Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for A two-period study in healthy male participants to determine the pharmacokinetics, balance/excretion, and metabolism of [^{14}C]-linerixibat following a single intravenous radiolabeled microtracer dose (concomitant with a non-radiolabeled oral dose) and a single oral radiolabeled dose.
Compound Number	:	GSK2330672
Effective Date	:	17-JAN-2020

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol [205895].
- This RAP is intended to describe and to assess pharmacokinetics (PK), mass balance/excretion, metabolism of safety and tolerability 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.

RAP Author(s):

Approver	Date
PPD Principal Statistician (FPD, Clinical Statistics)	17-01-2020

RAP Team Approvals:

Approver	Date	Approval Method
PPD Clinical Development Director, Clinical Science (Respiratory & Specialty)	17-01-2020	Email
PPD Global Clinical Development Manager, PCPS GCSD	17-01-2020	Email
PPD Drug Transporter SME, Global Disposition & Biotransformation	17-01-2020	Email
PPD Senior Programmer, Biostatistics (Bangalore, India), Clinical Programming	17-01-2020	Email
PPD On behalf of CPMS, GSK, Director, Quantitative Clinical Development, (Parexel International)	16-01-2020	Email

Clinical Statistics and Clinical Programming Line Approvals:

Approver	Date	Approval Method
PPD Director (FPD, Clinical Statistics)	17-01-2020	Email
PPD Programming Manager (FPD, Clinical Programming)	16-01-2020	Email

TABLE OF CONTENTS

PAGE

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 205895:

Revision Chronology:		
205895	11-APR-2019	Original critical component

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the 205895 protocol Dated: 11/April/2019.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To determine parent linerixibat and total drug-related radioactivity systemic concentrations following a single IV microtracer dose of [^{14}C]-linerixibat (concomitantly with an oral dose of nonradiolabelled linerixibat) and oral dose of [^{14}C]-linerixibat[1]	• AUC(0–inf), AUC(0–t), Cmax, tmax and $t_{1/2}$ of parent and total drug-related material (radioactivity) in plasma. • Volume (Vss) and clearance (CL) of parent after IV dose (Period 1 only). • Hepatic clearance (CLh) will be estimated from IV clearance (CL_{IV}) and renal clearance (CLr)
• To estimate the oral bioavailability of linerixibat	• Direct estimation of F (absolute oral bioavailability), indirect calculation of Fh (fraction of drug escaping first pass hepatic clearance), and Fa (fraction absorbed)
• To determine the rate and extent of excretion of total radioactivity in urine and feces and the total recovery of radioactivity, following IV and oral administration of [14C]-linerixibat	• Urinary and fecal cumulative excretion as a percentage of the total radioactive dose
Secondary Objectives	**Secondary Endpoints**
• To describe the safety and tolerability of linerixibat after single IV and oral doses in healthy participants.	• Characterize observed adverse events, and abnormal laboratory, 12-lead ECG, and vital signs assessments observed.

Objectives	Endpoints
Exploratory Objectives	**Exploratory Endpoints**
• To generate samples that will be used to characterize the metabolite profile of linerixibat following a single IV microtracer dose of [^{14}C]-linerixibat concomitantly with an oral dose of nonradiolabelled linerixibat (plasma, urine, feces, duodenal bile) and a single, oral dose of [^{14}C]-linerixibat (plasma, urine and feces).	• Characterization and quantification of metabolites in plasma, urine, feces, and duodenal bile (qualitative identification in bile). These analytical investigations will be conducted, and the results reported under a separate GSK nonclinical protocol.

[1] For measured concentrations of linerixibat in plasma, the nomenclature **[^{14}C]-linerixibat** describes the parent linerixibat concentration derived via analysis by liquid chromatography (LC) + Accelerator Mass Spectrometry (AMS), whereas **linerixibat** describes the parent linerixibat concentration derived via liquid chromatography-tandem mass spectrometry (LC/MS/MS).

2.3. Study Design

Overview of Study Design and Key Features

Up to 30 days	*9-day inpatient stay*	*At least 13 days between doses*	*~9-day inpatient stay*		*1-2 weeks later*
Screening	**Treatment Period 1**		**Treatment Period 2**		**Follow-up**
	Single IV microtracer dose of 100 µg [^{14}C]-linerixibat concomitantly with 90 mg dose (two 45 mg tablets) of non-radiolabelled GSK-2330672		Single oral 90 mg dose of [^{14}C]-linerixibat solution *Radioactivity Recovery Checked*[a]		

[a] In Period 2, on Day 8, radioactivity recovery will be evaluated for the first six samples and sample collection for the 7th sample will complete.

- If >90% of the administered radioactivity has been recovered in samples from Day 1-6 , then the participant will be discharged on Day 8.
- If ≤90% has been recovered, then the results of the 7th sample (144-168 h sample) will be included in evaluation on Day 9.
- *On Day 9*, if >90% of radioactivity has been recovered or <1% has been excreted on two consecutive days (Day 6 and Day 7 samples), then the participant may be discharged. Otherwise, the participant will remain in the clinical unit and 24-hr samples will continue to be collected and radioactive recovery re-evaluated on a daily basis until meeting the criteria for discharge.
- All subjects will be discharged on or before Day 15. If radioactive recovery criteria have not yet been met, then subjects will continue to collect samples at home and return to the clinical unit for assay.

Design Features	This is a single group, single center, [^{14}C]-linerixibat mass balance study with a two period, single sequence, and no masking. This open-label, single-center, non-randomised, 2-period, single-sequence, mass balance study will enroll a cohort of 6 healthy male participants. The aim of the study is to assess the pharmacokinetics, balance/excretion, and metabolism of linerixibat using [^{14}C]- radiolabelled drug substance administered as an IV infusion of a microtracer dose (concomitant with an oral, non-radiolabelled dose) and orally.
Dosing	• 90 mg Linerixibat Oral Tablets and Oral solution Dose (Periods 1 and 2). • Linerixibat Intravenous (IV) Micro-Dose (Period 1) The dose of [^{14}C]-linerixibat to be administered intravenously is a microdose of 100 µg, which will be infused over 3 hours. • Radiolabelled doses will be individualized for the ^{14}C-IV infusion (period 1) and ^{14}C 90 mg oral solution dose (period 2). Each dose is slightly different from the nominal dose.
Time & Events	• [Refer to Appendix 2: Schedule of Activities]
Treatment Assignment	• Linerixibat 90mg ORAL tablets or solution and [^{14}C]-Linerixibat IV
Interim Analysis	• No interim analysis will be performed for this study.

2.4. Statistical Hypotheses / Statistical Analyses

This is an investigative study to determine the pharmacokinetics (absorption, distribution, metabolism and excretion; ADME), mass balance excretion, and metabolism of linerixibat (GSK2330672) using [^{14}C]- radiolabelled drug substance administered as an IV infusion of a microtracer dose (concomitant with an oral, non-radiolabelled dose of 90 mg linerixibat tablets) Period 1 and 90 mg Linerixibat oral solution Period 2.

Due to its descriptive nature, there will be no formal statistical hypothesis tested; an estimation approach will be adopted to assess the study objectives.

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal 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.
3. Final PK analyses will be completed as the final merged plasma concentration and actual time files become available. There will be one to two ARM releases via BIB/DMPK for plasma concentration data.
4. The urine and feces reports for mass balance recovery of total radioactivity will be provided by Pharmaron and Covance. These reports will be appended to the final clinical study report.

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
Enrolled	• Enrolled: All participants who passed screening and entered the study. Participants who were assigned a treatment in a non-randomised study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• Study Population
Safety	• All participants who take at least 1 dose of study treatment. • Participants will be analysed according to the treatment they actually received.	• Safety and Study population

Population	Definition / Criteria	Analyses Evaluated
Pharmacokinetic (PK)	• All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).	• PK

Refer to Appendix 8: 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.

Include the following text only if a Per Protocol Population is being defined: Important deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan [27-June-2019 and versionV1].
  - Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis 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 CRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

The treatment groups will be labelled and administered as follows:

Treatment Group Descriptions				
Treatment Description		**Data Displays for Reporting**		
Code	**Description**	**Description (Safety)**	**Description (PK Analysis)**	**Order [1]**
A	Linerixibat 90 mg Oral Tablets + [^{14}C]-Linerixibat 100 µg IV infusion	A	A1 A2	1 2
B	[^{14}C]-Linerixibat 90 mg Oral solution	B	B	3

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

Study population displays will be summarized by total column.

Please add footnote in all the displays as follows for the treatment group

- **Note: For Safety Displays**

  A: 90 mg Linerixibat Oral Tablets + 100 µg [^{14}C]-Linerixibat IV infusion

  B: 90 mg [^{14}C]-Linerixibat Oral Solution

- **Note: For PK displays:**

  A1: 90 mg Linerixibat Oral Tablets

  A2: 100 µg [^{14}C]-Linerixibat IV infusion

  B: 90 mg [^{14}C]-Linerixibat Oral Solution

5.2. Baseline Definitions

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
[Safety]				
Vital Signs	X	X	X [1]	Day 1 (mean pre-dose) [2]
Laboratory safety tests	X	X		Day -1
12-lead ECG	X			
PK	X	X	X	Mean of Day -1 & 1

[1] Taken in triplicate

[2] Mean of the triplicate pre-dose assessments on Day 1 in Treatment Period.

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.

5.4. 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
11.1	Appendix 1: Protocol Deviation Management and Definitions
11.2	Appendix 2: Schedule of Activities
11.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
11.4	Appendix 4: Data Display Standards & Handling Conventions
11.5	Appendix 5: Reporting Standards for Missing Data
11.6	Appendix 6: Values of Potential Clinical Importance
11.7	Appendix 7: Abbreviations & Trade Marks
11.8	Appendix 8: List of Data Displays
11.9	Appendix 9: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Screened/Enrolled/Safety/PK population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 8: List of Data Displays.

7. EFFICACY ANALYSES

This is not applicable for this study.

8. SAFETY ANALYSES

No formal statistical analysis of safety data will be performed. Safety data will be descriptively summarized and presented in a tabular form. In addition, listings of the safety data will be provided. The safety analyses will be based on the Safety population, unless otherwise specified.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 8: List of Data Displays.

8.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 8: List of Data Displays.

8.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 8: List of Data Displays.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

9.1.1. Endpoints / Variables

Period 1 - 205895
Total radioactivity in <u>plasma</u> from IV dose in Period 1
• AUC(0–inf),iv14C, AUC(0–t),iv14C, Cmax,iv14C, tmax,iv14C, λz,iv14C, and t½,iv14C of total drug-related material (radioactivity) in plasma.
[^{14}C]-linerixibat in <u>plasma</u> following IV infusion dose 100ug over 3 hours
• AUC(0–inf),iv14C-L, AUC(0–t),iv14C-L, AUC(0-24),iv14C-L, %AUCex,iv14C-L,Cmax,iv14C-L, tmax,iv14C-L, λz,iv14C-L, and t½,ivC14-L CLiv, Vss,iv, CLrenal,iv of [^{14}C]-linerixibat (L) in plasma.
Linerixibat in <u>plasma</u> following oral tablet dose of linerixibat 90mg in Period 1
• AUC(0–inf),poP1, AUC(0–t),poP1, %AUCex,poP1, Cmax,poP1, tmax,poP1, λz,poP1 and t½,poP1of linerixibat in plasma.
Ratio of [^{14}C] linerixibat / total radioactivity for Cmax, AUC(0-t) and AUC(0-inf) for Period 1 Cmax, ratio P1 -(pg/mL)/(pgEq/mL AUC(0-t), ratio P1 (h*pg/mL)/h*pgEq/mL) AUC(0-inf), ratio P1 (h*pg/mL)/h*pgEq/mL)
Absolute bioavailability (F) from the oral tablet and IV doses administered in Period1 for AUC(0-inf) and AUC(0-t) PK parameter calculated as: (linerixibat AUC,poP1/Dose,poP1 (90mg)) _____ (^{14}C linerixibat AUC,iv14C-L / Dose,iv14C-L(100μg) Oral and IV Dose (100μg) will be converted into same units (pg or ng) using conversion values as needed below. The 100 μg dose will vary slightly for each subject and final corrected doses will be provided in Covance/Pharmaron reports 1mg=1000 mcg (or μg) 1mcg (or μg) = 1000 ng 1ng = 1000 pg 1 pg = 1000 femtograms (fg)
Clearance (CLiv) Total systemic clearance will be calculated as: Dose ≅ 100μg (iv14C-L)/AUC(0-inf)(iv14C-L) Period 1, analyte: [^{14}C]- linerixibat.
Cumulative amount of [^{14}C]-linerixibat in urine at 24 hours (Ae(0-24) iv14C-L) ***(****data derived from GSK DMPK metabolite profiling study 19DMM027)*
Renal Clearance (CLrenal,iv) [^{14}C] linerixibat-Ae(0-24),iv14C-L / AUC(0-24),iv14C-L (t=available time interval is 24hours), (i.e., Amount of [14C]-linerixibat from pooled urine samples (0-24 hours) for all subjects divided by each subject's AUC(0-24) in plasma resulting in 6 values.
Hepatic Clearance (CLhepatic or CLh) **CLh,iv = CLiv – CLrenal,iv** If [^{14}C] linerixibat-Ae(0-24), iv 14C-L is BQL, it will be assumed to be zero for the calculation of CLrenal,iv and subsequently CLh,iv,

CLh,iv,in plasma divided by linerixibat blood-to-plasma ratio (B:P) = CLiv,h,blood [Mehvar, 2016] The blood-to-plasma ratio for human = 0.678 (GSK Report Number: 2017N342697_00)
Hepatic extraction ratio (Eh) Eh = CLh,iv blood / hepatic blood flow Human hepatic blood flow estimate = 1200-1450 mL/min [Edginton, 2006, Davies and Morris, 1993], liver blood flow estimate used will be reported in the CPSR.
Fraction of linerixibat that escapes first pass liver extraction = Fh = 1 – Eh
Fraction of linerixibat absorbed (includes fraction escaping gut extraction) = Fabs = F/Fh

Period 2 – 205895
Total radioactivity in plasma following oral dose in Period 2 • AUC(0–inf)po14C, AUC(0–t)po14C, Cmax,po14C, tmax,po14C, λz,po14C, and t½,po14C of total drug-related material (radioactivity) in plasma.
Linerixibat in plasma following oral dose of linerixibat 90mg • AUC(0–inf),poP2, AUC(0–t),poP2, %AUCex,poP2, Cmax,poP2, tmax,poP2, λz,poP2 and $t_{1/2}$,poP2 of linerixibat in plasma.
Ratio of linerixibat / total radioactivity for Cmax, AUC(0-t) and AUC(0-inf) for Period 2 Cmax, ratio P2 (pg/mL)/(pgEq/mL) AUC(0-t), ratio P2 (h*pg/mL)/h*pgEq/mL) AUC(0-inf), ratio P2 (h*pg/mL)/h*pgEq/mL)

Radioactivity Mass Balance in Periods 1 and 2 - Parameter Endpoints and Description	
Fe%[urine]	% of total dose excreted as total radioactivity for each collection interval Data will be provided by Covance/Pharmaron:
Fe%[feces]	% of total dose excreted as total radioactivity for each collection interval Data will be provided by Covance/Pharmaron:
Fe%[total]	% of total dose excreted as radioactivity will be estimated in each collection interval as: Sum of Fe%[urine] and Fe%[feces] – Data to be provided by Covance/Pharmaron

9.1.1.1. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 11.4.3 Reporting Standards for Pharmacokinetic).

Plasma linerixibat, [^{14}C]-linerixibat, plasma total radioactivity, concentration-time data will be listed for each participant and standard summary statistics will be calculated (i.e. arithmetic mean, standard deviation, median, minimum and maximum) by period, analyte, treatment dose and planned sampling time.

Individual subject, mean and median plasma linerixibat, [^{14}C]-linerixibat, plasma total radioactivity concentration-time profiles will be plotted for each period and treatment on both a linear and semi-log scale.

9.1.1.2. Derived Plasma, Urine and Fecal Pharmacokinetic Parameters

PK parameters will be calculated by standard non-compartmental analysis according to current working practices (GUI_51487 (4.0)) and using the currently supported version of Phoenix WinNonlin Version 6.4 or above. All calculations of non-compartmental parameters will be based on actual sampling times. PK parameters listed will be determined from the plasma linerixibat, [^{14}C]-linerixibat, and plasma total radioactivity concentration-time data, as data permits. The calculation of CLh,in blood for the purpose of estimating Fh is shown below.

Derivation of the urine and fecal total radioactivity mass balance parameters will be the responsibility or under the direct auspices, of the BIB/DMPK department within GSK. All mass balance parameters for urine and fecal radiolabelled drug-related material (total radioactivity) will be provided in QC/QA reports provided by Pharmaron and Covance. Urine and feces analytical data will not be entered into the SMS2000 system. No further data manipulation will be required and those reports will be used to write the clinical study report.

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.
AUC (0-inf)	Area under the concentration-time curve extrapolated to infinity will be calculated as: $AUC = AUC(0\text{-}t) + C(t) / \lambda_z$
%AUCex	The percentage of AUC (0-∞) obtained by extrapolation (%AUCex) will be calculated as: $[AUC(0\text{-}inf) - AUC(0\text{-}t)] / AUC(0\text{-}inf) \times 100$
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Cmax ratio AUC(0-t) ratio AUC (0-inf)	Ratios for period 1 = [^{14}C] linerixibat /Total radioactivity for Cmax, AUC(0-t) and AUC(0-inf) Ratios for period 2 = linerixibat / total radioactivity for Cmax, AUC(0-t) and AUC(0-inf) for Period 2
CLiv	Total clearance will be calculated as: Dose(iv)/AUC(0-inf)iv Treatment period 1, analyte [^{14}C]- linerixibat only.
CLh,iv,plasma	Hepatic Clearance (CLhepatic or CLh) in plasma following IV dose CLh,iv = CLiv – CLrenal,iv If CLrenal,iv is not available, assume 0.00
CLh,iv,blood	Hepatic Clearance in blood following IV dose

Parameter	Parameter Description
	CLh,plasma divided by blood to plasma ratio = CLh, blood
CLrenal,iv	Renal Clearance (CLrenal,iv) ^{14}C linerixibat-Ae(0-t),iv14C-L/AUC(0-t),iv14C-L As data permits, (t=available time interval, Ae(0-24) may be a pooled estimate from 6 subjects in Period 1
B:P ratio (blood to plasma ratio)	In vitro estimate of human blood-to-plasma ratio for linerixibat
F	Absolute bioavailability from the oral tablets and IV doses administered in Period1 for AUC(0-inf) and AUC(0-t)
Fh	Fraction of linerixibat that escapes first pass liver extraction = Fh = 1 – Eh
Fabs	Fraction of linerixibat absorbed (includes fraction escaping gut extraction) = Fabs = F/Fh
λz	The first order rate constant associated with the terminal (log-linear) portion of the concentration-time curve.
Tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: $t_{½} = \ln 2 / \lambda_z$
Vss,iv	Volume of distribution of at steady-state will be calculated as: $CL*MRT_{iv}$ where the mean residence time (MRT) is calculated as AUMC(0-inf) (area under the first moment curve)/AUC(0-inf). Treatment period 1, analyte [^{14}C]- linerixibat.

Radioactivity Mass Balance in Periods 1 and 2 - Parameter Endpoints and Description	
Parameter	**Description**
Fe%[urine]	% of total dose excreted as total radioactivity for each collection interval : Data provided by Covance/Pharmaron.
Fe%[feces]	% of total dose excreted as total radioactivity for each collection interval: Data provided by Covance/Pharmaron. .
Fe%[total]	% of total dose excreted as radioactivity will be estimated in each collection interval as: Sum of Fe%[urine] and Fe%[feces] - Data provided by Covance/Pharmaron.

9.1.2. Summary Measure

- Summary measures of PK parameters detailed in above table 9.1.1
- Derived PK parameter estimates from plasma linerixibat, plasma^{14}C-linerixibat and plasma total radioactivity in plasma for IV and oral along with other derived PK parameters will be listed and summarised.

- Urinary and fecal recovery, cumulative excretion as percentage of the total radioactive dose over time will be listed and summarised (Treatment Periods 1 and 2 as data permits) in reports provided by Pharmaron and Covance and appended to the Clinical Study Report
- Absolute bioavailability after oral and IV dosing (Treatment Period 1) will be analysed by using AUC(0-t), AUC (0-inf) parameters.

9.1.3. Population of Interest

The PK analyses will be based on the PK population, unless otherwise specified.

9.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 8: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

Plasma linerixibat concentration-time data will be listed for each subject and summarized by period, analyte, treatment and planned sampling time. [^{14}C]-linerixibat and total radioactivity concentrations in plasma will be reported similarly. Individual subject, mean and median plasma linerixibat, [^{14}C]-linerixibat, and total radioactivity concentration–time profiles will be plotted for each treatment on both a linear and semi-log scale. Pharmacokinetic analysis will be performed by or under the direct auspices of Clinical Pharmacology Modelling & Simulation, GSK. Plasma linerixibat, [^{14}C]-linerixibat, and total radioactivity concentration–time data will be analysed by non-compartmental methods with Phoenix WinNonlin Version 6.4 or above. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data the following pharmacokinetic parameters will be determined, for linerixibat, [^{14}C]-linerixibat, and total radioactivity, as data permits: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0–t) and AUC(0-inf)], terminal phase rate constant (λz), and apparent terminal phase half-life (t1/2) following oral and IV dosing. Additionally, volume of distribution at steady state (Vss), renal clearance (CLr), and total systemic clearance (CL) will be derived following IV dosing. These parameters will be summarized descriptively.

All pharmacokinetic data will be stored in the Archives, GlaxoSmithKlinePharmaceuticals, R&D. Production of the summaries, tables, figures and listings of the plasma data will be performed under the direct auspices of Clinical Statistics, GSK. The urine and fecal data for dose recovery estimations will be provided by Pharmaron and Covance under the auspices of BIB/DMPK, GSK.

9.1.4.1. 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
• AUC(0-inf)/dose • AUC(0-t)/dose
Model Specification
• Will be statistically analyzed using a mixed model (MM) for Period1. • Terms fitted in the mixed effect ANOVA model will include: o Fixed effect : Treatment (IV dose/Oral dose in Period1) o Random Effect : Subject • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. Point estimates for the adjusted means on the loge scale, the mean difference between treatments and associated 90% confidence interval for the contrast (test-reference) will be constructed using the residual variance.
Model Checking & Diagnostics
• Dose normalized PK parameters should be used for the analysis. • For the Mixed Model analysis, Model assumptions will be applied, but appropriate adjustments may be made based on the data. • 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. - If there are any departures from the distributional assumptions, alternative transformations, such as data squared, or square root of data, will be explored.
Model Results Presentation
• The point estimate and confidence interval obtained from MM analysis will be exponentially back-transformed to obtain adjusted (least square) geometric means for each treatment. • Point estimates (Absolute Bioavailability of Linerixibat and associated 90% confidence interval for the ratio Oral dose/IV dose (see 9.1.1 for equation)) along with within-subject variability (%CVw) will be reported. Where %CVw=100*(SQRT (EXP(σ_w^2)-1)) and σ_w^2 is the mean squares error (MSE) from the statistical Mixed model.

9.2. Metabolite Profiling Analyses in Plasma, Urine, Feces and Bile

The metabolic profiling/structural characterization aspect of this work will be performed by GSK (or a GSK representative) in a separate BIB/DMPK study report. Data from the quantification of unchanged linerixibat in urine following IV administration will be used in the estimate of renal clearance, as detailed above.

10. REFERENCES

Covance Study Number 8412194. GSK2330672: Absorption and elimination following administration of [14C]-linerixibat to human subjects, 2019.

Davies, B.; Morris, T. Physiological parameters in laboratory animals and humans. Pharm. Res. 1993,10, 1093–1095.

Edginton, A.N., Schmitt, W., Willmann, S. Development and evaluation of a generic physiologically based pharmacokinetic model for children. Clin Pharmacokinetics, 2006, 45(10), 1013-1034.

GlaxoSmithKline Document Number 2010N111289_06. Linerixibat (GSK2330672) Investigator's Brochure, 29-AUG-2019.

GlaxoSmithKline Document Number 2018N388243_00. A two-period study in healthy male volunteers to determine the pharmacokinetics, balance/excretion, and metabolism of [^{14}C]-GSK2330672 following a single intravenous radiolabeled microtracer dose (concomitant with a non-radiolabelled oral dose) and a single oral radiolabeled dose, 22-FEB-2019.

GlaxoSmithKline Study Protocol 19DMM027. Quantification and characterization of [^{14}C]-GSK2330672 and its major metabolites in healthy adult male subjects following a single intravenous radiolabelled microtracer dose (concomitant with a non-radiolabelled oral dose) and a single oral radiolabelled dose.

GlaxoSmithKline Study Report Number 2017N342697_00 and Protocol Number 8367797. A Study to Investigate the In Vitro Plasma Protein Binding and Blood-to-Plasma Partitioning of 14C-GSK2330672 in Mouse, Rat,Rabbit, Dog, and Human Plasma and Blood

GUI_137354: Information for Authors – Reporting and Analysis Plan, Global; GSK.

GUI_51487 (4.0) Non-Compartmental Analysis of Pharmacokinetic Data, CPMS Global.

Mehvar R. Application of organ clearance to estimation of the in vivo hepatic extraction ratio. *Curr Clin Pharmacol*. 2016,11(1),47-52. doi: 10.2174/1574884710666150817104746.

Pharmaron Study Number 001/039. Determination of total radioactivity in urine and feces samples derived from humans administered an IV dose of 250 nCi / 100 µg ^{14}C-linerixibat, 2019.

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

11. APPENDICES

11.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

A Per Protocol Population is not being defined for this study.
Please Refer to Section 4.1 for handling and Reporting of Protocol Deviations.

11.2. Appendix 2: Schedule of Activities

11.2.1. Protocol Defined Schedule of Events

Period 1

Hrs Post-dose / Procedure			-3.5	0	0.5	1.0, 1.5	2.0, 2.5	3.0, 3.5	4.0, 4.5	5.0, 5.5	6	8	10	12	24	36	48	72	96	120	144	168	
Standard small high fat meal[8]							X-2h																
String bile collection device removed[9]								X 3h															
Blood samples for plasma radioactivity[10]	X	X		X	X	X, X	X, X	X, X	X, X	X, X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood samples for plasma drug assay[10]				X	X	X, X	X, X	X, X	X, X	X, X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood samples for plasma metabolites[11]						X 1h	X 2h	X 3h			X 6h												
Genetic sample		X																					
Fecal collection[12]	Day -2 or -1				←																→		
Urine collection[12]			X		←																→		
AE/SAE/Concomitant med. review[13]	←																					→	

Visit	Screening[1]	Day -1	Pre-dose (incl. 0h)	Treatment Period 1																			
Day	-30 to -2	-1	1														2		3	4	5	6	7	8
Hrs Post-dose / Procedure			-3.5	0	0.5	1.0, 1.5	2.0, 2.5	3.0, 3.5	4.0, 4.5	5.0, 5.5	6	8	10	12	24	36	48	72	96	120	144	168	
Informed consent	X																						
Adm. to unit pre-tx		X																					
Discharge from unit[2]																							X
Medical history (including drug/alcohol use)	X																						
Demography	X																						
12-lead ECG [3]	X																						X
Vital signs [4]	X	X	X						X														X
Drugs of abuse screen	X	X																					
Alcohol, cotinine, & CO breath tests	X	X																					
HIV and hepatitis B and C screen	X																						
Laboratory safety tests (incl. LFTs)	X	X																					X
Physical exam [5]	X-full	X																					X
String bile collection test initiated [6]			X																				
Oral linerixibat [7]				X																			
14C-linerixibat IV				←				3h															
Monitor local tolerability (IV)				←				3h															

Abbreviations: AE: adverse event; ECG: electrocardiogram; HIV: human immunodeficiency virus; IV: intravenous; LFTs: liver function tests; PGx: pharmacogenetics; Pre-tx: pre-treatment; SAE: serious adverse event.

Notes:

[1] Screening will be within 30 days before Day 1.

[2] Participants will be discharged for a washout period prior to dosing in Treatment Period 2; there will be at least 13 days between a participant's oral doses. Participants who withdraw from the study early should be subject to those assessments that would be required at discharge in that treatment period, if participants agree.

[3] Single ECG measurements will be obtained. If any measurement is considered abnormal, then two additional ECGs will be taken. The mean of the triplicate measurements will be used. The Screening measurement will be evaluated for eligibility and used as baseline.

[4] Triplicate measurements of heart rate and systolic and diastolic blood pressure; single measurements of tympanic temperature and respiratory rate.
[5] A full physical exam should be performed at baseline, including at minimum: assessments of the eyes, skin, joints, and the cardiovascular, respiratory, gastrointestinal and neurological systems; height, and weight should be measured and recorded, and BMI calculated and recorded. Brief physical exams should be performed at later visits, including at minimum: assessments of the skin, lungs, cardiovascular system, abdomen (liver and spleen) and weight.
[6] The string bile collection device will be swallowed 3.5 h before the oral dose/start of IV infusion, while participants are in a fasted state.
[7] Participants will fast for at least 8 h before oral dosing and continue to fast for 2 h after oral dosing.
[8] Meal time is specified for Day 1 mid-day only: approximately 2h (i.e., 2h ± 15 mins) after oral dose/start of IV infusion to stimulate gall bladder emptying. On all other days, meals will be served at the unit's standard times.
[9] The string bile collection device will be removed 3 h after the oral dose/start of IV infusion (immediately after the end of the IV infusion).
[10] Background radiation will be measured in plasma samples obtained from blood collected at screening, on admission (Day –1), and pre-dose on Day1. Total radioactivity, [^{14}C]-linerixibat analysis, and linerixibat analysis will be performed for all post-dosing plasma samples. All pre-dose plasma samples should be obtained from blood taken immediately prior to the oral dose/start of IV infusion; sampling times are relative to the oral dose on Day 1, unless otherwise indicated.
[11] Plasma samples for metabolite profiling will be obtained from blood samples collected on Day 1 at 1h, 2h, 3h, and 6h post-dosing.
[12] Urine and feces will be collected at pre-dose (up to 3 h pre-dose for the urine sample; up to 24 h pre-dose for the fecal sample). Starting at the time of oral dosing, all urine and feces will be collected as seven 24-h samples throughout Period 1 (total of 168 hours post-dose) in addition to pre-dose samples.
[13] AEs will be collected from the start of study intervention until the final follow-up visit. All SAEs will be recorded from the time each participant consents to participate in the study.

Period 2 Oral solution

Visit	Day -1	Pre-dose (incl. 0h)	Treatment Period 2																		F/up
Day	Day -1	1												2		3	4	5	6	7	8[1]	14 – 21[2,3]
Hrs Post-dose / Procedure		*0*	*0.5*	*1*	*2*	*3*	*4*	*5*	*6*	*8*	*10*	*12*	*24*	*36*	*48*	*72*	*96*	*120*	*144*	*168*		
Admission to unit	X																					
Discharge from unit[4]																					X[4]	
12-lead ECG[5]		X																			X	(X)
Vital signs[6]	X	X					X														X	X
Drugs of abuse screen	X																					
Alcohol, cotinine, & CO breath tests	X																					
Laboratory safety tests (including LFTs)	X																				X	(X)
[^{14}C]-linerixibat oral solution		X																				
Brief physical exam[7]	X																				X	X
Standard small high fat meal[8]					X																	
Blood samples for plasma radioactivity[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood samples for plasma drug assay[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood samples for plasma metabolites[10]				X	X	X			X													
Urine collection[11]		X	←																	→		
Fecal collection[11]		X	←																	→		
AE/SAE/concomitant medication review[12]	←																					→

Abbreviations: AE: adverse event; ECG: electrocardiogram; FU: follow-up; HIV: human immunodeficiency virus; LFTs: liver function tests; SAE: serious adverse event; (X): at follow-up visit, these assessments would only be performed to follow-up a result from the day of discharge.
Notes:
[1] If discharge does not occur on Day 8, the following assessments should be performed on the day of discharge instead of Day 8: vital signs, 12-lead ECG, brief physical examination.
[2] The follow-up will be between 7–14 days after the participant's last assessment in Treatment Period 2.
[3] Participants who withdraw from the study early should be subject to those assessments that would be required at discharge in that treatment period, if participants agree.
[4] Discharge from Period 2 will be contingent upon demonstration of adequate recovery of radioactivity (see Section 4.1.4).
[5] Single ECG measurements will be obtained. If any measurement is considered abnormal, then two additional ECGs will be taken, and the mean of the triplicate measurements used. The Screening measurement will be evaluated for eligibility and used as baseline.
[6] Triplicate measurements of heart rate and systolic and diastolic blood pressure; single measurements of tympanic temperature and respiratory rate.
[7] Brief physical exams should include at minimum assessments of the skin, lungs, cardiovascular system, abdomen (liver and spleen), and weight.
[8] Participants will fast for at least 8 h before oral dosing and continue to fast for 2 h after dosing. Meal time is specified for approximately 2h (i.e., 2h ± 15 mins) after the oral dose on Day 1, when the same small standard high fat meal as in Period 1 will be provided. On all other days, meals will be served at the unit's standard times.
[9] Total radioactivity, [^{14}C]-linerixibat analysis, and linerixibat analysis will include predose and all post-dosing samples: at 0.5h post-dose, then every hour through 8h, then at 10h, 12h, 24h, 36h, 48h, and then daily until discharge. All pre-dose samples should be obtained immediately prior to the oral dose; sampling times are relative to the oral dose on Day 1, unless otherwise indicated.
[10] Plasma samples for metabolite profiling will be obtained from blood samples collected on Day 1 at 1h, 2h, 3h, and 6h post-dosing.
[11] Urine and feces will be collected at pre-dose (up to 3 h pre-dose for the urine sample; up to 24 h pre-dose for the fecal sample). Starting at the time of oral dosing, all urine and feces will be collected as 24-h samples throughout Period 2 (at minimum for 168 hours post-dose) in addition to pre-dose samples. If subjects are required to stay after 168 h post-dose (Day 8), collections will continue at 24-h intervals (see Section 4.1.4).
[12] AEs and SAEs will be collected until the final follow-up visit.

11.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

11.3.1. Study Phases

11.3.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 15 days prior to screening visit
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 5: 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.

11.3.1.2. Treatment Phases for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-Treatment	If AE onset date is on or after treatment start date & on or before treatment stop date. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 1 day
Post-Treatment	If AE onset date is after the treatment stop date. AE Start Date > Study Treatment Stop Date + 1 day
Onset Time Since 1st Dose (Days, hours, mins)	Start/Stop Time is Collected: (AE Onset Date/time - Treatment Start Date/time) / 60 Start or Stop Time is missing: If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 day Missing otherwise.
Duration (Days, hours, Mins)	Start/Stop Time is Collected: Onset Time = (AE Resolution Date/time – AE Onset Date/time) / 60 Start or Stop Time is missing: AE Resolution Date – AE Onset Date + 1 day
Drug-related	If relationship is marked 'YES' on [Inform/CRF OR value is missing].

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.

11.3.2. 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. • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date+ 1 day • 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 + 1 day

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.

11.4. Appendix 4: Data Display Standards & Handling Conventions

11.4.1. Reporting Process

Software	
• The SAS Version 9.4 or above and Phoenix WinNonlin Version 6.4 or above will be used.	
Reporting Area	
HARP Server	: us1salx00259
HARP Compound	: \ARPROD\ GSK2330672\mid205895
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards SDTM IG Version 3.1.3 ADaM IG Version 1.1. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for final SAC.	

11.4.2. 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

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.

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.	

11.4.3. 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 as per GUI_51487 (4.0), Noncompartmental Analysis of Pharmacokinetic Data. Note: Concentration values will be imputed as per GUI_51487
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 for descriptive summary statistics/analysis and summarized graphical displays only.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	• Ratios will be provided by CPMS. [AUC/Dose, (dose from IV infusion of [14C]-linerixibat in Period 1 (~100 µg) and oral dose of [^{14}C]-linerixibat in Period 2 (~90 mg) will be slightly different for each participant and will be corrected, calculated and provided in Pharmaron and Covance reports. A listing of dose will not be needed for CSR. • Ratio of plasma [^{14}C] linerixibat / total radioactivity for Cmax, AUC(0-inf), AUC(0-t) for periods 1 and 2 (refer to 9.1.1 for calculation of ratio) • Total radioactivity only - Fe%[urine], Fe%[feces], Fe%[total] – These will be provided by Pharmaron and Covance
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. Refer to IDSL Statistical Principle 6.06.1.

11.4.4. 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

11.4.5. Study Population

Demographics
Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: • Any subject with a missing day will have this imputed as day '15'. • Since Year of Birth is recorded in pCRF, date and month will be imputed as '30th June' of that year. • Birth date will be presented in listings as 'YYYY'. • The Date of Birth will be assumed to be 30 June YYYY and age will be calculated at screening visit using this assumed date of birth.
Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height (m)]2
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** • For each period consider start date and stop date for duration of exposure. Subjects who were allocated to treatment but did not report a treatment start date will be categorized as having zero days of exposure.

11.4.6. 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 decimal places in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  • Example 1: 2 Decimal Places = '< x' becomes x – 0.01
  • Example 2: 1 Decimal Places = '> x' becomes x + 0.1
  • Example 3: 0 Decimal Places = '< x' becomes x – 1

ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as : [1] If QTcB is machine read & QTcF is not provided, then :

ECG Parameters
$$RR = \left[\left(\frac{QT}{QTcB}\right)^{2}\right] * 1000$$ [2] If QTcF is machine read and QTcB is not provided, 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. • Machine read values of RR should not be replaced with derived values.
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as : $$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}}$$ $$QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

11.4.7. Pharmacokinetic

PK Endpoints
Listed in 9.1.1
• PK endpoints used to assess the bioavailability i.e. AUC(0-t) and AUC (0-∞) will be divided by corresponding dose (converted into pg and assuming AUC is h*pg/mL) before passing to MM model for estimation of mean and 90% confidence intervals for absolute bioavailability(F). AUC/Dose ratios will be provided by CPMS. Actual doses for radiolabelled doses will be provided in Pharmaron and Covance reports. • The ratio of plasma [^{14}C] linerixibat/total radioactivity for Cmax, AUC(0-inf),and AUC(0-t) will be calculated and summarized for radiolabelled dose in periods 1 and 2. (see calculation in 9.1.1)

11.5. Appendix 5: Reporting Standards for Missing Data

11.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as one who has completed all phases of the study including the last follow-up visit. • The end of the study is defined as the date of the last contact with the last participant in the study. • Withdrawn subjects will not be replaced unless the total number of participants who complete dosing and all critical assessments drops below 4. • All available data from subjects 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.

11.5.2. 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 subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.5.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	○ The pCRF 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 3: Study Phases and Treatment Emergent Adverse Events. ○ Missing Start Month: January will be used as the Month unless this is before the Month of start of the study treatment; in that case the Month of study treatment start will be used. ○ 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. ○ Missing Month of Stop: December will be used as the Month unless this is after the Month of stop of the study treatment; in that case the Month of study treatment stop, 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.

Element	Reporting Detail
	○ Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the pCRF 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. • The recorded partial date will be displayed in listings.

11.6. Appendix 6: Values of Potential Clinical Importance

11.6.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Δ from BL	↓0.075	
Hemoglobin	g/L	Male		180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
White 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	2.75
Creatinine	µmol/L	Δ from BL	>30% increase from Baseline	
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150

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

11.6.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTcF	msec		500
Absolute PR Interval	msec	110	240
Absolute QRS Interval	msec		120

11.6.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	85	160
Diastolic Blood Pressure	mmHg	40	90
Heart Rate	bpm	35	100
Respiration Rate	BREATHS/min	8	20

11.7. Appendix 7: Abbreviations & Trade Marks

11.7.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
AUC(0–inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0–t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments
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
DR	Dry Run
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
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control

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

11.7.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
Excel
Phoenix WinNonlin
SAS

11.8. Appendix 8: List of Data Displays

11.8.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.10	
Safety	2.1 to 2.12	
Pharmacokinetic	3.1 to 3.7	3.1 to 3.6
Section	**Listings**	
ICH Listings	1 to 25	
Other Listings	26 to 34	

11.8.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 9: 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.'

11.8.3. Deliverables

Delivery	Description
DR	Dry Run
SAC	Final Statistical Analysis Complete

11.8.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1xo	Summary of Participant Disposition for the Participant Conclusion Record		DR, SAC
1.2.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure		DR, SAC
1.3.	Enrolled	NS1	Summary of Number of Participant by Country and Site ID		DR, SAC
Protocol Deviation					
1.4.	Safety	DV1	Summary of Important Protocol Deviations		DR, SAC
Population Analysed					
1.5.	Screened	SP1A	Summary of Study Populations		DR, SAC
Demographic and Baseline Characteristics					
1.6.	Safety	DM1xo	Summary of Demographic Characteristics	Include height, weight & BMI.	DR, SAC
1.7.	Enrolled	DM11	Summary of Age Ranges		DR, SAC
1.8.	Safety	DM5	Summary of Race and Racial Combinations		DR, SAC
Prior and Concomitant Medications					
1.9.	Safety	CM1	Summary of Concomitant Medications	ICH E3	DR, SAC
Exposure and Treatment Compliance					
1.10.	Safety	EX1	Summary of Exposure to Study Treatment	ICH E3	DR, SAC

11.8.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
2.1.	Safety	AE1xo	Summary of All Adverse Events by System Organ Class and Preferred Term		DR, SAC
2.2.	Safety	AE1xo	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and by Overall Frequency		DR, SAC
Serious and Other Significant Adverse Events					
2.3.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)		DR, SAC
Laboratory: Chemistry					
2.4.	Safety	LB1	Summary of Chemistry Changes from Baseline	Includes baseline values.	DR, SAC
2.5.	Safety	LB1	Summary of Chemistry Values		DR, SAC
2.6.	Safety	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline		DR, SAC
Laboratory: Hematology					
2.7.	Safety	LB1	Summary of Hematology Changes from Baseline	Includes baseline values.	DR, SAC
2.8.	Safety	LB1	Summary of Hematology values		DR, SAC
2.9.	Safety	LB15	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline		DR, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
2.10.	Safety	EG1	Summary of ECG Findings		DR, SAC
2.11.	Safety	EG2	Summary of ECG Values		DR, SAC
Vital Signs					
2.12.	Safety	VS1	Summary of Change from Baseline in Vital Signs	Includes baseline values.	DR, SAC

11.8.6. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Plasma linerixibat and Plasma [^{14}C] linerixibat					
3.1.	PK	pkct1	Summary of Plasma Linerixibat and [^{14}C] Linerixibat Concentration by period, treatment and time	Linerixibat: Summarized for A1 and B [^{14}C] linerixibat: Summarized for A2 and if available for B treatment Group by period and dose	DR, SAC
3.2.	PK	pkpt1	Summary of Untransformed Plasma Linerixibat and [^{14}C] Linerixibat Pharmacokinetic Parameters	Linerixibat : Summarized for A1 and B [^{14}C] linerixibat: Summarized for A2 and if available for B Group by period and treatment	DR, SAC
3.3.	PK	pkpt3	Summary of Loge-transformed Plasma Linerixibat and [^{14}C] Linerixibat Pharmacokinetic Parameters	Linerixibat: Summarized for A1 and B [^{14}C] linerixibat: Summarized for A2 and if available for B treatment group Group by period and treatment	DR, SAC
Total Radioactivity					
3.4.	PK	pkct1	Summary of Plasma Total Radioactivity Concentration by Period, Treatment and Time	Summarized by Period A1 and B Group by period and treatment	DR, SAC
3.5.	PK	pkpt1	Summary of Untransformed Plasma Total Radioactivity Pharmacokinetic Parameters	Summarized by Period A1 and B Group by period and treatment	DR, SAC
Other Output					
3.6.	PK	pkpt3	Summary of Loge-transformed Plasma Total Radioactivity Pharmacokinetic Parameters	Same as Table 3.3 Group by period	DR, SAC
PK Statistical Analysis					
3.7.	PK	PK_T2	Summary of Statistical Analysis of Loge-transformed Plasma Linerixibat PK Parameter	Summarize for Period 1	DR, SAC

11.8.7. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Plasma linerixibat and Plasma [^{14}C] linerixibat					
3.1.	PK	pkcf6	Individual Subject Plasma Linerixibat and [^{14}C] Linerixibat Concentration-time Plot (Linear and Semi-log) by Period and Treatment	Different plot symbols will be used for each subject	DR, SAC
3.2.	PK	pkcf2	Arithmetic Mean Plasma Linerixibat and [^{14}C] Linerixibat Concentration-time Plot (Linear and Semi-log) by Period and Treatment		DR, SAC
3.3.	PK	pkcf3	Median Plasma Linerixibat and [^{14}C] Linerixibat Concentration -time Plot (Linear and Semi-log) by Period and Treatment		DR, SAC
Total Radioactivity					
3.4.	PK	pkcf6	Individual Subject Plasma Total Radioactivity Concentration-time Plot (Linear and Semi-log) by Period and Treatment		DR, SAC
3.5.	PK	pkcf2	Arithmetic Mean Plasma Total Radioactivity Concentration-time Plot (Linear and Semi-log) by Period and Treatment		DR, SAC
3.6.	PK	pkcf3	Median Plasma Total Radioactivity Concentration -time Plot (Linear and Semi-log) by Treatment		DR, SAC

11.8.8. 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		DR, SAC
2.	Safety	ES2xo	Listing of Reasons for Study or Treatment Withdrawal		DR, SAC
Protocol Deviations					
3.	Safety	DV2xo	Listing of Important Protocol Deviations		DR, SAC
4.	Safety	IE3xo	Listing of Participants with Inclusion/Exclusion Criteria Deviations		DR, SAC
Demographic and Baseline Characteristics					
5.	Safety	DM2xo	Listing of Demographic Characteristics		DR, SAC
6.	Safety	DM9xo	Listing of Race		DR, SAC
Prior and Concomitant Medications					
7.	Safety	CM10xo	Listing of Concomitant Medications		DR, SAC
Exposure and Treatment Compliance					
8.	Safety	EX3xo	Listing of Exposure Data		DR, SAC
Adverse Events					
9.	Safety	AE8CPxo	Listing of All Adverse Events		DR, SAC
10.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		DR, SAC
11.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		DR, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Serious and Other Significant Adverse Events					
12.	Safety	AE8CPAxo	Listing of Serious Adverse Events		DR, SAC
13.	Safety	AE8CPxo	Listing of Adverse Events Leading to Withdrawal from Study		DR, SAC
14.	Safety	AE8CPxo	Listing of Treatment Emergent AEs		DR, SAC
Hepatobiliary (Liver)					
15.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		DR, SAC
16.	Safety	MH2xo	Listing of Medical Conditions for Subjects with Liver Stopping		DR, SAC
17.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events		DR, SAC
All Laboratory					
18.	Safety	LB5xo	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance/Outside Normal Range		DR, SAC
19.	Safety	LB5xo	Listing of Laboratory Values of Potential Clinical Importance		DR, SAC
20.	Safety	UR2xo	Listing of Urinalysis Data for Subjects with Positive Dipstick Results		DR, SAC
ECG					
21.	Safety	EG3xo	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance		DR, SAC
22.	Safety	EG3xo	Listing of ECG Values of Potential Clinical Importance		DR, SAC
23.	Safety	EG5xo	Listing of All ECG Findings for Participants with an Abnormal ECG Finding		DR, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
24.	Safety	VS4xo	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL Required for ClinPharm studies only. Display ALL Vital Signs for a subject who experienced a value of potential clinical importance.	DR, SAC
25.	Safety	VS4xo	Listing of Vital Signs of Potential Clinical Importance	IDSL Required for ClinPharm studies only.	DR, SAC

11.8.9. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
26.	PK	pkcl1x	Listing of Plasma Linerixibat and [^{14}C] – Linerixibat Concentration-Actual Time Data by period, treatment and time		DR, SAC
27.	PK	pkpl1x	Listing of Plasma Linerixibat and [^{14}C] – Linerixibat Pharmacokinetic Parameters by period and treatment		DR, SAC
28.	PK	pkcl1x	Listing of Plasma Total-Radioactivity Concentration -Actual Time Data by period, treatment and time		DR, SAC
29.	PK	pkpl1x	Listing of Plasma Total -Radioactivity Pharmacokinetic Parameters by period and treatment		DR, SAC
30.	PK	N/A	Supportive SAS Output from Statistical Analysis of Loge-transformed Plasma Linerixibat GSK Pharmacokinetic Parameters		DR , SAC

11.9. Appendix 9: Example Mock Shells for Data Displays

Data Display Specification will be made available on request.