TITLE PAGE

Protocol Title: 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

Protocol Number: 206224

Compound Number or Name: GSK2330672

Study Phase: I

Short Title: Linerixibat and obeticholic acid drug interaction study in healthy participants

Sponsor Name and Legal Registered Address:

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6/5/2019
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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: 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

Short Title: Linerixibat and obeticholic acid drug interaction study in healthy participants

Rationale: GSK2330672 (linerixibat) is a selective inhibitor of the human ileal bile acid transporter (IBAT) and is designed to be a non-absorbable agent restricted to the gastrointestinal tract. It is currently in development in Phase IIb as a novel oral treatment for pruritus in cholestatic liver disease. For patients with Primary Biliary Cholangitis (PBC), increased excretion of bile acids following IBAT inhibition is expected to reduce bile acid concentrations in the liver and systemic circulation, resulting in reduced hepatobiliary inflammation and improvement of the systemic symptom of pruritus.

Obeticholic acid (OCA), also known as Ocaliva is a farnesoid X receptor (FXR) agonist. FXR agonism reduces bile acid synthesis both by increasing ileal FGF19 secretion and by direct effects on hepatic CYP7A1 regulation. OCA is indicated for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

In the clinical setting there is potential for linerixibat to be used in combination with OCA, in patients with inadequate response/intolerance to UDCA taking OCA who experience pruritus (due to PBC, OCA, or both). The addition of linerixibat to OCA therapy may be considered following marketing approval. This drug-drug interaction (DDI) study is being conducted to characterize any potential effect of linerixibat on the pharmacokinetics of OCA or it's conjugates in healthy participants at clinically relevant dosages.

Objectives and Endpoints:

Primary objectives	**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-	• Same as Part A

Primary objectives	**Endpoints**
OCA) and glycine (glyco-OCA) conjugates) when linerixibat and OCA administration is separated by 12 hours or an alternative dose or dosing regimen	
Secondary objectives:	**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
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
Parts A & B: 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, and Tmax (Linerixibat Day 1 (Study Day 20) and Day 14 (Study Day 33)).

Overall Design:

Study 206224 is an 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. The study will be conducted in a single research centre specialized in the conduct of Phase 1 clinical trials.

If a clinically important OCA/linerixibat drug-drug interaction (DDI) (average Ctrough of total-OCA <20ng/mL) is detected using this definition, the sponsor may consider the merit of conducting a follow-up study part (**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 decision to conduct **Part B**, the dose and the dosing regimen to be used will require careful assessment of all PK parameters measured and analyzed in Part A. Based on the analysis of preliminary PK from Part A for OCA and conjugates the

results and conclusion must be reached that alternative once-daily linerixibat dosing separated by 12 hours has the potential to reduce the DDI observed in Part A.

Importantly, 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.

Disclosure Statement: This is an Intervention Model (O)

Number of Participants:

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 15 participants complete Part B of the study (if it is conducted).

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

Intervention Groups and Duration:

The total duration of study participation in Parts 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 an initial 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).

1.2. Schema

Figure 1 Part A Study Design

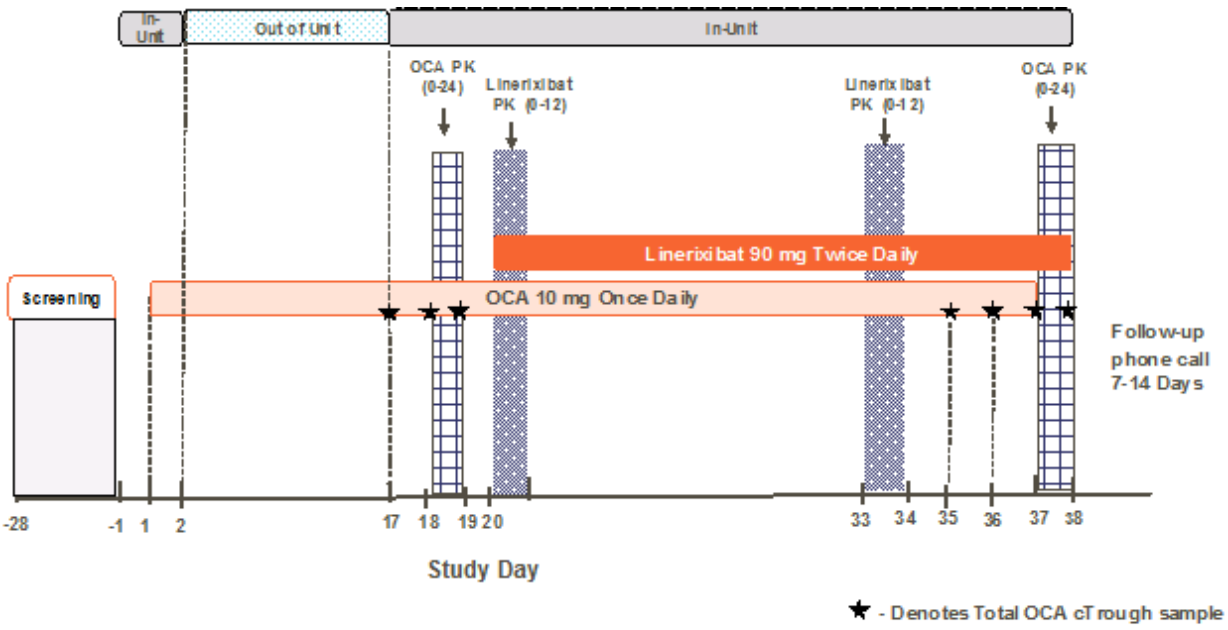
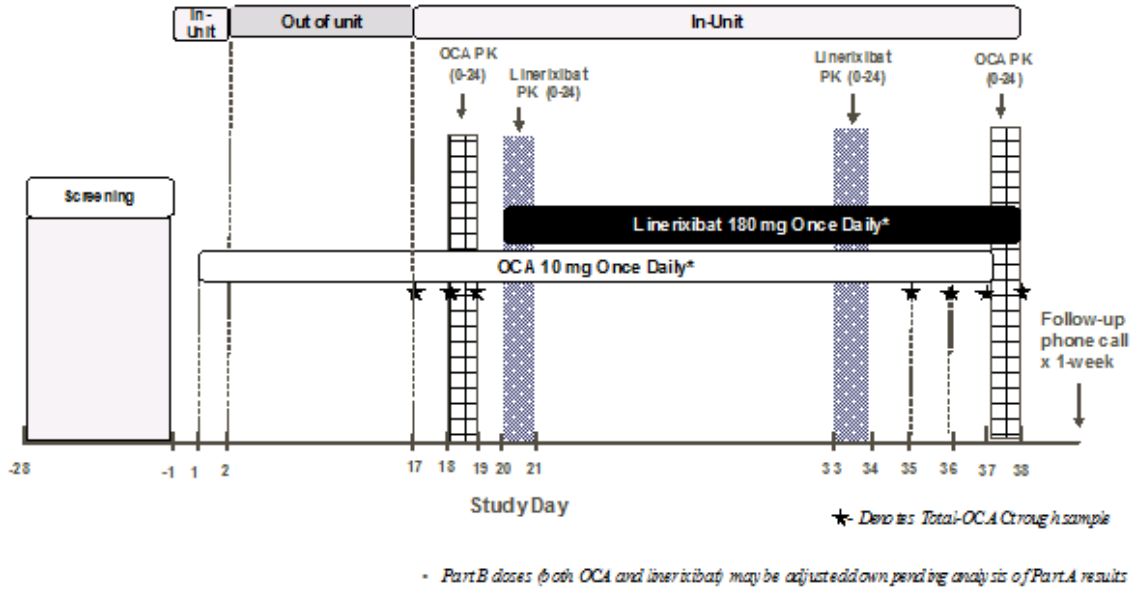


Figure 2 Part B (Optional) Study Design



1.3. Schedule of Activities (SoA)

Table 1 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 8.2.1 for minimum requirements. Weight measurement to be included
Brief Physical Exam			X	Please see Section 8.2.1 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				

Table 2 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
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 8.2.1 for minimum requirements. Weight measurement to be included

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	
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 8.5
OCA PK Sampling					X	X	X						X	X	X	X	
PGx sample		X															
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.

Table 3 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.
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 8.2.1 for minimum requirements. Weight measurement to be included

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	
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 8.5.
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
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.

2. INTRODUCTION

2.1. Study Rationale

Primary biliary cholangitis (PBC), formally known as primary biliary cirrhosis is a chronic autoimmune liver disease characterized by chronic, progressive cholestasis [Metcalf, 1996], resulting in impaired flow of bile through the biliary tree and bile acid retention in the enterohepatic circulation (EHC). Additionally, upregulation of intestinal bile acid transport has been reported and is thought to contribute to the symptoms and progression of PBC [Hofmann, 2009] by exceeding the capacity of the canalicular bile acid export pump. This failure of normal homeostasis could lead to accumulation of bile acids in the hepatocyte, resulting in hepatocyte necrosis or apoptosis [Woolbright, 2012], and often end stage liver disease. In the cholangiocyte, the accumulation of these potentially toxic molecules may exacerbate inflammation and necrosis of the bile ductules further. The primary symptom of cholestasis is pruritus (itching), which has an identified mechanistic association with the accumulation of bile acids [Hegade, 2016] and represents a significant unmet medical need for patients.

GSK2330672 (linerixibat) is a selective inhibitor of the human ileal bile acid transporter (IBAT) and is designed to be a non-absorbable agent restricted to the gastrointestinal tract. It is in development as a novel oral treatment for pruritus in cholestatic liver disease. The IBAT is a member of the sodium-dependent bile salt transport protein family, SLC10A2 [Dawson, 2003]. Preferentially expressed in the distal ileum of the gastrointestinal tract, the IBAT actively carries bile acids from the gut lumen across the brush border of the ileal enterocytes for delivery to the liver via portal blood flow, resulting in efficient enterohepatic conservation of bile acids. It maintains ileal negative feedback regulation of hepatic bile acid synthesis via FGF19 signalling to the liver, which leads to down-regulation of hepatic CYP7A1 and reduced plasma levels of the bile acid synthesis intermediate called 7α-Hydroxy-4-cholesten-3-one (C4). For patients with PBC, decreased absorption and increased excretion of bile acids following IBAT inhibition is expected to reduce bile acid concentrations in the liver and systemic circulation, resulting in reduced hepatobiliary inflammation and improvement of the systemic symptom of pruritus. GSK2330672 is currently in development Phase 2B where it is being studied in a population of patients with PBC and pruritus.

Obeticholic acid (OCA), also known as Ocaliva is a farnesoid X receptor (FXR) agonist. FXR agonism reduces bile acid synthesis both by increasing secretion of ileal FGF19, which regulates bile acid synthesis by inhibiting CYP7A1 and by direct effects on regulation of hepatic CYP7A1.which converts cholesterol to 7-alpha-hydroxycholesterol, required for bile acid synthesis. OCA is indicated for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

2.2. Background

In the clinical setting there is potential for linerixibat to be used in combination with OCA. In patients with inadequate response/intolerance to UDCA taking OCA who

experience pruritus (due to PBC, OCA, or both) the addition of linerixibat to OCA therapy may be considered following marketing approval. It is therefore important to characterize any potential effect of linerixibat on the pharmacokinetics of OCA in humans at clinically relevant dosages. OCA is a bile acid and may rely to some extent on the IBAT receptor in the terminal ileum for its absorption. Additionally, OCA has biologically active conjugates which enter the EHC and since linerixibat inhibits the IBAT receptor, it is important to determine whether linerixibat inhibits the absorption of OCA or its conjugates to a clinically significant degree. Accordingly, a drug interaction (DDI) study with linerixibat (potential perpetrator) and OCA (potential victim) is being conducted to inform both future clinical trials with linerixibat and the potential concomitant administration of these drugs in a clinical setting. Participants taking OCA have heretofore been ineligible for clinical trials with linerixibat, including a completed Phase IIa trial (BAT117213) and an ongoing Phase IIb trial (Study 201000), and data from this study may allow future participation of these patients.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and potential adverse events of linerixibat (GSK2330672) may be found in the GSK2330672 Investigator's Brochure (GSK Document number 2010N111289_05) and in the current full prescribing information for Ocaliva.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK2330672]		
• Diarrhoea/GI symptoms	• Animal studies have shown diarrhoea and GI symptoms including altered bowel motions (see Investigator's Brochure (IB) GSK Document number 2010N111289_05; Section 4.5). • AEs for diarrhoea and GI symptoms have been recorded in human studies to date including loose stools (see IB GSK Document number 2010N111289_05 Section 5.3).	• Exclusion criteria have been added excluding participants with a history of gastrointestinal disease, cholesystectomy and any current episode or recent chronic history of clinically significant diarrhoea (See Section 5.2) • In this DDI study participants who may experience diarrhoea will not be permitted the use of anti-diarrheal medications of any kind.
• Potential gallstones due to interruption of enterohepatic recirculation of bile acids	• Report of gallstone formation associated with genetic polymorphisms of the iBAT gene SLC10A2 in human studies (See IB, Version 05, GSK Document number 2010N111289_05 Section 5.3.1). A nonfatal SAE of acute cholecystitis leading to hospitalisation for cholecystectomy and withdrawal from study intervention: Prior to dosing with metformin and linerixibat, the participant experienced diarrhoea, back pain and WBC count above the reference range. The SAE was considered not attributable to study drug by the investigator.	• Exclusion criteria have been added to exclude participants with current symptomatic cholelithiasis or inflammatory gall bladder disease (See Section 5.2). • Participants will be informed that a possible risk of gallstones exists, but that studies in participants taking linerixibat have not shown an increase in reports of gallstones • Investigative staff will monitor participants for symptoms and signs of cholelithiasis in the informed consent form.
• Increase in alanine aminotransferase (ALT).	• Minor reversible ALT elevations have been reported in healthy participant studies (see IB GSK Document number	• Clear stopping criteria have been added as described in Section 7.1.1. • Exclusion criteria have been added to exclude participants with elevated ALT (see

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	2010N111289_05 Section 5.3).	Section 5.2.
Ocaliva		
• Pruritus	• Risk of pruritis as described in the summary of product characteristics (SMPc) for Ocaliva	• The risk of pruritus in healthy participants is small. Exclusion criteria have been added to exclude participants with a history of dermatologic disorders or clinically significant itching as described in Section 5.2.
Other		
• Self-Administration of OCA by Participants	• Participants will be self-administering OCA outside of the clinical unit. There is a risk that if participants do not administer the intervention during the required time window. This may introduce variability and affect data interpretation	• During the period of self-administration, the clinical unit will be confirming compliance with the participants on a daily basis and ensure daily compliance from the participants to the extent possible. Participants will be given training and instructions prior to discharge from the clinical unit on Day 2 and drug accountability will be performed when the participants return to the unit.
• Study participation outside of the unit	• During study participation outside of the until participants may violate protocol specified procedures by taking prohibited medications, consuming prohibited food items or engaging in prohibited behaviours (i.e. smoking)	• Participants who report non-compliance or demonstrate non-compliance with study medication or violate protocol procedures will be assessed on a case-by-case basis with the sponsor and may be asked to perform early withdrawal assessments and be withdrawn from study participation.

2.3.2. Benefit Assessment

There is no clinical benefit for healthy participants taking part in this study. However, participants will undergo a medical evaluation during screening (including a physical examination, ECG, vital signs and laboratory assessments), which may provide important health information.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures that will be implemented to minimise the risk to participants participating in the clinical study, the potential risks associated with the administration of GSK2330672 are considered to be justified by the potential benefits that may be afforded to patients with PBC if this and future studies with GSK2330672 are deemed successful for the participants from the study treatment.

3. OBJECTIVES AND ENDPOINTS

Primary objectives	**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:	**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
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-	• Same as Part A

Primary objectives	Endpoints
OCA) and glycine (glyco-OCA) conjugates) when linerixibat and OCA administration is separated by 12 hours or an alternative dose or dosing regimen	
Parts A & B: 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, and Tmax (Linerixibat Day 1 (Study Day 20) and Day 14 (Study Day 33)).

4. STUDY DESIGN

4.1. Overall Design

This is a single-centre, 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. The study will be conducted in a single clinical unit specialized in the conduct of Phase 1 clinical trials.

Each participant will be screened up to 28-35 days before their first dose and will have a follow up call at 7-14 days post-last linerixibat dose.

The study is designed to assess the effect of oral linerixibat as a potential perpetrator on the pharmacokinetics of OCA (victim), its taurine (tauro-OCA) and glycine (glyco-OCA) conjugates, and total-OCA (summation of OCA + both conjugates). OCA, tauro-OCA and glyco-OCA are equipotent.

In a Phase 3 study with PBC patients, an exposure-response relationship was derived for % reduction of alkaline phosphatase (ALP) and Ctrough of total-OCA concentrations. At 6 months the median total-OCA Ctrough was 45.3 ng-eq/mL. Therefore, average total-OCA Ctrough concentrations >40ng/mL were predicted to decrease ALP by at least 30%. There was plateauing of ALP reduction with higher trough concentrations. Therefore, total-OCA Ctrough concentrations of >40ng/mL are clinically important concentrations for PBC patients.

In the FDA CDER Clin Pharm review, the reviewers compared steady state plasma concentrations in PBC patients to steady state plasma concentrations in healthy participants. In general, PBC patients had higher plasma total-OCA trough concentrations compared to healthy participants though exact quantitation is difficult to know from the available data. Therefore 2-fold difference was deemed to be the best estimate. These comparisons were made across studies and ranged from 0.76 to 3.46 with most data

pointing to PBC greater than healthy participants. Because this study will be conducted in healthy participants, the plasma target has been adjusted to reflect the study population. Therefore, average total-OCA Ctrough (predose concentrations) of 40 ng-eq/mL in PBC patients has been adjusted down to 20 ng-eq/mL for healthy participants. In the context of this study, a clinically important threshold of total-OCA Ctrough following coadministration with linerixibat 90 mg twice-daily for 18 consecutive days is ≥20ng-eq/mL.

If a clinically important OCA/linerixibat DDI (average Ctrough of total-OCA <20ng/mL) is detected using this definition the sponsor may consider the merit of conducting a follow-up study part (**Part B**) investigating a suggested alternative 180 mg once daily morning dose of linerixibat separated by 12 hours from OCA (once daily) dosed in the evening. The final doses of OCA and linerixibat used in Part B will be decided based on emerging PK data. The decision to conduct **Part B** will require careful assessment of all PK parameters measured and analyzed in Part A. Based on the analysis of preliminary PK from Part A for OCA and conjugates the results and conclusion must be reached that alternative once-daily linerixibat dosing separated by 12 hours has the potential to reduce the DDI observed in Part A.

Pharmacokinetic sampling of linerixibat is included in this protocol due to the general lack of plasma PK data available for linerixibat. In the early development of linerixibat, the assay used to quantify linerixibat in plasma had a lower limit of quantitation (LLQ) of 1ng/mL and most of the samples collected in clinical trials were below the LLQ. Recently, a new bioanalytical method was developed with a 100-fold improvement in the LLQ to, 10 pg/mL. The risk of OCA interfering with linerixibat PK sampling is considered minimal and acceptable and saves conduct of an additional cohort of participants.

4.1.1. Part A

The total duration of study participation in Part A is expected to be 52 days exclusive of the screening visit (up to 28-35 days). Participants will stay in the clinical unit for an initial 2 nights (Day-1 to Day 2) before being discharged for 15 days of home dosing (Day 3 to Day 17). Participants will then return to the clinical unit for a further 21 overnight stays (Day 17 to Day 38).

Approximately 19 participants will be enrolled providing 15 completers estimating an approximate 20% withdrawal rate. Additional participants may be enrolled to ensure 15 completers. A participant is considered to have completed the study if he/she has completed all phases of the study up until discharge from the clinical unit on Day 38.

OCA will be dosed at 10 mg once-daily (once daily) 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.

Following informed consent and successful screening, enrolled participants will take OCA once-daily in the afternoon at approximately 12:00 – 14:00 while in the clinical unit

on Study Days 1 and 2. Upon completion of all study assessments on Day 2, participants will be dispensed OCA for home dosing (Days 3-16), a diary card to record dosing information (date and times) and detailed study instructions and be permitted to leave the clinical unit for 15 days returning on the morning of study Day 17. While participating in the study outside of the clinic participants will be required to report adverse events, contact centre personnel with questions and record the time of their daily OCA administration using study provided materials.

On Study Days 3-16, participants will self-administer the OCA dose in the afternoon (between approximately 12:00 and14:00) with a meal or snack. Participants will use a paper diary to record the date and time the dose was taken. The clinical unit will be in regular contact daily with the participants to remind them to take their daily dose of OCA within the specified period.

Participants will return to clinic on the morning of Day 17 to prepare for their next scheduled OCA dose. On Study Days 17, 18 and 19 pre-dose total-OCA Ctrough samples will be collected. On Day 18 samples for OCA PK profiles will be collected for 24 hours as described in Section 8.5.1. Eighteen days is considered sufficient time for OCA to reach steady state after continuous daily dosing. On Study Days 20 and 33, PK samples (0 to 12 h) for linerixibat will be collected. The last dose of OCA will be administered in the afternoon of Day 37 and the last dose of linerixibat will be administered in the morning of Study Day 38. Predose total-OCA Ctrough samples will be collected on Study Days 35, 36, 37 and 38. On Study Day 37 samples will be collected for OCA PK (0 to 24 h). Participants will be discharged from the clinical unit following the final PK sample on Study Day 38, once after all protocol specified lab samples are collected participants will be provided complete discharge instructions. These instructions will include details of how to contact the clinical unit with any questions, or concerns. A follow-up phone call will take place for all participants approximately 7 to 14 days following final dose of linerixibat.

4.1.2. Part B (Optional)

Part B is optional. If required, it will be conducted as demonstrated in Section 1.2 following procedures as demonstrated in Section 1.3. In Part B, it is intended that linerixibat will be dosed as 180mg once daily in morning (e.g., 8:00am) and OCA will be dosing once daily in the evening (e.g., 8:00pm) separated by approximately 12 hours from the morning linerixibat dose. The PK sampling schedule will also differ and will be taken over 24 h., as described in Section 8.5.2.

On Days 3-16 the OCA dose will be self-administered from the participant's home. The OCA dose will be taken in the evening (approximately 20:00), with a snack or meal.

The doses, dose regimen (once or twice daily) and dosing window of linerixibat and/or OCA once daily (5mg or 10mg) in Part B may be changed as necessary based upon analysis of emerging PK, safety or tolerability findings.

4.2. Scientific Rationale for Study Design

The absorption, metabolism and excretion of linerixibat have been studied in pre-clinical animal models, in vitro, and in previous clinical trials. However, no dedicated clinical studies of drug absorption, metabolism, and excretion have been conducted for linerixibat to date. The dose of 90 mg (twice daily) of linerixibat is dose tested in a completed Phase 2a study (BAT117213) and currently being evaluated in an ongoing randomized, double-blind Phase IIb study (Study 201000) assessing linerixibat as a treatment for cholestatic pruritus in patients with PBC. There have been no human studies assessing a potential DDI between linerixibat and OCA.

Several clinical pharmacology studies have been conducted in healthy participants with doses of OCA ranging from 5mg to 250mg (FDA CDER Clin Pharm Review, 2016) Five drug interaction studies have been completed with 10mg and 25mg in healthy volunteers for up to 28 days (Edwards, 2017). The pharmacokinetics of OCA is described below as referenced in product labelling [Ocaliva SMPc, 2018].

Absorption

Following multiple oral doses of OC 10 mg given once daily, peak plasma concentrations (Cmax) of OCA occurred at a median time (Tmax) of approximately 1.5 hours. The median Tmax for both the glyco- and tauro-conjugates of OCA was 10 hours. Coadministration with food did not alter the extent of absorption of OCA.

Following multiple-dose administration of OCA 5, 10, and 25 mg given once daily (2.5 times the highest recommend dosage) for 14 days, systemic exposures of OCA increased dose proportionally. Exposures to glyco-OCA and tauro-OCA, and total OCA (the sum of OCA and its two active conjugates) increased more than proportionally with dose.

Distribution

Human plasma protein binding of OCA and its conjugates is greater than 99%. The volume of distribution of OCA is 618 L. The volumes of distribution of glyco- and tauro-OCA have not been determined.

Metabolism

Obeticholic acid (OCA) is conjugated with glycine or taurine in the liver and secreted into bile. These glycine and taurine conjugates of OCA are absorbed in the small intestine leading to enterohepatic recirculation. The conjugates can be deconjugated in the ileum and colon by intestinal microbiota, leading to the conversion to OCA that can be reabsorbed or excreted in feces, the principal route of elimination.

After daily administration of OCA, there was accumulation of the glycine and taurine conjugates of OCA, which have *in vitro* pharmacological activities similar to the parent drug, OCA. The metabolite-to-parent ratios of the glycine and taurine conjugates of OCA were 13.8 and 12.3 respectively, after daily administration. An additional third OCA metabolite, 3-glucuronide, was formed but was considered to have minimal pharmacologic activity. Total-OCA (OCA+OCA conjugates) t1/2 is reported as 4 days.

Excretion

After administration of radiolabeled OCA, about 87% of the dose was excreted in feces through biliary secretion. Less than 3% of the dose was excreted in the urine with no detection of OCA.

Specific Populations

Age, Sex Race/Ethnicity: Based on population pharmacokinetic analysis, the pharmacokinetics of OCA would not be expected to be altered based on age, sex, or race/ethnicity, therefore there is no need to restrict age range to a younger or older population.

4.3. Justification for Dose

4.3.1. Linerixibat

PBC patients have received linerixibat (GSK2330672) in clinical trials at a dose of 45 mg twice daily increased to 90 mg twice daily after 3 days and continued for 14 days in total (BAT117213). The linerixibat dose chosen in Part A of this study is 90 mg twice daily. The optional/flexible Part B dose of linerixibat is intended to be 180 mg once daily, but may be amended based on emerging PK, safety and tolerability data. 90mg twice daily and 180mg once daily doses are being evaluated in a randomized, double-blind, placebo-controlled dose-ranging Phase 2b study with a 3-month treatment duration (201000). The range doses of linerixibat being evaluated in the 201000 study are:

- Placebo
- 20 mg once daily (anticipated minimally effective dose)
- 90 mg once daily
- 180 mg once daily (anticipated to identify plateau of efficacy)
- 90 mg twice daily (demonstrated efficacy in previous study)

The maximum total daily dose is 180mg as stated in the Investigator Brochure (GSK Document number 2010N111289_05). This 180mg dose has adequate nonclinical toxicology cover for local gastrointestinal tract exposure (based on administered oral dose, i.e., 3.6 mg/kg/day assuming 50 kg body weight): 278-fold No Observed Adverse Effect Level (NOAEL) in the rat and 139-fold NOAEL in the dog for local gastrointestinal tract exposure (mg/kg/day dose). Further information on nonclinical toxicology studies can be found in the IB (GSK Document number 2010N111289_05).

Participants in Part A of 206224 will receive their first 90 mg dose of linerixibat in the morning of Study Day 20 (corresponding to 20 days of OCA dosing). Participants will continue taking linerixibat 90 mg twice daily for a total of 17.5 days receiving their last dose in the morning of Study Day 38. The linerixibat doses chosen for this study were carefully considered in the context of available pre-clinical and clinical data including those data describing the safety, tolerability and pharmacodynamic biomarker response to treatment in healthy participants and in patients with PBC. However, the exact doses used may change at the discretion of the sponsor but will not exceed those which have

been shown to be safe and tolerable. The linerixibat Investigator Brochure (GSK Document number 2010N111289_05) provides further details.

4.3.2. OCA

The recommended starting dose for OCA in patients with PBC is 5mg with guidance to increase to 10mg once daily if needed after assessing efficacy at 3 months. To inform the drug interaction labelling for OCA, healthy participants in five separate studies received repeat doses of 10mg and 25mg for 19 to 24 days (Edwards, 2017). The early PK/tolerability studies dosed up to 250mg once daily for 12 days. Therefore, the 10mg dose chosen for this study will provide a more comparable Ctrough to the patient population than the 5mg dose providing a more meaningful result. It is anticipated that linerixibat will either reduce or have no effect on OCA and conjugates in plasma.

OCA and conjugates undergo enterohepatic cycling and PBPK models predict the time to steady state is between 14 and 21 days. This study will dose OCA once-daily for 18 days prior to the first OCA PK sampling (0 to 24 h). Daily OCA dosing will continue to Study Day 37 at approximately 12pm.

Linerixibat is assumed to achieve gut lumen steady state exposure by 3-6 days. This timeframe allows for slow and fast GI motility rates.

It is difficult to estimate when OCA will reach a new steady state with linerixibat added on because IBAT inhibition has the potential to alter the clearance and half-life of OCA. In this study linerixibat dosing begins on Study Day 20 after participants have been taking OCA 10 mg once-daily for a period of 20 days thereby ensuring OCA is at steady state. Linerixibat (90mg twice daily and OCA 10 mg once daily) will continue concomitantly for a period of 18 days thereafter providing sufficient time for OCA to again reach steady state following the initiation of linerixibat dosing. This robust study design provides confidence that OCA PK sampling on Study Day 37 (0 to24 h) is sufficient to assess the effects of steady state linerixibat on steady state OCA PK.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study up until discharge from the clinical unit on Day 38.

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

AGE
1. Between 18 and 80 years of age inclusive, at the time of signing the informed consent.

TYPE OF PARTICIPANT
2. Healthy, as determined by the investigator or medically qualified designee, based on a medical evaluation including medical history, physical examination, vital signs, laboratory tests, and ECG. A participant with a clinical abnormality or laboratory parameter (i.e., outside the reference range for the population being studied), which is not specifically listed in the eligibility criteria, may be included only if the investigator agrees in consultation with the GSK Medical Monitor and documents in the source documentation that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures or outcomes. Note: Screened participants with laboratory values outside of the normal range may be repeated once for inclusion into the study at the discretion of the Investigator. 3. Body weight >50kg and body mass index (BMI) within the range 18.5 – 32kg/m^2 (inclusive)

INFORMED CONSENT
4. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

SEX
5. Male and female **Female participants:** A female participant is eligible to participate if she is not pregnant not breastfeeding, and at least one of the following conditions applies: • Not a woman of childbearing potential as defined in Section 10.4**: Appendix 4** OR • A WOCBP who agrees to follow the contraceptive guidance in Section 10.4**: Appendix 4** during the treatment period and until at least 4 weeks after the last dose of study treatment. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

MEDICAL CONDITIONS:
1. 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. 2. 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. 3. Participants with a history of cholecystectomy. 4. Current symptomatic cholelithiasis or inflammatory gall bladder disease. 5. 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. 6. Any clinically relevant abnormality identified at the screening medical assessment (physical examination/medical history) clinical laboratory tests, or 12-lead ECG. 7. Current episode, recent history (within 1 month of screening visit), or chronic history

MEDICAL CONDITIONS:
of clinically significant diarrhoea. 8. 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. 9. 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.

PRIOR/CONCOMITANT THERAPY
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. 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.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
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.

DIAGNOSTIC ASSESSMENTS

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.

    Note: 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.

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.

    NOTES:

    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.

OTHER EXCLUSIONS

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.

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.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Participants will receive standard meals while in the clinical unit. Water will be provided ad libitum.
- Participants will be provided meals or snacks at the same time as OCA dosing while inpatient.
- Participants will be instructed to take OCA with meal or snack as outpatients between 12:00 and 2:00 PM.
- On PK sampling days for OCA, identical meals will be provided.
- Participants will be provided meals or snacks 30 minutes after linerixibat doses.
- On PK sampling days for linerixibat, identical meals will be provided.
- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days prior to the first dose of study intervention until follow up.
- Participants should be fasted for at least 6 hours prior to clinical safety laboratory sampling at screening and admission to the clinical unit on Day -1.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants should abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours prior to screening and for 48 hours before admissions on Days -1 and 17. This restriction will be in place until after collection of the final pharmacokinetic (PK) and/or pharmacodynamic sample for a given dosing session.
- During the period of home dosing (from Day 3 – Day 15), participants should limit caffeine or xanthine-product intake to a maximum of one typical beverage (or chocolate bar) per day.

- During each dosing session, participants will abstain from alcohol for 24 hours prior to screening and before the first dose of OCA until after collection of the final PK and/or pharmacodynamic sample.
- Use of tobacco or nicotine containing products will not be allowed throughout the study and from 3 months prior to screening until the end of study participation, as described in exclusion criteria #12.

5.3.3. Activity

Participants will abstain from strenuous exercise for 72 hours before each blood collection and for clinical laboratory tests. Participants may take part in light recreational activities during stays in the clinical unit (e.g., walking, watching television, reading).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under the following conditions:

- The reason for prior screen failure is deemed temporary or has been fully resolved.
- It is a clinical abnormality or laboratory parameter which is/are not specifically listed in the inclusion/exclusion criteria.

In either case, the rescreening must be approved in writing by the medical monitor. Rescreening decisions should be documented to indicate that rescreening the participant will not introduce additional risk factors and will not interfere with study procedures or ability to interpret results.

If the start of the study is delayed for an individual participant for any reason (but the participant has previously met the inclusion/exclusion criteria) and more than 28 days has elapsed between screening assessments and the first dosing day, all or part of the screening procedures may be repeated at the discretion of the investigator.

Participants may only be rescreened once and must be given a new participant number.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s) or marketed product(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

6.1.1. Part A

Study Treatment Name	GSK2330672 (linerixibat)	Ocaliva (Obeticholic acid) (OCA)
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	45mg	5mg or 10mg
Dosage Level(s)	90mg Twice Daily	10mg Once Daily
Route of Administration	Oral	Oral
Use	Experimental, potential perpetrator	Experimental, Potential victim
Dosing Instructions	Swallowed whole with approximately 240mL water	Swallowed whole with approximately 240mL water
Sourcing	Provided centrally by GlaxoSmithKline	Provided centrally by GlaxoSmithKline
Packaging and Labelling	Study Intervention will be provided in bottles. Each bottle will be labelled as required per country requirement.	Study Intervention will be provided in bottles. Each bottle will be labelled as required per country requirement.

6.1.2. Part B (Optional)

Study Treatment Name	GSK2330672 (linerixibat)	Ocaliva (Obeticholic acid) (OCA)
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	45mg	10mg
Dosage Level(s)	180mg Once Daily	10mg Once Daily
Route of Administration	Oral	Oral
Use	Experimental, potential perpetrator	Experimental, Potential victim
Dosing Instructions	Swallowed whole with approximately 240mL water	Swallowed whole with approximately 240mL water
Sourcing	Provided centrally by GlaxoSmithKline	Provided centrally by GlaxoSmithKline
Packaging and Labelling	Study Intervention will be provided in bottles. Each bottle will be labelled as required per country requirement.	Study Intervention will be provided in bottles. Each bottle will be labelled as required per country requirement.

*The dosage and administration of linerixibat and/or OCA may be adjusted in the optional Part B if conducted. Any adjustments will be made prior to commencement of Part B and will be based upon the full analysis of the Part A results.

6.2. Measures to Minimize Bias: Randomisation and Blinding

This is an open-label study with no randomization and no blinding of participants, site personnel, or sponsor personnel.

6.3. Preparation/Handling/Storage/Accountability

- To the extent possible, the investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

- Only participants enrolled in the study may receive study intervention. Only authorized site staff may supply or administer study intervention during inpatient stays, and only participants may administer study intervention during home-dosing period (Days 3-16). All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.4. Study Intervention Compliance

- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.
- When participants self-administer study intervention(s) at home, compliance with OCA will be assessed by the site using a daily compliance check and returned tablets will be counted and reconciled during the site visits. This will be documented in the source documents and eCRF.

6.5. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or non-prescription drugs (including anti-diarrhoeal medication, vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol, at doses of ≤ 2 grams/day and other concomitant medication may be permitted for use any time during the study and must be reported to the site staff. Other medications may be used on a case-by-case basis as permitted by the investigator in consultation with the Medical Monitor (if required).

Anti-diarrhoeal medications of any kind are not permitted for use throughout the study.

6.6. Dose Modification

Dose modification is not permitted.

6.7. Intervention after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study as only healthy participants are eligible for study participation.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention and be withdrawn from the study. If study intervention is permanently discontinued, the participant should be encouraged to attend for early termination assessments, and these should be as per early withdrawal procedures as per Table 1. See the SOA for data to be collected at the time of early withdrawal.

7.1.1. Liver Chemistry Stopping Criteria

Study intervention will be discontinued **for a participant** if liver chemistry stopping criteria are met:

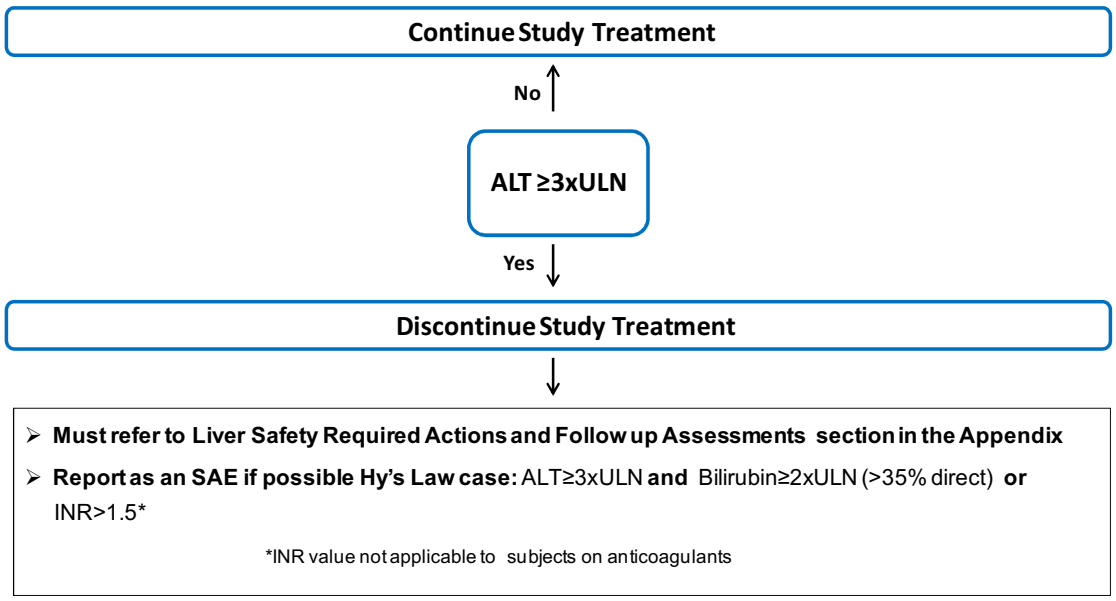
Liver Safety Required Actions and Follow up Assessments can be found in Appendix 6**.**

Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology. These protocol guidelines are in alignment with the FDA premarketing clinical liver safety guidance:

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined or
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

7.1.2. QTc Stopping Criteria

A participant that meets either bulleted criterion below will be withdrawn from the study.

- QTcF > 500 msec,
- Change from baseline in healthy volunteer participants: QTcF >60 msec

If an automated reading is not available, the ECG should be manually over-read by the investigator or adequately trained physician.

See the SoA for data to be collected at the time of early withdrawal for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early withdrawal visit should be conducted, as soon as possible after the point of withdrawal as shown in Table 1. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Participants who report non-compliance or demonstrate non-compliance with study medication or violate protocol procedures will be assessed on a case-by-case basis with the sponsor and may be asked to perform early withdrawal assessments and be withdrawn from study participation.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known

mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- At timepoints where more than one procedure is to be completed at the same timepoint, the preferred order of assessments is as follows:
  - Electrocardiograms (ECGs)
  - Vital Signs
  - Pharmacokinetic (PK) blood sampling (nominal time to be recorded)

  The timing of the assessments should allow the PK blood draw to occur as close as possible to the exact nominal time. All safety assessments will be timed and performed relative to the start of dosing. A table defining the allowed variance in

timings of assessments without being considered a protocol deviation will be included in the SRM.

8.1. Efficacy Assessments

There are no efficacy assessments associated with this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A full physical examination will include, at a minimum, assessments of the eyes, skin, joints, cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded in the eCRF.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Weight will also be measured.

8.2.2. Vital Signs

- Tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a supine position using a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vitals signs will be performed in triplicate (blood pressure and heart rate only) will be taken at screening and Day -1, and in single at all other timepoints. At timepoints where triplicate values will be measured, blood pressure readings will be separated by at least one minute and the average of the 3 readings will be recorded in the eCRF.

8.2.3. Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. The mean of these measurements will be recorded in the eCRF.
- ECGs should be taken in a supine position should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

8.2.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Medical Monitor consulted.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the informed consent form until completion of the follow up phone call at the time points specified in the SoA (Section 1.3).
- All AEs will be collected from the start of dosing until completion of the follow-up phone call at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study on Day 38, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 6-8 weeks following the delivery date, providing the participant consents to follow-up.
- If a pregnancy is reported, the investigator should inform the Medical Monitor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.4. Treatment of Overdose

For this study, any dose of linerixibat greater than 180mg within a 24-hour period will be considered an overdose.

GSK does not recommend specific treatment for an overdose as there is no specific antidote for linerixibat. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the participant's clinical status.

In the event of an overdose, the Investigator should:

1. Contact the GSK Medical Monitor immediately

2. Closely monitor the participant for AE/SAEs and laboratory abnormalities as agreed with the Medical Monitor on a case-by-case basis.

3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis)

4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

8.5. Pharmacokinetics

Whole blood samples will be collected for measurement of plasma concentrations of GSK2330672 and OCA as specified in the SoA and below in Section 8.5.1 and Section 8.5.2.

- Additional samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the Medical Monitor.
- The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection (including the volume to be collected), handling and processing of biological samples will be provided in the Study Reference Manual. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples collected for plasma concentration analyses of GSK2330672 and OCA may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these samples.

8.5.1. Part A PK Sampling Schedule

8.5.1.1. PK Sampling Schedule Day 17-19 for OCA and Metabolites

Study Day	Time relative to OCA dose (h)	Example Time of Day (24hr)	OCA Dose	PK (OCA) Sample Collection	Meals
17	-3.5	08:30			X
	0	12:00	X	X[1]	X[2]
	4	16:00			X
	8.5	20:30			X
18	-3.5	08:30			X
	0	12:00	X	X[1]	X[2]
	0.25	12:15		X	
	0.5	12:30		X	
	0.75	12:45		X	
	1	13:00		X	
	1.5	13:30		X	
	2	14:00		X	
	3	15:00		X	
	4	16:00		X	X
	5	17:00		X	
	6	18:00		X	
	7	19:00		X	
	8	20:00		X	
	8.5	20:30			X
	9	21:00		X	
	10	22:00		X	
	11	23:00		X	
19	12	00:00		X	
	14	02:00		X	
	20.5	08:30			X
	24	12:00	X	X[1]	X[2]
	28	16:00			X
	32	20:00			X

[1]Sample taken predose, approx. 15 minutes prior to dosing
[2]To be given with a meal

8.5.1.2. PK Sampling Schedule Day 35-38 for OCA and Metabolites

Study Day	Time relative to OCA dose (h)	Example Time of Day (24hr)	OCA Dose	Linerixibat Dose	PK (OCA) Sample Collection	Meals
35	-4	08:00		X		
	-3.5	08:30				X
	0	12:00	X		X[1]	X[2]

Study Day	Time relative to OCA dose (h)	Example Time of Day (24hr)	OCA Dose	Linerixibat Dose	PK (OCA) Sample Collection	Meals
	4	16:00				X
	8	20:00		X		
	8.5	20:30				X
36	-4	08:00		X		
	-3.5	08:30				X
	0	12:00	X		X[1]	X[2]
	4	16:00				X
	8	20:00		X		
	8.5	20:30				X
37	-4	08:00		X		
	-3.5	08:30				X
	0	12:00	X		X[1]	X[2]
	0.25	12:15			X	
	0.5	12:30			X	
	0.75	12:45			X	
	1	13:00			X	
	1.5	13:30			X	
	2	14:00			X	
	3	15:00			X	
	4	16:00			X	X
	5	17:00			X	
	6	18:00			X	
	7	19:00			X	
	8	20:00		X	X[1]	
	8.5	20:30				X
	9	21:00			X	
	10	22:00			X	
	11	23:00			X	
38	12	00:00			X	
	14	02:00			X	
	20	08:00		X		
	20.5	08:30				X
	24	12:00			X	X

[1]Sample to be collected predose, approx. 15 minutes prior to dosing

[2]To be given with a meal

8.5.1.3. PK Sampling Schedule Day 19-20 (Day -1 and 1 Linerixibat) and Day 33 (Day 14 Linerixibat) for Linerixibat Twice Daily Dosing

Study Day	Time relative to linerixibat dose (h)	Example. Time of Day (24hr)	OCA Dose	Linerixibat Dose	PK (Linerixibat)	Meals
19	0	08:00		X		
	0.5	08:30				X
	4	12:00	X			X[1]
	8	16:00				X
	12	20:00		X		X
20	0	08:00		X	X[2]	
	0.25	08:15			X	
	0.5	08:30			X	X
	0.75	08:45			X	
	1	09:00			X	
	1.5	09:30			X	
	2	10:00			X	
	3	11:00			X	
	4	12:00	X		X[2]	X[1]
	5	13:00			X	
	6	14:00			X	
	7	15:00			X	
	8	16:00			X	X
	9	17:00			X	
	10	18:00			X	
	11	19:00			X	
	12	20:00		X	X[2]	
	12.5	20:30				X
33	0	8:00		X	X[2]	
	0.25	08:15			X	
	0.5	08:30			X	X
	0.75	08:45			X	
	1	09:00			X	
	1.5	09:30			X	
	2	10:00			X	
	3	11:00			X	
	4	12:00	X		X[2]	X[1]
	5	13:00			X	
	6	14:00			X	
	7	15:00			X	
	8	16:00			X	X
	9	17:00			X	
	10	18:00			X	
	11	19:00			X	
	12	20:00		X	X[2]	

Study Day	Time relative to linerixibat dose (h)	Example. Time of Day (24hr)	OCA Dose	Linerixibat Dose	PK (Linerixibat)	Meals
	12.5	20:30				X

[1]To be given with a meal
[2]Sample taken predose, approx. 15 minutes prior to dosing

8.5.2. Part B (Optional) PK Sampling Schedule

8.5.2.1. PK Sampling Schedule Day 17-19 for OCA and Metabolites

Study Day	Time relative to OCA dose (h)	Example Time of Day (24hr)	OCA Dose	PK (OCA) Sample Collection	Meals
17	-11.5	08:30			X
	-8	12:00			X
	-4	16:00			X
	0	20:00	X	X[1]	X[2]
18	-11.5	08:30			X
	-8	12:00			X
	-4	16:00			X
	0	20:00	X	X[1]	X[2]
	0.25	20:15		X	
	0.5	20:30		X	
	0.75	20:45		X	
	1	21:00		X	
	1.5	21:30		X	
	2	22:00		X	
	3	23:00		X	
19	4	00:00		X	
	5	01:00		X	
	6	02:00		X	
	7	03:00		X	
	8	04:00		X	
	9	05:00		X	
	10	06:00		X	
	11	07:00		X	
	12	08:00		X	
	12.5	08:30			X
	14	10:00		X	
	16	12:00			X
	20	16:00			X
	24	20:00	X	X[1]	X[2]

[1]Sample to be collected predose. Approx. 15 minutes prior to dosing
[2]To be given with a meal

8.5.2.2. PK Sampling Schedule Day 35-38 for OCA and Metabolites

Study Day	Time relative to OCA dose (h)	Example Time of Day (24hr)	OCA Dose	Linerixibat Dose	PK (OCA) Sample Collection	Meals
35	-11.5	08:30				X
	-8	12:00				X
	-4	16:00				X
	0	20:00	X		X[1]	X[2]
36	-11.5	08:30				X
	-8	12:00				X
	-4	16:00				X
	0	20:00	X		X[1]	X[2]
37	-12	08:00		X		
	-11.5	08:30				X
	-8	12:00				X
	-4	16:00				X
	0	20:00	X		X[1]	X[2]
	0.25	20:15			X	
	0.5	20:30			X	
	0.75	20:45			X	
	1	21:00			X	
	1.5	21:30			X	
	2	22:00			X	
	3	23:00			X	
38	4	00:00			X	
	5	01:00			X	
	6	02:00			X	
	7	03:00			X	
	8	04:00			X	
	9	05:00			X	
	10	06:00			X	
	11	07:00			X	
	12	08:00		X	X[2]	
	12.5	08:30				X
	14	10:00			X	
	16	12:00				X
	20	16:00				X
	24	20:00			X	X

[1]Sample to be collected predose. Approx. 15 minutes prior to dosing
[2]To be given with a meal

8.5.2.3. PK Sampling Schedule Day 19-21 (Day -1, 1 and 2 Linerixibat) for Linerixibat Once Daily Dosing

Study Day	Time relative to linerixibat dose (h)	Example Time of Day (24hr)	OCA Dose	Linerixibat Dose	PK (Linerixibat)	Meals
19	0	08:00		X		
	0.5	08:30				X
	4	12:00				X
	8	16:00				X
	12	20:00	X			X[1]
20	0	08:00		X	X[2]	
	0.25	08:15			X	
	0.5	08:30			X	X
	0.75	08:45			X	
	1	09:00			X	
	1.5	09:30			X	
	2	10:00			X	
	3	11:00			X	
	4	12:00			X[2]	X[1]
	5	13:00			X	
	6	14:00			X	
	7	15:00			X	
	8	16:00			X	X
	9	17:00			X	
	10	18:00			X	
	11	19:00			X	
	12	20:00	X		X[2]	X[1]
21	14	22:00			X	
	16	00:00			X	
	18	02:00			X	
	24	08:00		X	X[2]	
	24.5	08:30				X
	28	12:00				X
	32	16:00				X
	36	20:00	X			X[1]

[1]To be given with a meal

[2]Sample taken predose, approx. 15 minutes prior to dosing

8.5.2.4. PK Sampling Schedule Days 33-34 (Days 14-15 of Linerixibat) for Linerixibat Once Daily Dosing

Study Day	Time relative to linerixibat dose (h)	Example Time of Day (24hr)	OCA Dose	Linerixibat Dose	PK (Linerixibat)	Meals
33	0	8:00		X	X[2]	
	0.25	08:15			X	
	0.5	08:30			X	X
	0.75	08:45			X	
	1	09:00			X	
	1.5	09:30			X	
	2	10:00			X	
	3	11:00			X	
	4	12:00			X	X
	5	13:00			X	
	6	14:00			X	
	7	15:00			X	
	8	16:00			X	X
	9	17:00			X	
	10	18:00			X	
	11	19:00			X	
	12	20:00	X		X[2]	X[1]
34	14	22:00			X	
	16	00:00			X	
	18	02:00			X	
	24	08:00		X	X[2]	
	24.5	08:30				X
	28	12:00				X
	32	16:00				X
	36	20:00	X			X[1]

[1]To be given with a meal
[2]Sample taken predose, approx. 15 minutes prior to dosing

8.6. Pharmacodynamics

Pharmacodynamic parameters are not collected in this study.

8.7. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Study Reference Manual.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

There are no immunogenicity assessments to be performed in this study

8.10. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

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..

9.2. Sample Size Considerations

Approximately 19 participants will be recruited with the goal of having at least 15 participants complete the study, to allow for up to an approximate 20% withdrawal rate.

If the optional Part B is conducted the same number of participants are planned to be recruited with the identical provision for study withdrawals.

Reported coefficients of variance for Cmax and AUC (0-24) for total-OCA are 27.7% and 28.6%, respectively, while the coefficient of variance for Ctrough for total-OCA is 20.7%. To reflect all the reported variance, a CV of 30% (on the log scale SD = 0.294) will be used to accommodate the variance of the primary PK parameter endpoints being measured. With this CV, a sample size of 15 participants will provide a precision (half-width of the 90% confidence interval, CI) within 17% of the point estimate.

9.3. Sample Size Sensitivity

A sensitivity analysis was conducted assuming a larger than expected CV in the study. Assuming a CV of 40% (on the log scale SD = 0.385), a sample size of 15 participants would provide a precision of the 90% CI within 21.7% of the point estimate for the primary PK parameters.

An additional sensitivity analysis was conducted assuming there are fewer participants than originally planned for in the study. Assuming the original CV of 30% and a new sample size of 11 participants, the precision of the 90% CI would be within 20% of the point estimate for the primary PK parameters.

9.4. Populations for Analyses

The following populations are defined:

Population	Description
Screened	All participants who sign the ICF. This will be the population for reporting screened population data.
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.
Pharmacokinetic Concentrations	All participant for whom pharmacokinetic concentration are reported.
Pharmacokinetic Parameters	All participants for whom pharmacokinetic parameters are derivable.

9.5. Interim Analysis

No interim analysis will be performed.

9.6. Data Monitoring Committee

No independent data monitoring committee will be used for this study.

9.7. Statistical Analyses

This study is intended to compare changes in steady state PK parameters AUC(0-t), AUC (0-24), Cmax, Ctrough for total-OCA as well as steady state PK parameters for OCA, tauro-OCA, and glyco-OCA before and following dosing of linerixibat 90 mg twice-daily for 18 consecutive days. This full assessment is important to understand the presence of a DDI and to fully characterize the drug interaction potential. After log transforming these parameters, they will be analysed by a mixed effect model by fitting a fixed effect term for regimen (OCA or OCA + linerixibat) and treating participant as a random effect. Point estimates and 90% CI for the difference between OCA + linerixibat and OCA will be constructed. These point estimates and CI will then be back-transformed exponentially to obtain point estimates 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) and between-subject variability (CVb) for the PK parameters will also be calculated using the following equations:

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

where MSE is the residual mean squared error from the model, and

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

where SD is the standard deviation on the log scale.

Descriptive statistics (n, arithmetic mean and associated 95% confidence interval, standard deviation, minimum, median, maximum) will be calculated for all PK parameters by OCA and OCA + linerixibat.

In addition to this assessment, the back-transformed mean and 90% CI of Ctrough for total-OCA following dosing of linerixibat will be compared to the clinically important threshold of 20 ng-eq/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 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 back-transformed mean 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 relevant 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 analysed 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.

The PK parameters, including accumulation, for linerixibat will be summarized using descriptive statistics.

The statistical analysis plan will be finalized prior to database freeze (DBF) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.7.1. General Considerations

9.7.1.1. Treatment Assignment

This is a non-randomized study. All participants will receive OCA and OCA + linerixibat in a fixed sequence.

9.7.1.2. Missing Data

Missing data will not be imputed.

9.7.1.3. Derived and Transformed Data

AUC(0-t), AUC (0-24), Cmax, and Ctrough will be log transformed prior to statistical analysis.

9.7.1.4. Sample Size Re-estimation

No sample size re-estimation is planned.

9.7.2. Primary Comparisons of Interest

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 + linerixibat relative to OCA alone for each of the pharmacokinetic endpoints.

9.7.3. Other Analyse(s)

There are no other comparisons of interest.

9.7.4. Other Safety Analyse(s)

No formal statistical analysis of safety data will be performed. Safety and tolerability data will be descriptively summarized and presented in a tabular and/or graphical form.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant

reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Source Document Identification Form or equivalent form.

10.1.8. Study and Site Start and Closure

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified

by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing:
- Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's involvement in the study.

Table 4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count RBC Count Haemoglobin Haematocrit	RBC Indices: MCV MCH Absolute and %Reticulocytes		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasted[2])	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite,			

Laboratory Assessments	**Parameters**
	leukocyte by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Alcohol breath test and urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Smoking breath test • Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3] • Follicle stimulating hormone and oestradiol (as needed for women of childbearing potential). • Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) The results of each test must be entered into the CRF.

NOTES:

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.6 (Appendix 6)All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Glucose fasting at screening and admission on Day -1 only.
3. Serum pregnancy test will be taken at screening only and urine pregnancy test will be taken at other timepoints. Positive urine pregnancy tests will be confirmed with serum pregnancy tests.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that

Events NOT Meeting the AE Definition
leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
o Results in death
o Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the eCRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical monitor or the SAE coordinator by telephone. • Contacts for SAE reporting can be found in the Study Reference Manual.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical monitor or the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in Study Reference Manual.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance:

Female Participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described below

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency**
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent**

• Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

10.4.3. Collection of Pregnancy Information:

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study medication immediately and be withdrawn from the study. A follow-up appointment will be scheduled with the centre.

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to PBC and/or related diseases. They may also be used to develop tests/assays including diagnostic tests) related to PBC and/or related diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.
- DNA samples will be analysed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to GSK2330672 or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on PBC (or study interventions of this class) continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase I Liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology. These guidelines are in alignment with FDA premarketing clinical liver safety guidance:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN

If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.

See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event eCRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)

MONITORING:

If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5

• Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline</td><td>• Viral hepatitis serology[3]
• Obtain international normalized ratio (INR) and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained as soon as possible after liver event identified[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report</td></tr>
</table>

Liver Chemistry Stopping Criteria	
phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24 h** • Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 h** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the threshold value stated will not apply participants receiving anticoagulants
3. Includes: Hepatitis A immunoglobulin (gM) antibody; HBsAg and HBcAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM. Not required for single-dose parts of this study

10.7. Appendix 7: Abbreviations and Trademarks

Abbreviation	Explanation
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC (0-12)	Area under the Concentration curve from time 0 to 12 hour
AUC $_{(0-24)}$	Area under the Concentration curve from time 0 to 24 hour
AUC (0-t)	Area under the Concentration curve from time 0 to t
BID	Twice Daily
BMI	Body Mass Index
BP	Blood Pressure
Cmax	Maximum Observed Plasma Concentration
CRF	Case Report Form
Ctrough	Trough Concentration
DBF	Database Freeze
DDI	Drug-drug Interaction
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EHC	Enterohepatic Circulation
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
FSH	Follicle Stimulating Hormone
FXR	Farnesoid X Receptor
GI	Gastrointestinal
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface antigen
HIV	Human Immunodeficiency Virus
HR	Heart Rate
H	Hour
IBAT	Ileal bile acid Transport
ICF	Informed Consent Form
IDSL	Independent Data Standards Library
IEC	Independent Ethics Committee
IRB	Institutional Review Board
Kg	Kilogram
LFT	Liver Function Tests
LLQ	Lower Limit of Quantitation
mg	Milligram
mmHg	Millimetres of Mercury
ng	Nanogram
NOAEL	No-Observed Adverse Effect Level
OCA	Obeticholic Acid
PBC	Primary Biliary Cholangitis
PD	Pharmacodynamics
PGx	Pharmacogenetics

Abbreviation	Explanation
PK	Pharmacokinetics
QD	Once Daily
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SMPc	Summary of Product Characteristics
SoA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reaction
Tlast	Time to last observation
Tmax	Time to maximum concentration
UDCA	Ursodeoxycholic Acid
ULN	Upper Limit of Normal
WOCBP	Women of Child Bearing Potential
WONCBP	Women of non-child bearing potential

Trademark Information

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11. REFERENCES

Dawson PA; Haywood J; Craddock AL; Wilson M; Tietjen M; Kluckman K; Maeda N; Parks J.S. Targeted Deletion of the Ileal Bile Acid Transporter Eliminates Enterohepatic Cycling of Bile Acids in Mice; Journal of Biological Chemistry 2003; 278; 33920-33927.

Edwards JE; Eliot L; Parkinson A; Karan S; MacConell L. Assessment of Pharmacokinetic Interactions Between Obeticholic Acid and Caffeine, Midazolam, Warfarin, Dextromethorphan, Omeprazole, Rosuvastatin and Digoxin in Phase 1 Studies in Healthy Subjects. Adv Ther (2017) 34:2120-2138.

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

GSK2330672 Investigator's Brochure, Version 05, 03-Sep-2018.GSK Document Number 2010N111289_05.

Hegade VS; Boier R, Oude Eferink R, Beuers U, Kendrick S, Jones D. A systematic approach to the management of cholestatic pruritus in primary biliary cirrhosis. Frontline Gastroenterology 2016; 7(3): 158-166.

Hofmann AF. Bile Acids: Trying to Understand Their Chemistry and Biology with the Hope of Helping Patients. Hepatology 2009; 49:1402-1418

Metcalf, JV; Mitchison HC; Palmer JM; Jones DE; Primary Biliary Cirrhosis: Epidemiology Helping the Clinician. British Medical Journal 1996; 312:1181

Ocaliva® EMA prescribing information (Summary of Product Characteristics) 2018.

Woolbright BL; Jaeschke H. Novel Insight into Mechanisms of Cholestatic Liver Injury. World Journal of Gastroenterology; 2012; 18 (36): 4985-4993.