistical Analyses / Methods

Not applicable.

11.1.5.1. Statistical Methodology Specification

Not applicable.

11.2. Secondary Pharmacodynamic and Biomarker Analyses

11.2.1. Endpoint / Variables

Not applicable.

11.2.2. Summary Measure

Not applicable.

11.2.3. Population of Interest

Not applicable.

11.2.4. Strategy for Intercurrent (Post-Randomization) Events

Not applicable.

11.2.5. Statistical Analyses / Methods

Not applicable.

11.2.5.1. Statistical Methodology Specification

Not applicable.

11.3. Exploratory Pharmacodynamic and Biomarker Analyses

Not applicable.

12. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

Not applicable.

12.1. Statistical Analyses / Methods

Not applicable.

13. REFERENCES

Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Clinical Pharmacology and Biopharmaceutics Review(s) for Obeticholic Acid for the treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as a monotherapy in adults unable to tolerate UDCA. Last Updated 2016. Website Link: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207999Orig1s000ClinPharmR.pdf

GlaxoSmithKline Document Number 2019N406556_00. An open-label, single sequence crossover, drug interaction study to investigate the effect of linerixibat (GSK2330672) on plasma concentrations of obeticholic acid and conjugates in healthy participants, 05-JUN-2019.

GUI_51487 (5.0) Non-Compartmental Analysis of Pharmacokinetic Data, CPMS Global.

SOP_54838: Development, Review & Approval of Reporting & Analysis Plan, Global; GSK.

14. APPENDICES

14.1. Appendix 1: Protocol Deviation Management and Definitions for All Participants Population

14.1.1. Exclusions from All Participants Population

A participant meeting any of the following criteria will be excluded from the All Participants population:

Number	Exclusion Description
01	Any active dermatologic disorder leading to or with the potential to cause pruritus or a recent history of unexplained clinically significant itching locally or generally within the prior 3 months.
02	Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) and/or confirmed hepatocellular carcinoma or biliary cancer.
03	Participants with a history of cholecystectomy.
04	Current symptomatic cholelithiasis or inflammatory gall bladder disease
05	Significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data.
06	Any clinically relevant abnormality identified at the screening medical assessment (physical examination/medical history) clinical laboratory tests, or 12-lead ECG.
07	Current episode, recent history (within 1 month of screening visit), or chronic history of clinically significant diarrhea.
08	Lymphoma, leukaemia, 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.
09	Any current medical condition (e.g. psychiatric disorder, senility, dementia, or other condition), clinical or laboratory abnormality, or examination finding that the investigator considers would put the participant at unacceptable risk, which may affect study compliance or prevent understanding of the aims or investigational procedures or possible consequences of the study.
10	Regular use of known drugs of abuse or history of drug abuse or dependence within 6 months of the study.
11	Regular alcohol consumption within 6 months prior to the study defined as an average weekly intake of >14 units for females and >21 units for males. One unit is equivalent to 8 g of alcohol: a glass (~240 mL) of beer, 1 small glass (~100 mL) of wine or 1 (~25 mL) measure of spirits.
12	History of or regular use of tobacco- or nicotine-containing products (confirmed by smokerlyzer test) in the 3 months prior to screening.

Number	Exclusion Description
13	Administration of any IBAT inhibitor (including linerixibat) or OCA in the 3 months prior to screening.
14	Past or intended use of over-the-counter or prescription medication (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inhibitor) or 5 half-lives (whichever is longer) prior to the first dose of study medication, unless approved by the Investigator in conjunction with GSK.
15	Current enrolment in a clinical trial; recent participation in a clinical trial and has received an investigational product within 30 days (or 5 half-lives of previous trial intervention, whichever is longer) before the first dose in the current study.
16	Exposure to more than 4 new chemical entities within 12 months before the first dose in the current study.
17	Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5x ULN.
18	Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
19	Presence of Hepatitis B surface antigen (HBsAg) at screening or positive Hepatitis C antibody test result at screening or within 3 months of the screening visit.
20	Positive serum pregnancy test at screening or positive urine pregnancy test at admission in women of child bearing potential only.
21	Positive human immunodeficiency virus (HIV) antibody test.
22	QTc >450 msec on ECG performed at Screening.
23	Positive pre-study drug/alcohol screen or positive drug/alcohol screen at any time during the study.
24	Female participants unable or unwilling to comply with specific contraception restrictions as detailed in Section 10.4 of the protocol.
25	Where participation in the study would result in donation of blood or blood products in excess of 500mL within a 56-day period.
26	Unwillingness or inability to follow the procedures outlined in the protocol for the expected duration of study participation.
27	Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.

NOTES:

- Medical Monitor Note: Specific medications may be allowed as listed in Concomitant Medication section (Section 6.5) of the protocol. Approved medications may be considered on a case by case basis by the Investigator in consultation with the Medical Monitor.
- Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.
- The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.

The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.

14.2. Appendix 2: Schedule of Activities

14.2.1. Protocol Defined Schedule of Events

Schedule of Screening, Follow Up and Early Withdrawal Activities

Procedure	Screening (within 28-35 days of Day 1)[1]	Follow Up (7-14 days post last linerixibat dose)	Early Withdrawal (within 7 days of the last dose)	Comments
Informed Consent	X			
Outpatient Visit	X		X	Early withdrawal visit to be performed as soon as possible after withdrawal date, and within 7 days of last dose.
Phone Call		X		
Demography	X			
Inclusion and Exclusion Criteria	X			
Medical History	X			Including drug/alcohol use and family history of disease
12-Lead ECG	X		X	Triplicate ECG measurements will be taken at screening, and in single at other timepoints
Vital Signs	X		X	Triplicate measurements of heart rate and systolic and diastolic blood pressure (respiratory rate and temperature recorded in single), at screening. Single measurements at other timepoints.
Urine drugs of abuse screen	X			
Alcohol and smoking breath tests	X			
HIV and hepatitis B and C screen	X			Not required if a test has been performed within 3 months prior to first dose of study intervention
Pregnancy Test	X			Serum pregnancy test for WOCBP only
FSH, Oestradiol	X			To confirm post-menopausal status in WONCBP only
Laboratory safety tests	X		X	Haematology, Biochemistry (including Liver Function Tests (LFTs)) and urinalysis is to be performed

Procedure	Screening (within 28-35 days of Day 1)[1]	Follow Up (7-14 days post last linerixibat dose)	Early Withdrawal (within 7 days of the last dose)	Comments
Full physical exam	X			Please see Section **Error! Reference source not found.** of protocol for minimum requirements. Weight measurement to be included
Brief Physical Exam			X	Please see Section **Error! Reference source not found.** of protocol for minimum requirements. Weight measurement to be included
OCA PK Sample			X	
OCA drug Accountability			X	To be performed only if participant withdraws between Day 3 and Day 16
AE review		X	X	AE's will be collected from the start of oral dosing until the final follow up
SAE review	X	X	X	SAE's will be collected from the signing of the ICF until final follow up
Concomitant medication review	X	X	X	Concomitant medications will be collected from the signing of the ICF until the final follow up
[1]The suggested screening is 28 days but may be increased to 35 days if necessary and in consultation with the medical monitor				

Part A Schedule of Activities (Day -1 to Day 38)

Procedure	Study Day																Comments
	Inpatient			OP	Inpatient												
	-1	1	2	3 to 16	17	18	19	20	21	22 to 32	33	34	35	36	37	38	
Admission to clinical unit	X				X												
Discharge from clinical unit			X													X	Participants will be discharged from the unit following OCA dosing on Day 2 with instructions to take OCA daily and return on Day 17 (am). Participant stay may be extended for safety reasons if deemed necessary at the discretion of the investigator.
Inclusion/Exclusion Criteria	X	X															Recheck clinical status at Day -1 and Day 1 predose
Medical history	X																Medical history updates only

Procedure	Study Day																Comments
	Inpatient			OP	Inpatient												
	-1	1	2	3 to 16	17	18	19	20	21	22 to 32	33	34	35	36	37	38	
12-lead ECG	X				X											X	Triplicate measurements taken Day -1. Single measurements will be taken at all other timepoints. If any single measurement is outside normal ranges, triplicate measurements to be taken and the mean of the triplicate measurements used.
Vital signs	X	X			X											X	Triplicate measurements of heart rate and systolic and diastolic blood pressure at Day -1 (respiratory rate and temperature to be taken in single); single measurements to be taken at all other timepoints. Additional vital signs may be taken for safety reasons at the discretion of the investigator
Urine drugs of abuse screen	X				X												
Alcohol and smoking breath tests	X				X												
Pregnancy Test	X				X												Urine pregnancy test at admissions for females of child bearing potential only. Positive urine pregnancy test should be confirmed with serum pregnancy test.
Laboratory safety tests	X				X											X	Haematology, Biochemistry (including liver function tests (LFTs)) and urinalysis is to be performed
Brief physical exam	X				X											X	Please see Section **Error! Reference source not found.** for minimum requirements. Weight measurement to be included
OCA 10 mg Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X		OCA will be dosed once daily (afternoon dose) at approximately 12:00 hours (between 12:00 and 14:00). Dosing on Day 2 will occur prior to discharge from the clinical unit.
Dispense OCA for self-administration			X														To be dispensed after dosing on Day 2
OCA Accountability Check					X												Clinical site to confirm OCA taken as required
Compliance Check				X	X												Participants will be required to confirm compliance with dosing schedule daily during this period
Linerixibat 90 mg Administration								X	X	X	X	X	X	X	X	X	GSK2330672 will be dosed twice daily with an interval of approximately 12 hours. The last linerixibat dose will be taken in the morning on Day 38.
Linerixibat PK Sampling								X			X						Blood samples for plasma drug assays should follow the sampling schedules in Section **Error! Reference source not found.**
OCA PK Sampling					X	X	X						X	X	X	X	
PGx sample		X															

Procedure	Study Day																		Comments
	Inpatient			OP	Inpatient														
	-1	1	2	3 to 16	17	18	19	20	21	22 to 32	33	34	35	36	37	38			
AE Review		←																→	AE's will be collected from the start of oral dosing until final follow up
SAE Review	←																	→	SAE's will be collected from the time each participant consents until final follow up
Concomitant Medication Review	←																	→	Concomitant medications will be collected from the signing of the ICF until the final follow up

- The timing and number of planned study assessments, including PK and safety assessments may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

Part B (Optional) Schedule of Assessments (Day -1 to Day 38)

Procedure	Study Day																Comments
	Inpatient			OP[1]	Inpatient												
	-1	1	2	3 to 16	17	18	19	20	21	22 to 32	33	34	35	36	37	38	
Admission to clinical unit	X				X												
Discharge from clinical unit			X													X	Participants will be discharged from unit following OCA dosing on Day 2 with instructions to take OCA daily and return on Day 17 (am). Participant stay may be extended for safety reasons if deemed necessary at the discretion of the investigator.
Inclusion/ Exclusion Criteria	X	X															Recheck clinical status at Day -1 and Day 1 predose
Medical history	X																Medical history updates only
12-lead ECG	X				X											X	Triplicate ECG measurements will be taken Day -1. Single ECG measurements will be taken at all other timepoints. If any single measurement is outside normal ranges, triplicate measurements will be taken, and the mean of the triplicate measurements used.

Procedure	Study Day																Comments
	Inpatient			OP[1]	Inpatient												
	-1	1	2	3 to 16	17	18	19	20	21	22 to 32	33	34	35	36	37	38	
Vital signs	X	X			X											X	Triplicate measurements of heart rate and systolic and diastolic blood pressure at Day -1 (respiratory rate and temperature to be taken in single); single measurements to be taken at all other timepoints. Additional vital signs may be taken for safety reasons at the discretion of the investigator
Urine drugs of abuse screen	X				X												
Alcohol and smoking breath tests	X				X												
Pregnancy Test	X				X												Urine pregnancy test at admissions for females of child bearing potential only. Positive urine pregnancy test should be confirmed with serum pregnancy test.
Laboratory safety tests	X				X											X	Haematology, Biochemistry (including LFTs) and Urinalysis is to be performed
Brief physical exam	X				X											X	Please see Section **Error! Reference source not found.** for minimum requirements. Weight measurement to be included
OCA Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X		OCA will be dosed once daily (evening dose) at approximately 20:00. Dosing on Day 2 will occur prior to discharge.
Dispense OCA for self-administration			X														To be dispensed after dosing on Day 2
OCA Accountability Check					X												Clinical site to confirm OCA taken as required
Compliance Check				X	X												Participants will be required to confirm compliance with dosing schedule daily during this period
Linerixibat Administration								X	X	X	X	X	X	X	X	X	GSK2330672 will be dosed once daily (morning dose) at approximately 08:00. The last linerixibat dose will be taken in the morning on Day 38.
Linerixibat PK Sampling								X	X		X	X					Blood samples for plasma drug assays should follow the sampling schedules in Section **Error! Reference source not found.**.
OCA PK Sampling					X	X	X						X	X	X	X	
PGx sample		X															
AE Review		◄———														———►	AEs to be recorded from the start of oral dosing until final follow up
SAE Review	◄———															———►	SAEs to be recorded from the time each subject consent's to participate in the study until final follow up

Procedure	Study Day																Comments
	Inpatient			OP[1]	Inpatient												
	-1	1	2	3 to 16	17	18	19	20	21	22 to 32	33	34	35	36	37	38	
Concomitant medication	◄———															———►	Concomitant medications will be collected from the signing of the ICF until the final follow up

- The timing and number of planned study assessments, including PK and safety assessments may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

14.3. Appendix 3: Assessment Windows

Nominal time will be used for all analysis except PK analysis where planned and actual time will be used.

14.3.1. Definitions of Assessment Windows for Analyses

Not applicable.

14.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

14.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to the first dose of OCA.

Study Phase	Definition
Pre-Treatment	Screening ≤ Date ≤ Day -1
OCA	Day 1 ≤ Date ≤ Day19
OCA+Linerixibat	Day 20 ≤ Date ≤ Day 38
Follow up	Day 39 ≤ Date ≤ Day 52

NOTES:

- Screening can occur within 28-35 days of Day 1.

14.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 28 days prior to screening visit
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

14.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date. (plus washout or protocol-specified time limit (e.g. half-life of drug, certain number of days, etc.). • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date • For studies with greater than one treatment period (e.g., crossover study), if AE onset is during one period and worsens during a later period it would be counted in both periods. For the initial period the logic would be as above. For the later period the logic would use the treatment dates associated with the later period: • Treatment Period Start Date ≤ AE Worsening Date ≤ Study Treatment Stop Date

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

14.5. Appendix 5: Data Display Standards & Handling Conventions

14.5.1. Reporting Process

Software	
• The currently supported version of SAS software will be used.	
Reporting Area	
HARP Server	us1salx00259.corpnet.com
HARP Compound	/arenv/arprod/gsk2330672/mid206224
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.1)	
Generation of RTF Files	
• RTF files will be generated for SAC.	

14.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and/or figures. • All unscheduled visits will be included in listings.

• Unscheduled visits will be used for calculating worst case QTcB and QTcF.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

14.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the Non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to current working practices with WinNonLin 5.2 or higher Note: Concentration values will be imputed as per Non-Compartmental Analysis of Pharmacokinetic Data, CPMS Global (GUI_51487 v5.0)
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 v5.0 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Not applicable.
NONMEM/PK/PD File	Not applicable.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	The following PK parameters will be derived by the Programmer: RAUC for Linerixibat, RCmax for Linerixibat, Average Ctrough of OCA, glyco-OCA, tauro-OCA, and total-OCA from days 17, 18, and 19, and days 35, 36, 37, and 38. Formulas for these derivations are given in section 14.6.5.
PK Parameter to be Derived by CPMS	The following PK parameters will be derived by CPMS: AUC(0-t) for OCA, glyco-OCA, tauro-OCA, total-OCA, and Linerixibat AUC(0-12) for Linerixibat AUC(0-24) for OCA, glyco-OCA, tauro-OCA, and total-OCA CMax for OCA, glyco-OCA, tauro-OCA, total-OCA, and Linerixibat Ctrough for OCA, glyco-OCA, tauro-OCA, and total-OCA Tmax for OCA, glyco-OCA, tauro-OCA, total-OCA, and Linerixibat Tlast for OCA, glyco-OCA, tauro-OCA, total-OCA, and Linerixibat Accumulation Ratios (RAUC and RCmax) for Linerixibat. Note: PK Parameters are derived as per Non-Compartmental Analysis of Pharmacokinetic Data, CPMS Global (GUI_51487 v5.0)
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	No
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards or refer to Appendix shell wherever applicable.

14.6. Appendix 6: Derived and Transformed Data

14.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

14.6.2. Study Population

Treatment Compliance
• Treatment compliance will be calculated based on the formula: **Treatment Compliance = Number of Actual Doses / (Planned Treatment Duration in Days * Frequency)** • Frequency is 2 for BID and 1 for QD. Treatment compliance could be greater than 100% if there are events of overdose. Cumulative compliance (since Day 1) at each visit will be calculated. • Planned Treatment Duration is defined as Day 1 to Day 37 for OCA and Day 20 to Day 38 for Linerixibat.
Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Exposure should be calculated for both OCA and OCA+Linerixibat. • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

14.6.3. Efficacy

Not applicable.

14.6.4. Safety

Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. o Example 1: 2 Significant Digits = '< x ' becomes x – 0.01 o Example 2: 1 Significant Digit = '> x' becomes x + 0.1 o Example 3: 0 Significant Digits = '< x' becomes x – 1

ECG Parameters
RR Interval
• If RR interval (msec) is not provided directly, then RR can be derived as: [1] If QTcF is machine read, then: $$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$ • If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value. THEN do not derive.
Corrected QT Intervals
• When not entered directly in the ClinBase, corrected QT intervals by Fredericia's (QTcF) formula will be calculated in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcF will be derived as: $$QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

No adverse events of special interest have been defined for this analysis.

14.6.5. Pharmacokinetic

PK Derivations and Conversions
Analytes
• Total-OCA = OCA + (0.8805 x glyco-OCA) + (0.7969 x tauro-OCA) Note: If OCA, glyco-OCA, or tauro-OCA are non-quantifiable, then let that analyte be equal to 0 in the above equation. See CDER document for reference.
PK Parameters
• AUC(0-t), AUC(0-12), AUC(0-24), Cmax, Ctrough, Tmax, and Tlast will be calculated using Phoenix WinNonlin • RAUC = (AUC(0-12) on Day 33) / (AUC(0-12) on Day 20) • RCmax = (Cmax on Day 33) / (Cmax on Day 20) • Average Ctrough when dosed on OCA alone = (Ctrough Day 17 + Ctrough Day 18 + Ctrough Day 19) / (Number of non-missing Ctrough measurements from Days 17, 18, and 19) • Average Ctrough when dosed on OCA+Linerixibat = Ctrough Day 35 + Ctrough Day 36 + Ctrough Day 37 + Ctrough Day 38 / (Number of non-missing Ctrough measurements from Days 35, 36, 37, and 38)
Log Scale Conversions
• Geometric mean = exp(mean on $\log_e$ scale) • CVb(%) = SQRT (exp (SD^2) – 1) x 100 where SD is the standard deviation on the $\log_e$ scale • CVw(%) = SQRT (exp (MSE) – 1) x 100 where MSE is the residual mean squared error from the model • Lower bound of 90% CI = exp(lw) where lw is the lower bound of the 90% CI on the $\log_e$ scale • Upper bound of 90% CI = exp(up) where up is the upper bound of the 90% CI on the $\log_e$ scale

NOTE: PK Derivations and Conversions will be performed by clinical programming.

14.6.6. Population Pharmacokinetic (PopPK)

Not applicable.

14.6.7. Pharmacodynamic and Biomarker

Not applicable.

14.7. Appendix 7: Reporting Standards for Missing Data

14.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion is defined as completion of all phases of the study including the follow up phone call. • Withdrawn subjects will be replaced in the study if there are less than 15 completers. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

14.7.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:
	  • These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
	  • Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
PK	• Missing PK parameters will not be imputed. • For missing and NQ values in PK concentration data, refer GUI_51487 v5.0

14.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.

Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event:
	  • Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events.
	  • Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used.
	• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  • If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.

Element	Reporting Detail
	• The recorded partial date will be displayed in listings.

14.8. Appendix 8: Values of Potential Clinical Importance

14.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Δ from BL	>0.075	
	Ratio of 1			0.54
Haemoglobin	g/L	Δ from BL	>25	
	g/L			180
Lymphocytes	$x10^9$/ L		<0.8	
Neutrophil Count	$x10^9$/ L		<1.5	
Platelet Count	$x10^9$/ L		<100	>550
While Blood Cell Count (WBC)	$x10^9$/ L		<3	>20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Calcium	mmol/L		<2.0	>2.75
Creatinine	umol/L	Δ from BL		>44.2
Glucose	mmol/L		<3.0	>9.0
Potassium	mmol/L		<3.0	>5.5
Sodium	mmol/L		<130	>150

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	>=2xULN
AST/SGOT	U/L	High	>=2xULN
AlkPhos	U/L	High	>=2xULN
T Bilirubin	µmol/L	High	>=1.5xULN
T. Bilirubin + ALT	µmol/L U/L	High	1.5xULN T. Bilirubin + ≥ 2x ULN ALT

14.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	**Upper**
Absolute			

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute QTc Interval	msec		>450
Absolute PR Interval	msec	<110	>220
Absolute QRS Interval	msec	<75	>110
Change from Baseline			
Increase from Baseline QTc	msec		>60

14.8.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	<85	>160
Diastolic Blood Pressure	mmHg	<45	>100
Pulse Rate	bpm	<40	>110

14.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

14.9.1. Population Pharmacokinetic (PopPK) Dataset Specification

Not applicable.

14.9.2. Population Pharmacokinetic (PopPK) Methodology

Not applicable.

14.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses

14.10.1. Pharmacokinetic / Pharmacodynamic Dataset Specification

Not applicable.

14.10.2. Pharmacokinetic / Pharmacodynamic Methodology

Not applicable.

14.11. Appendix 11: Abbreviations & Trade Marks

14.11.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
MMRM	Mixed Model Repeated Measures
MSE	Mean Squared Error
OCA	Obeticholic Acid, Ocaliva®
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System

Abbreviation	Description
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
SQRT	Square Root
TA	Therapeutic Area
TFL	Tables, Figures & Listings

14.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
Phoenix WinNonlin (6.3 or greater)
SAS 9.4
Ocaliva®

14.12. Appendix 12: List of Data Displays

14.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.12	
Safety	2.1 to 2.15	2.1 to 2.3
Pharmacokinetic	3.1 to 3.10	3.1 to 3.9
Section	**Listings**	
ICH Listings	1 to 30	
Other Listings	31 to 34	

14.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 13: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

14.12.3. Deliverables

Delivery [Priority] [1]	Description
HLR [1]	Headline Results
SAC [2]	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort

14.12.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Participants	ES1A	Summary of Participant Disposition for the Participant Conclusion Record	ICH E3, FDAAA, EudraCT	SAC [2]
1.2.	All Participants	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	SAC [2]
1.3.	All Participants	ES4	Summary of Participant Disposition at Each Study Phase	ICH E3	HLR [1]
1.4.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC [2]
1.5.	All Participants	NS1	Summary of Number of Participant by Country and Site ID	EudraCT/Clinical Operations	SAC [2]
Protocol Deviation					
1.6.	All Participants	DV1	Summary of Important Protocol Deviations	ICH E3	SAC [2]
Population Analysed					
1.7.	Screened	SP1	Summary of Study Populations	IDSL	HLR [1]
Demographic and Baseline Characteristics					
1.8.	All Participants	DM3	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	HLR [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.9.	All Participants	DM11	Summary of Age Ranges	EudraCT Only have Total. We can use All Participants flag, for this study it is the same as Enrolled population flag.	HLR [1]
1.10.	All Participants	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	HLR [1]
Prior and Concomitant Medications					
1.11.	All Participants	CM1	Summary of Concomitant Medications	ICH E3	HLR [1]
Exposure and Treatment Compliance					
1.12.	All Participants	EX1	Summary of Exposure to Study Treatment	ICH E3 Use OCA and OCA+Linerixibat treatment regimens.	HLR [1]

14.12.5. Efficacy Tables

Not applicable.

14.12.6. Efficacy Figures

Not applicable.

14.12.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
2.1.	All Participants	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC [2]
2.2.	All Participants	AE1	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3	HLR [1]
Serious and Other Significant Adverse Events					
2.3.	All Participants	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	HLR [1]
Laboratory: Chemistry					
2.4.	All Participants	LB1	Summary of Chemistry Changes from Baseline	ICH E3	SAC [2]
2.5.	All Participants	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range	ICH E3	SAC [2]
Laboratory: Hematology					
2.6.	All Participants	LB1	Summary of Hematology Changes from Baseline	ICH E3	SAC [2]
2.7.	All Participants	LB15	Summary of Worst Case Hematology Results Relative to Normal Range	ICH E3	SAC [2]
Laboratory: Urinalysis					
2.8.	All Participants	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline	ICH E3	SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Hepatobiliary (Liver)					
2.9.	All Participants	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL Keep: ALT ≥3xULN and BIL ≥2xULN ALT ≥3xULN and INR >1.5 ALT ≥3xULN ALT ≥5xULN BIL ≥2xULN ALP ≥2xULN and Baseline ALP <2xULN or Baseline ALP missing Time from First Dose to First ALT Elevation ≥3xULN (days)	HLR [1]
ECG					
2.10.	All Participants	EG1	Summary of ECG Findings	IDSL	SAC [2]
2.11.	All Participants	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC [2]
2.12.	All Participants	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC [2]
2.13.	All Participants	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC [2]
Vital Signs					
2.14.	All Participants	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.15.	All Participants	VS3	Summary of Worst Case Vital Signs Results Relative to Potential Clinical Importance Range	IDSL	SAC [2]

14.12.8. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory					
2.1.	All Participants	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT	IDSL	SAC [2]
2.2.	All Participants	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin	IDSL	SAC [2]
2.3.	All Participants	SAF_F1	Individual Plots of ALT at Day -1, 17, and 38		HLR [1]

14.12.9. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
OCA					
3.1.	Pharmacokinetic Concentrations	PK01	Summary of Plasma Total-OCA, OCA, Glyco-OCA, and Tauro-OCA Pharmacokinetic Concentration-Time Data	Treatment will be OCA and OCA+Linerixibat. Separated by analytes of Total-OCA, OCA, Glyco-OCA, and Tauro-OCA.	SAC [2]
3.2.	Pharmacokinetic Parameters	PK06	Summary of Derived Plasma Total-OCA, OCA, Glyco-OCA, and Tauro-OCA Pharmacokinetic Parameters by Treatment Regimen	Use AUC(0-t), AUC(0-24), Cmax, and average Ctrough. Generate for OCA, OCA+Linerixibat, and the difference between the two periods (OCA+Linerixibat) – (OCA). Separated by analytes of Total-OCA, OCA, Glyco-OCA, and Tauro-OCA.	HLR [1]
3.3.	Pharmacokinetic Parameters	PK04	Summary of Derived Plasma Total-OCA, OCA, Glyco-OCA, and Tauro-OCA Pharmacokinetic Time Parameters by Treatment Regimen	Use Tmax and Tlast. Generate for OCA, OCA+Linerixibat, and the difference between the two periods (OCA+Linerixibat) – (OCA). Separated by analytes of Total-OCA, OCA, Glyco-OCA, and Tauro-OCA	SAC [2]
3.4.	Pharmacokinetic Parameters	PK03	Summary of Derived Ctrough of Total-OCA by Days 17, 18, and 19 and Days 35, 36, 37, and 38	Treatment will be OCA and OCA+Linerixibat	SAC [2]
3.5.	Pharmacokinetic Parameters	PK_T1	Analysis of Derived Plasma Total-OCA, OCA, Glyco-OCA, and Tauro-OCA Pharmacokinetic Parameters	Use AUC(0-t), AUC(0-24), Cmax, and average Ctrough. Separated by analytes of Total-OCA, OCA, Glyco-OCA, and Tauro-OCA	HLR [1]
3.6.	Pharmacokinetic Parameters	PK_T2	Analysis of Ctrough of total-OCA Compared to 20 ng/mL Threshold.	Use average Ctrough from OCA+Linerixibat treatment regimen.	HLR [1]
Linerixibat					

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.7.	Pharmacokinetic Concentrations	PK01	Summary of Plasma Linerixibat Pharmacokinetic Concentration-Time Data	The two treatment time points are Day 20 and Day 33.	SAC [2]
3.8.	Pharmacokinetic Parameters	PK06	Summary of Derived Plasma Linerixibat Pharmacokinetic Parameters by Day 20 and Day 33	The two treatment time points are Day 20 and Day 33. Use AUC(0-t), AUC(0-12), and Cmax.	SAC [2]
3.9.	Pharmacokinetic Parameters	PK04	Summary of Derived Plasma Linerixibat Pharmacokinetic Time Parameters by Day 20 and Day 33	Use Tmax and Tlast. The two treatment time points are Day 20 and Day 33. Generate for Day 20, Day 33, and the difference between the two time points (Day 33 – Day 20).	SAC [2]
3.10.	Pharmacokinetic Parameters	PK_T3	Summary of Derived Plasma Linerixibat Pharmacokinetic Accumulation Parameters by Day 20 and Day 33	Use RAUC and RCmax.	SAC [2]

14.12.10. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
OCA					
3.1.	Pharmacokinetic Concentration	PK24	Individual Concentration-Time Plots of Total-OCA, OCA, Glyco-OCA, and Tauro-OCA by Treatment Regimen	All OCA analytes represented, separated by OCA and OCA+IBAT regiments.	SAC [2]
3.2.	Pharmacokinetic Concentration	PK24	Individual Concentration-Time Plots of Treatment Regimen by Total-OCA, OCA, Glyco-OCA, and Tauro-OCA	Represent OCA and OCA+IBAT regiment on z-axis, separated by all OCA analytes.	SAC [2]
3.3.	Pharmacokinetic Concentration	PK17	Mean Concentration-Time Plot of Total-OCA, OCA, Glyco-OCA, and Tauro-OCA by Treatment Regimen	All OCA analytes represented, separated by OCA and OCA+IBAT regiments.	SAC [2]
3.4.	Pharmacokinetic Concentration	PK17	Mean Concentration-Time Plot of Treatment Regimen by Total-OCA, OCA, Glyco-OCA, and Tauro-OCA	Represent OCA and OCA+IBAT regiment on z-axis, separated by all OCA analytes.	SAC [2]
3.5.	Pharmacokinetic Parameters	PK17	Mean Ctrough of Total-OCA, OCA, Glyco-OCA, and Tauro-OCA by Days 17, 18, and 19, and Days 35, 36, 37, and 38	X-axis is study day rather than Planned Relative Time. One plot for Days 17, 18, and 19, and another plot for Days 35, 36, 37, and 38, for each analyte.	HLR [1]
3.6.	Pharmacokinetic Parameters	PK30	Linear Plot of Individual PK Parameters by Total-OCA, OCA, Glyco-OCA, and Tauro-OCA	X-axis is the study day rather than log(dose). Days when OCA and OCA+Linerixibat PK draw occurred labelled on the x-axis study day.	SAC [2]
Linerixibat					
3.7.	Pharmacokinetic Concentration	PK24	Individual Concentration-Time Plots of Linerixibat by Day 20 and Day 33		SAC [2]

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.8.	Pharmacokinetic Parameters	PK17	Mean Concentration-Time Plot of Linerixibat by Day 20 and Day 33		SAC [2]
3.9.	Pharmacokinetic Parameters	PK30	Linear Plot of Individual PK Parameters for Day 20 and Day 33	X-axis is the study day rather than log(dose). Days when Linerixibat PK draw occurred labelled on the x-axis study day.	SAC [2]

14.12.11. Pharmacokinetic Population (PopPK) Tables

Not applicable.

14.12.12. Pharmacokinetic Population (PopPK) Figures

Not applicable.

14.12.13. Pharmacodynamic and Biomarker Tables

Not applicable.

14.12.14. Pharmacodynamic and Biomarker Figures

Not applicable.

14.12.15. Pharmacokinetic / Pharmacodynamic Biomarker Tables

Not applicable.

14.12.16. Pharmacokinetic / Pharmacodynamic Biomarker Figures

Not applicable.

14.12.17. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC [2]
2.	All Participants	ES2xo	Listing of Reasons for Study Withdrawal	ICH E3	SAC [2]
3.	All Participants	SD2xo	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC [2]
4.	All Participants	CP_RD1x	Listing of Planned and Actual Treatments	IDSL	SAC [2]
Protocol Deviations					
5.	All Participants	DV2	Listing of Important Protocol Deviations	ICH E3	SAC [2]
6.	All Participants	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC [2]
Populations Analysed					
7.	Screened	SP3xo	Listing of Participants Excluded from Any Population	ICH E3	SAC [2]
Demographic and Baseline Characteristics					
8.	All Participants	DM2	Listing of Demographic Characteristics	ICH E3	SAC [2]
9.	All Participants	DM9xo	Listing of Race	ICH E3	SAC [2]
Prior and Concomitant Medications					
10.	All Participants	CM10xo	Listing of Concomitant Medications	IDSL	SAC [2]
Exposure and Treatment Compliance					

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
11.	All Participants	EX3xo	Listing of Exposure Data	ICH E3 For OCA and for Linerixibat	SAC [2]
12.	All Participants	COMP2	Listing of Overall Compliance	ICH E3 For OCA and for Linerixibat	SAC [2]
Adverse Events					
13.	All Participants	AE8xo	Listing of All Adverse Events	ICH E3	SAC [2]
14.	All Participants	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC [2]
15.	All Participants	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC [2]
Serious and Other Significant Adverse Events					
16.	All Participants	AE8CPaxo	Listing of Serious Adverse Events	ICH E3	SAC [2]
17.	All Participants	E14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC [2]
18.	All Participants	AE8CPxo	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC [2]
Hepatobiliary (Liver)					
19.	All Participants	LIVER6	Listing of Liver Stopping Event Information	IDSL	SAC [2]
20.	All Participants	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL	SAC [2]
All Laboratory					
21.	All Participants	LB5xo	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC [2]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
22.	All Participants	LB5xo	Listing of Laboratory Values of Potential Clinical Importance		SAC [2]
23.	All Participants	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC [2]
24.	All Participants	UR2xo	Listing of Urinalysis Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC [2]
ECG					
25.	All Participants	EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	IDSL	SAC [2]
26.	All Participants	EG3	Listing of ECG Values of Potential Clinical Importance	IDSL	SAC [2]
27.	All Participants	EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	SAC [2]
28.	All Participants	EG5	Listing of Abnormal ECG Findings	IDSL .	SAC [2]
Vital Signs					
29.	All Participants	VS5	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL	SAC [2]
30.	All Participants	VS5	Listing of Vital Signs of Potential Clinical Importance	IDSL .	SAC [2]

14.12.18. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
OCA					
31.	Pharmacokinetic Concentrations	PK07	Listing of Total-OCA, OCA, Glyco-OCA, and Tauro-OCA Concentration-Time Data.	Total-OCA will need to be calculated. A separate listing for each analyte. OCA and OCA+Linerixibat will be the periods.	SAC [2]
32.	Pharmacokinetic Concentrations	PK14	Listing of Derived Total-OCA, OCA, Glyco-OCA, and Tauro-OCA PK Parameters.	Total-OCA will need to be calculated. A separate listing for each analyte. OCA and OCA+Linerixibat will be the periods.	SAC [2]
Linerixibat					
33.	Pharmacokinetic Concentrations	PK07	Listing of Linerixibat Concentration-Time Data	Day 20 and Day 33 will be the periods.	SAC [2]
34.	Pharmacokinetic Concentrations	PK14	Listing of Derived Linerixibat PK Parameters.	Day 20 and Day 33 will be the periods.	SAC [2]

14.13. Appendix 13: Example Mock Shells for Data Displays

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206224

Example: PK_T1
Protocol: 206224
Population: Pharmacokinetic Parameters

Table 4.5
Analysis of Derived Plasma Total-OCA Pharmacokinetic Parameters

Parameter	N	Mean OCA+Linerixibat	Mean OCA	Ratio: OCA+Linerixibat: OCA	90% C.I.	CVw(%)
AUC(0-t)	xx	x.xx	x.xx	x.xx	(x.xx,x.xx)	xx.xx%
AUC(0-24)	xx	x.xx	x.xx	x.xx	(x.xx,x.xx)	xx.xx%
Cmax	xx	x.xx	x.xx	x.xx	(x.xx,x.xx)	xx.xx%

Note: OCA+Linerixibat:OCA represents the ratio of adjusted geometric means between treatment regimens.

Treatment Regimen Key:

OCA+Linerixibat = 10 mg OCA QD for 18 days + Linerixibat 90 mg BID for 18 days

OCA = 10 mg OCA QD for 18 days

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206224

Example: PK_T2
Protocol: 206224
Population: Pharmacokinetic Parameters

Table 4.6
Analysis of Ctrough of total-OCA Compared to 20 ng/mL Threshold

Parameter	N	Mean OCA+Linerixibat	90% C.I.	20 ng/mL Threshold
Average Ctrough	xx	x.xx	(x.xx,x.xx)	Above/Below

Note: Average Ctrough is the average Ctrough ng/mL from Study Days 35, 36, 37, and 38.

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Example: PK_T3
Protocol: 206224
Population: Pharmacokinetic Parameters

Table 4.6
Summary of Derived Plasma Linerixibat Pharmacokinetic Accumulation Parameters by Day 20 and Day 33

Parameter	Summary Statistics	Ratio: Day33/Day20
RAUC	N	xxx
	n	xxx
	Arith. Mean	xxx.xx
	95% CI	(xxx.xx,xxx.xx)
	SD	xxx.xxx
	Median	xxx.xx
	Min	xxx.x
	Max	xxx.x
RCmax	N	xxx
	n	xxx
	Arith. Mean	xxx.xx
	95% CI	(xxx.xx,xxx.xx)
	SD	xxx.xxx
	Median	xxx.xx
	Min	xxx.x
	Max	xxx.x

Note: RAUC is the ratio of AUC(0-12) on Day 14 of the Linerixibat dosing interval (Study Day 33) to the start of the Linerixibat dosing interval (Study Day 20).
RCmax is the ratio of Cmax on Day 14 of the Linerixibat dosing interval (Study Day 33) to the start of the Linerixibat dosing interval (Study Day 20).

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Example: SAFE_F1
Protocol: 206224
Population: All Participants

Figure 3.3
Individual Plots of ALT at Day -1, 17, and 38