TITLE PAGE

Protocol Title:

A two-part, randomized, placebo controlled, double blind, multicenter, Phase 3 study to evaluate the efficacy and safety of linerixibat for the treatment of cholestatic pruritus in participants with primary biliary cholangitis (PBC).

Protocol Number: 212620/Amendment 04

Compound Number or Name: GSK2330672 (linerixibat)

Brief Title:

*G*lobal *L*inerixibat *I*tch *ST*udy of *E*fficacy and Safety i*N* PBC (GLISTEN)

Study Phase: Phase 3

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s):

IND: 130391

EudraCT: 2021-000007-21

Approval Date: 20 Nov 2023

INVESTIGATOR PROTOCOL AMENDMENT AGREEMENT PAGE

PROTOCOL NUMBER: 212620

AMENDMENT NUMBER: 04

PROTOCOL TITLE: A two-part, randomized, placebo controlled, double blind, multicenter, Phase 3 study to evaluate the efficacy and safety of linerixibat for the treatment of cholestatic pruritus in participants with primary biliary cholangitis (PBC)

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:

_____

Investigator Address:

_____

_____

_____ _____

Investigator Signature Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 04	20 Nov 2023	TMF-16740250
Amendment 03 ISR-1	24-MAR-2022	TMF-14529451
Amendment 03	02-SEP-2021	TMF-13946603
Amendment 02	12-JUL-2021	TMF-13852487
Amendment 01	01-MAR-2021	TMF-11835634
Original Protocol	27-JAN-2021	TMF-2096421

Amendment [04]: 20 Nov 2023

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Change in analysis strategy to perform primary analysis after the end of Part A including available Part B data and final analysis after the end of Part B, addition of allowed early access to certain data to enable kinetic-pharmacodynamic (K-PD) modelling, and introduction of blinding strategy to support these changes. Removal of exclusion criteria no longer needed, other changes to fulfill the EU CTR requirements, and clarifications in line with updated sponsor protocol template also included.

Section # and Name	Description of Change	Brief Rationale
Meaningful Content Changes and Notable Clarifications		
Synopsis, Section 1.1, and throughout Protocol	• The terminology of Mean Worst Daily Itch (MWDI) Score was changed to Weekly Itch Score (WIS). • The terminology of Mean Daily Sleep Score was changed to Weekly Sleep Score.	Adoption of more intuitive terminology for the concept – the calculation remains the same.
Section 2.3.1, Risk Assessment; Section 5.2, Exclusion Criteria	• Updated rationale for the potential increased risk of colon cancer in association with increased fecal excretion of bile acids' and removed mitigation excluding participants from the study with current/ previous diagnosis of colorectal cancer. • Exclusion criteria for current/previous diagnosis of colorectal cancer was removed. (Any current malignancies remains as an exclusion criterion.)	Current review of the totality of data on the potential risk of 'colorectal cancer' is not consistent with this theoretical association with patients receiving linerixibat. Hence, to prevent unnecessary exclusion of participants with history of colorectal cancer, this exclusion has been removed.

Section # and Name	Description of Change	Brief Rationale
Meaningful Content Changes and Notable Clarifications		
Section 5.2, Exclusion Criteria	Removed Exclusion #1 regarding participants with recent positive COVID-19 test results, symptoms suggestive of active COVID-19 infection.	To prevent unnecessary screen failure of participants considering the changes in COVID pandemic and management.
Section 5.2, Exclusion Criteria	Exclusion criteria revised to clarify that the presence of viral hepatitis B (HBsAg positive) or C (anti-HCV positive and RNA detected) infection is exclusionary.	Clarification of exclusion criteria specificities.
Section 5.2, Exclusion Criteria	Exclusion criteria for skin disorders was updated to clarify that a current diagnosis of primary skin disorders with itch as a characteristic feature is exclusionary.	Clarification of exclusion criterion.
Section 5.4, Screen Failures	• Added additional rescreening and details of the rescreenings. • Added text for participants who have a COVID-19 diagnosis during the Screening period. • Clarified participant numbering and documentation in the eCRF for screening/ rescreening events.	Change in text to permit additional rescreenings.
Section 6.4, Blinding	Added text to indicate possible access to data for population K-PD modelling before study unblinding and blinding strategy around new analysis plan.	To facilitate activities for the new analysis strategy to perform primary analysis after the end of Part A.

Section # and Name	Description of Change	Brief Rationale
Meaningful Content Changes and Notable Clarifications		
Section 7.1.4, QTc Stopping Criteria	Clarified stopping criteria for QTc is based on increase in values.	Clarification text.
Section 8.4, Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting	Added all events meeting permanent stopping criteria, except for pregnancy, will be recorded as a (S)AE.	Clarification of approach already in place in line with new sponsor protocol template.
Section 8.4.1, Time Period and Frequency for Collecting AE and SAE Information	• Clarified AE/SAE reporting period. • Clarified the documentation required for participants meeting increased monitoring or stopping criteria at Week 32 requiring additional follow-up after being enrolled in the follow-on Study 212358 (LLSAT) and when AEs/ SAEs should be entered in the GLISTEN eCRF or the LLSAT eCRF.	In line with clarified definition of Last Visit in Section 4.4, End of Study Definition. Further clarification and guidance text.
Section 8.5, Pharmacokinetics	Added text that PK sample collection and/or analysis may be terminated when sufficient data has been collected, and any remaining samples may be discarded if not required.	To allow an earlier analysis as appropriate.

Section # and Name	Description of Change	Brief Rationale
Meaningful Content Changes and Notable Clarifications		
Section 8.7, Biomarkers	Added text that Biomarker sample collection and/or analysis may be terminated when sufficient data has been collected, and any remaining samples may be discarded if not required.	To allow an earlier analysis as appropriate.
Section 9.4, Statistical Analyses	Added details for the new statistical analysis strategy involving a primary analysis after all participants have completed the Part A intervention period and a final analysis after all participants have completed the Part B intervention period, and the follow-up period.	Change in analysis strategy.
Section 10.3.5, Reporting of SAE to GSK	Updated contact for SAE reporting by phone from SAE coordinator to GSK Medical Monitor.	In line with updated process of SAE reporting if done by phone.

Section # and Name	Description of Change	Brief Rationale
Other Changes: Clarifications; EU CTR Requirements; Sponsor Protocol Template requirements; formatting or typographical corrections		
Synopsis, Section 1.1 and Section 4.1, Overall Design	Separated details of Part A and Part B intervention treatment periods.	Change in analysis strategy to clarify that primary analysis will be completed after the end of Part A.
Section 1.3, Schedule of Assessments (SoA)	• Added a row and note for visit windows to indicate applicable visits. • Added a row and note for the medication diary. • Added notes that the medication diary, exploratory biomarker collection, and PK collection are not required if study treatment is discontinued permanently.	Clarification.
Section 1.3, Schedule of Assessments (SoA)	Added note that genetic samples will not be collected in China or Israel.	Incorporation of country specific requirements.

Section # and Name	Description of Change	Brief Rationale
Other Changes: Clarifications; EU CTR Requirements; Sponsor Protocol Template requirements; formatting or typographical corrections		
Section 3, Objectives and Endpoints/ Estimands	• In exploratory endpoints, added the Quality of Life and Patient-Reported Outcomes (PROs) endpoints for Part B on MSS, MFS, ESS, BDI-II, PGI-S, and PGI-C. • Clarified that exploratory biomarker endpoints and the effect of bile acid binding resins on linerixibat pharmacodynamics will be assessed in Part B. • In exploratory markers of liver fibrosis endpoints, clarified that ELF will be assessed in Part B.	Clarification of previously omitted Part B endpoints.
Section 4.1, Overall Design Section 4.2.2, Rationale for Stratification	Amended text describing concomitant medications for cholestatic pruritus medications to include fibrates and selective serotonin reuptake inhibitors (SSRIs).	Clarification.
Section 4.2.4, Rationale for Concomitant Medications	Added fibrates to the list. Updated the linerixibat interaction with OCA description based on data from Study 213688.	Clarification and modification in line with updated information.
Section 4.4, End of Study Definition	Clarified the last visit for participants.	Clarification.

Section # and Name	Description of Change	Brief Rationale
Other Changes: Clarifications; EU CTR Requirements; Sponsor Protocol Template requirements; formatting or typographical corrections		
Section 5.1, Inclusion Criteria	• Added note in Inclusion #4 to highlight that careful planning may be needed to confirm negative pregnancy test in time if serum test is required. • Removed reference to Pregnancy Testing details that is duplicated and with incorrect Section number.	Clarification of logistical approach for serum pregnancy as needed.
Section 5.2, Exclusion Criteria	In exclusion criteria for abnormal liver chemistry, updated note to clarify that Sample 1 and Sample 2 must be collected at least 4 weeks apart.	Clarification of exclusion criteria requirements.
Section 5.2, Exclusion Criteria	In exclusion criteria for initiation, discontinuation, or change in dose, fibrates replaced bezafibrate and fenofibrate.	Clarification of broader concomitant medication terminology.
Section 5.3.2, Caffeine, Alcohol, and Tobacco	Clarified number of alcoholic drinks for women and men.	Clarification from previous inconsistency.
Section 6, Study Interventions and Concomitant Therapy	• Referred the reader to the List of Definitions for study intervention. • Added authorization status of the IMP, linerixibat.	In line with the updated sponsor protocol template. Added to comply with EU CTR requirements.

Section # and Name	Description of Change	Brief Rationale
Other Changes: Clarifications; EU CTR Requirements; Sponsor Protocol Template requirements; formatting or typographical corrections		
Section 6.2, Preparation/ Handling/ Storage/ Accountability	• Added timing for start of study intervention. • Clarified allowable shipment of study intervention to and from the participant. • Added reference to Section 10.8.4 for home healthcare permissions.	Clarification.
Section 6.3, Assignment to Study Intervention	Heading changed from Measures to Minimize Bias: Randomization and Blinding to Assignment to Study Intervention.	In line with the updated sponsor protocol template.
Section 6.3.1, Unblinding Procedures	Heading was removed and details of blinded and unblinded data were moved to Section 6.4, Blinding.	In line with the updated sponsor protocol template.
Section 6.5, Study Intervention Compliance	Clarified study intervention administration should be documented daily in the eDiary and clarified the assessment of compliance.	Clarification.

Section # and Name	Description of Change	Brief Rationale
Other Changes: Clarifications; EU CTR Requirements; Sponsor Protocol Template requirements; formatting or typographical corrections		
Section 6.9.1, Permitted Medications	Under concomitant medications that must be stable prior to screening and throughout the screening and treatment periods, pregabalin was added and fibrates replaced bezafibrate and fenofibrate.	Clarification of previous inconsistency
Section 7, Discontinuation of Study Intervention and Participant Discontinuation/ Withdrawal	Added: No replacement is planned for participant discontinuing/withdrawing from the study.	Clarification to comply with EU CTR requirements.
Section 7.1, Discontinuation of Study Intervention	• Clarified the study assessments to be completed if participants withdraw from study treatment but remain on study. • Clarified the timing of Discontinuation Visit and follow-up phone call Visit requirements in certain circumstances.	Clarification of study assessment requirements.
Section 7.1.1.2, Stopping Criteria	Clarified that study intervention restart may be considered after liver safety follow-up if there is a clear underlying non-Drug Induced Liver Injury [DILI] event cause.	Clarification of previous inconsistency with 7.1.9, Restart of Study Intervention.

Section # and Name	Description of Change	Brief Rationale
Other Changes: Clarifications; EU CTR Requirements; Sponsor Protocol Template requirements; formatting or typographical corrections		
Section 7.2, Participant Discontinuation/ Withdrawal from the Study	• Clarified participants may withdraw from the study for any reason or without providing a reason. • Clarified data and samples to be included in the study analysis if participant withdraws from the study.	Clarification of text in line with revised sponsor protocol template.
Section 8, Study Assessments and Procedures	Referred to Section 10.8 for further details on home healthcare availabilities.	Clarification of approach.
Section 8.1, Administrative Procedures	Added this heading and new text to describe demographic data collected and rationale.	Clarification in line with revised sponsor protocol template.
Section 8.3.1, Physical Examination	Clarified that visits performed at locations other than a trial site include those by a home healthcare provider in the description of allowed physical exams and referred to Section 10.8 for home healthcare activities.	Clarification.
Section 8.3.4, Clinical Safety Laboratory Assessments	Added reference to List of Clinical Laboratories. Clarified when local laboratory results must be recorded in eCRF.	Clarification of local laboratory results recording and text in line with new sponsor protocol template
Section 8.3.5, Pregnancy Testing	Clarified requirements for pregnancy testing in females of childbearing potential.	Clarification.

Section # and Name	Description of Change	Brief Rationale
Other Changes: Clarifications; EU CTR Requirements; Sponsor Protocol Template requirements; formatting or typographical corrections		
Section 8.3.6, Study Safety Monitoring	Added heading and text to describe how participant safety will be monitored.	Clarification of approach already in place in line with new sponsor protocol template.
Section 8.4.7, Adverse Events of Special Interest	Clarified that details of AESIs will be recorded on the AESI eCRF and on the AE/SAE eCRF.	Clarification of approach already in place.
Section 8.4.8, Participant Card	Added heading and text that describes the participant card.	Clarification of approach already in place in line with updated sponsor protocol template.
Section 9.4.5, Other Analyses	Added additional details on blinded PRO data analysis to support the establishment of a clinically meaningful within-patient change threshold or range of thresholds.	Clarification of approach in line with FDA guidance.
Section 10.1.3, Informed Consent Process	• Clarified consent process for collecting information on the baby in case of unexpected pregnancy. • Clarified that investigator will explain the objectives of the exploratory research.	Clarification of expectations in line with updated sponsor protocol template.
Section 10.1.4, Recruitment Strategy	Added this heading and text on the recruitment strategy for the study.	Added details describing current strategy to support EU CTR requirements and in line with the updated sponsor protocol template.

Section # and Name	Description of Change	Brief Rationale
Other Changes: Clarifications; EU CTR Requirements; Sponsor Protocol Template requirements; formatting or typographical corrections		
Section 10.1.5, Data Protection	• Added text that GSK will ensure protection of personal data of the investigator and site staff and added that data protection is specified in the contract between sponsor and study sites. • Added text to indicate the information technology provides participant personal protection.	Clarification in line with updated sponsor protocol template.
Section 10.1.6.1, Safety Review Team	• Added heading and text on the Safety Review Team (SRT) and who comprises the SRT. • Added text that SRT contribute to the continual assessment of incoming new efficacy and safety information.	Clarification in line with updated sponsor protocol template.
Section 10.1.7, Dissemination of Clinical Study Data	• Added details regarding how/where key design elements of this protocol and results will be posted. • Added details regarding study results information to be available for the investigator.	Clarification in line with updated sponsor protocol template.
Section 10.1.9, Source Documents	Clarified the sponsor or designee will perform ongoing source data verification monitoring.	Clarification in line with updated sponsor protocol template.

Section # and Name	Description of Change	Brief Rationale
Other Changes: Clarifications; EU CTR Requirements; Sponsor Protocol Template requirements; formatting or typographical corrections		
Section 10.1.10, Study and Site Start and Closure	Clarified that site termination could occur if the total number of participants are included earlier than expected.	Clarification.
Section 10.1.11, Publication Policy	Clarified results of this study may be published in peer reviewed scientific literature.	Clarification in line with updated sponsor protocol template.
Section 10.2, Clinical Laboratory Test	Clarified investigators must document their review of each laboratory safety report.	Clarification in line with updated sponsor protocol template.
Section 10.3.2, Definition of SAE	Added in SAE definition table: Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).	More prominent placement of information in line with updated sponsor protocol template.
Section 10.3.4, Recording and Follow-up of AE and SAE	Clarified the follow-up process/procedures for pregnancies.	Clarification of process already in place and in line with updated sponsor protocol template.
Section 10.5, Genetics	• Clarified genetic samples may be analyzed as part of a multi-study assessment of genetic factors and may be reported in the CSR or in a separate study summary. • Clarified details of sponsor storage and retainment of DNA samples.	Clarification in line with updated sponsor protocol template.

Section # and Name	Description of Change	Brief Rationale
Other Changes: Clarifications; EU CTR Requirements; Sponsor Protocol Template requirements; formatting or typographical corrections		
10.7.1.3, China Schedule of Activities	Clarifications made to SoA for consistency with Section 1.3.	Consistency with Section 1.3, SoA.
Section 10.7.2, Israel	Added the Israel heading and content.	Consolidation of Israel-specific protocol version.
Section 10.7.3, France	Added the France heading and content.	Consolidation of country specific annex within protocol amendment.
Section 10.8, Home Healthcare/ Remote Activities	The heading was changed from COVID-19 to Home Healthcare/Remote Activities and the section clarified and restructured to remove specific references to COVID-19. Including: • Clarified the inclusion of a fully remote metasite, if allowed by country regulation/ ethics. • Clarified that the process for laboratory sample shipments must be agreed upon with GSK, if performed by the clinical site.	Clarification that remote activities and home healthcare is not limited to COVID-19 scenarios and can be used broadly across the study where permitted.

Section # and Name	Description of Change	Brief Rationale
Other Changes: Clarifications; EU CTR Requirements; Sponsor Protocol Template requirements; formatting or typographical corrections		
Section 10.8.4, Study Intervention(s)	• Clarified allowable shipment of study intervention to and from the participant. • Clarified the process for collection of used and/or unused IMP. • Clarified compliance with study intervention administration can be performed by trained home healthcare professionals.	Clarification.
Section 10.8.5, Data Management/ Monitoring	Corrected the eDC platform to Veeva CDMS.	Correction.
Section 10.10, Abbreviations, Definition of Terms, and Trademarks	Added the Definition of Terms header and table. Updated the list of abbreviations to align with protocol changes.	Clarification in line with updated sponsor protocol template.
Section 10.11, Protocol Amendment history	Added the overview and summary of changes table from the Israel amendment (Amendment 03 ISR-1).	Consolidation of full protocol amendment history.
Section 11, References	The original McKibben reference was corrected to Key 2020.	Correction of error in previous amendment.
Synopsis, Section 1.1 and throughout Protocol	General editorial and formatting changes made throughout the synopsis and protocol to improve clarity.	Clarification.

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Figure 3 Expected Change from Baseline in MWDI* 93

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A two-part, randomized, placebo controlled, double blind, multicenter, Phase 3 study to evaluate the efficacy and safety of linerixibat for the treatment of cholestatic pruritus in participants with primary biliary cholangitis (PBC).

Brief Title: *G*lobal *L*inerixibat *I*tch *ST*udy of *E*fficacy and Safety i*N* PBC (GLISTEN)

Rationale:

Cholestatic pruritus burdens up to three quarters of patients with PBC during the course of their disease. This itch due to this rare and chronic liver disease, represents a serious condition that continues to lack effective treatments.

Linerixibat, an ileal bile acid transporter inhibitor administered as an oral tablet, is minimally absorbed from gastrointestinal tract. Linerixibat is anticipated to reduce pruritus and associated symptoms in patients with PBC by increasing the excretion of bile acids and reducing bile acid concentrations in systemic circulation. Twice daily linerixibat has demonstrated significant improvement in cholestatic pruritus in PBC patients in previous Phase 2a and Phase 2b studies.

Moreover, the Phase 2b dose ranging study (201000 – NCT02966834 –referred to as the GLIMMER study) demonstrated linerixibat 40 mg twice daily (BID) as the minimally effective dose providing improvement in cholestatic pruritus over 12 weeks of treatment with a low rate of discontinuation due to gastrointestinal (GI) intolerability.

This Phase 3 study will further investigate the efficacy and safety of 24 weeks of 40 mg BID oral linerixibat for the treatment of pruritus in PBC patients with moderate to severe cholestatic pruritus (Part A), as well as assess the return of itch over 8-weeks after withdrawal of 40 mg BID oral linerixibat compared to placebo (Part B). Participants enrolled in the study may be treatment naïve, have been previously treated, or may take stable background itch therapy at the discretion of the physician in the best interest of the patient. Definitions of cholestatic pruritus treatments can be found in the main protocol text.

Participants will record itch scores twice daily using an electronic Diary (eDiary). A 0-10 Numerical Rating Scale (NRS), which has been validated in the PBC population, will be used to assess itch with a response option of 0 representing no itching and 10 the worst imaginable itching. Every morning the participant will record the worst itch experienced the night before and every evening, the participant will record the worst itch experienced that day.

The itch scores for any day, week, and month will then be determined as follows:

- **Worst Daily Itch Score:** the worst of the two scores recorded daily will be considered the score for that day

- **Weekly Itch Score** (WIS) (formerly referred to as Mean Worst Daily Itch [MWDI] Score)**:** the average of the Worst Daily Itch scores in one week
- **Monthly Itch Score:** the worst Weekly Itch Score for that month (i.e., worst week score of the 4 weeks)

Cholestatic pruritus has a negative impact on health-related quality of life (QoL) for PBC patients. The Primary Biliary Cholangitis-40 Questionnaire (PBC-40) is a disease-specific health-related QoL instrument consisting of 6 domains: social, emotional, symptoms, fatigue, itch (including an item on sleep disturbance from itching) and cognitive. Results from the GLIMMER study demonstrated significant improvement from baseline in the social and emotional domains of PBC-40 for participants receiving 40mg BID linerixibat. Therefore, this study will further evaluate the effect of linerixibat on PBC-40 domains. Since sleep is only a single item in PBC-40 and sleep disturbance is a major complaint of PBC patients, participant's sleep will also be evaluated using the daily eDiary. Participants will record a sleep interference score each morning using a 0-10 NRS, where 0 represents no sleep interference and 10 represents complete sleep interference. For each week, the average of the Daily Sleep Scores will be used to calculate the Weekly Sleep Score (formerly referred to as the Mean Daily Sleep Score). The Monthly Sleep Score is the worst Weekly Sleep Score for that month (i.e., worst week score of the 4 weeks).

Objectives:

Objectives*	**Endpoints**
Primary	
To investigate the effect of treatment with oral linerixibat compared with placebo on itch in PBC patients with cholestatic pruritus over 24 weeks (Part A)	• Change from Baseline in Monthly Itch Scores over 24 weeks using a 0-10 NRS
Secondary	
To evaluate the early effects of oral linerixibat compared to placebo on itch in PBC patients with cholestatic pruritus (Part A)	• Change from baseline in Weekly Itch Score at Week 2
To characterize the effects of treatment with oral linerixibat compared with placebo on health related QoL (Part A)	• Change from Baseline in Monthly Sleep Score as measured by 0-10 NRS over 24 weeks • Change from Baseline in PBC-40 domain scores at Week 24

Objectives*	Endpoints
Secondary (continued)	
To evaluate the effects of 24 weeks of treatment with oral linerixibat compared to placebo on itch response rates in PBC patients with cholestatic pruritus (Part A)	• Responder defined as achieving a ≥2-point reduction from Baseline in the Monthly Itch Score at Week 24. • Responder defined as achieving a ≥3-point reduction from Baseline in the Monthly Itch Score at Week 24. • Responder defined as achieving a ≥4-point reduction from Baseline in the Monthly Itch Score at Week 24.
To investigate the treatment effect of oral linerixibat compared with placebo on Patient's Global Impression of Severity (PGI-S) and Patient's Global Impression of Change (PGI-C) throughout the treatment period (Part A)	• Change from baseline in PGI-S over 24 weeks • PGI-C over 24 weeks
To evaluate the effects of treatment with linerixibat on markers of PBC disease activity and progression (Part A)	• Change from baseline in alkaline phosphatase (ALP) at Week 24 • Change from baseline in bilirubin at Week 24
Safety	
To evaluate the safety of oral linerixibat compared with placebo (Part A and Part B)	Clinical assessments including, but not limited to: • Adverse Events (AEs) and Serious Adverse Events (SAEs) • Vital signs • 12-lead Electrocardiogram (ECG) • Clinical laboratory evaluation (including liver chemistry panel and fasting lipids)
Exploratory	
To investigate the improvement, maintenance, or return of itch (Part B)	• Change from Baseline (Part A) in Weekly Itch Score at 8 weeks • Change from Baseline (Part B) in Monthly Itch Score over 8 weeks (maintenance)

*Linerixibat refers to linerixibat with stable background itch therapy if applicable. Placebo refers to placebo with stable background itch therapy if applicable.

Estimands:

Unless otherwise specified, all primary and secondary study objectives will be assessed using estimands defined with the following common elements in terms of population, treatment comparison and approach for managing intercurrent events.

Population	• PBC patients with cholestatic pruritus
Treatment	• Linerixibat + background itch therapy if applicable • Placebo + background itch therapy if applicable
Intercurrent events	• Permanent treatment discontinuation, disruptions in treatment or treatment delays unrelated to the COVID-19 pandemic: addressed with treatment policy strategy, i.e., regardless of the intercurrent event occurring. • Permanent treatment discontinuation, disruptions in treatment, or treatment delays related to the COVID-19 pandemic: addressed with hypothetical strategy, i.e., the outcomes impacted by the COVID-19 related intercurrent events will be discarded • Change in background itch therapy or use of rescue medication: addressed with treatment policy strategy, i.e., regardless of the intercurrent event occurring

Summary Measures for the study objectives are as follows:

Endpoint	Summary Measure
Primary objective	
Change from Baseline in Monthly Itch Scores over 24 weeks using a 0-10 NRS	Difference in means averaged over 24 weeks between treatment groups
Secondary objectives	
Change from baseline in Weekly Itch Score at Week 2	Difference in means between treatment groups
Change from Baseline in Monthly Sleep Score as measured by 0-10 NRS over 24 weeks	Difference in means averaged over 24 weeks between treatment groups
Responder defined as achieving a ≥2-point reduction from Baseline in the Monthly Itch Score at Week 24	Difference in proportions between treatment groups
Responder defined as achieving a ≥3-point reduction from Baseline in the Monthly Itch Score at Week 24	Difference in proportions between treatment groups
Responder defined as achieving a ≥4-point reduction from Baseline in the Monthly Itch Score at Week 24	Difference in proportions between treatment groups

Endpoint	Summary Measure
Secondary objectives (continued)	
Change from Baseline in PBC-40 domain scores at Week 24	Difference in means between treatment groups
Change from baseline in PGI-S over 24 weeks	Difference in means averaged over 24 weeks between treatment groups
PGI-C over 24 weeks	Difference in means averaged over 24 weeks between treatment groups
Change from baseline in ALP at Week 24	Difference in means between treatment groups
Change from baseline in bilirubin at Week 24	Difference in means between treatment groups

Supplementary Estimand for the Primary Objective

A supplementary estimand for the primary objective will be defined to assess the hypothetical treatment effect of linerixibat compared to placebo in the absence of intercurrent events including treatment discontinuation, disruptions in treatment or treatment delays, changes in itch therapy or use of rescue. In this case all Daily Itch Score data impacted by the intercurrent events will be discarded.

Overall Design:

This study is a Phase 3, multicenter, 2-part (Part A and Part B), randomized, double-blind, placebo-controlled study in PBC patients with moderate to severe pruritus. Part A will evaluate the efficacy, safety and impact on health-related quality of life of linerixibat compared with placebo over 24 weeks, while Part B will assess the return of itch over 8 weeks after withdrawal of linerixibat. In both Part A and Part B, participants may be treatment naïve, have had prior itch therapy and/or may take stable background itch therapy at the discretion of the physician in the best interest of the patient or rescue medication where applicable.

This study consists of four Periods (Screening, Intervention (Part A and Part B) and Follow-up):

Screening Period: Participants will attend two screening visits to assess eligibility as described below:

- Screening 1 (Visit 1): Assessments to be performed as described in the schedule of assessments (SoA). Itch severity will be assessed retrospectively based on participant recall and then prospectively for eligibility purposes using a twice daily eDiary throughout the screening period.
- Screening 2 (Visit 2): Additional liver biochemistry assessments to be performed at least 4 weeks after screening visit 1 to ensure stability of liver disease for participant safety and eligibility purposes.

Intervention (Treatment) Period Part A (Day 1 through Week 24): Eligible participants will be randomized in a 1:1:1:1 ratio to receive linerixibat 40 mg BID in Part A and Part B, linerixibat 40 mg BID in Part A and placebo in Part B, placebo in Part A and Part B, or placebo in Part A and linerixibat 40 mg BID in Part B.

The primary analysis will be performed when all randomized participants have completed the Part A intervention period (up to Week 24/Visit 9), as described in Section 9.4. The blinding strategy is described in Section 6.4.

Randomization will be stratified by:

- Severity of pruritus based on Monthly Itch Score for the 28 days preceding randomization:
    - Moderate: ≥ 4 and < 7
    - Severe: ≥ 7
- Concomitant cholestatic pruritus treatment regimen (definitions of cholestatic pruritus treatments can be found in the main protocol text):
    - Bile acid binding resin-containing regimen
    - Regimen that does not contain bile acid binding resins
    - No cholestatic pruritus treatment.

The region (US or rest of the world) and site categorized by whether the visits will be conducted fully remotely will serve as an administrative stratification factor. The primary analysis will not adjust for this administrative stratification factor. Further details will be provided in the SAP.

Intervention (Treatment) Period Part B (Week 24 through Week 32): Participants who had initially been taking linerixibat in Part A will either continue on linerixibat or switch to placebo at Week 24 for Part B. Participants who had been taking placebo in Part A will either continue on placebo or switch to linerixibat at Week 24 for Part B.

Follow-up Period or Follow-on Study:

Participants who complete treatment in Part A and Part B will be offered the opportunity to take part in a separate long-term follow-on study, where linerixibat will be provided in an open-label manner. This open-label, long-term study will assess safety and tolerability (and efficacy in participants transferring from this study). Participants who do not enter the follow-on study or are discontinued from study treatment but remain in the study will have a follow up phone call approximately 7-14 days after the last dose of study drug.

Where applicable country and local regulations allow, some or all of the participant visits may be conducted remotely or via a virtual trial platform. Home healthcare services may also be utilized to support these activities where local regulations and infrastructure allow.

Number of Participants:

This study plans to randomize approximately 230 participants with PBC and moderate to severe cholestatic pruritus.

Participants receiving concomitant bile acid binding resins may comprise up to 15% of the overall Phase 3 study population.

Based on GLIMMER (201000) study, it is expected that at least 20% of participants in the study will be receiving concomitant itch therapy and/or have had prior itch therapy; patients entering the study have moderate to severe itch and as such these patients have not adequately responded to or are intolerant to available standard of care.

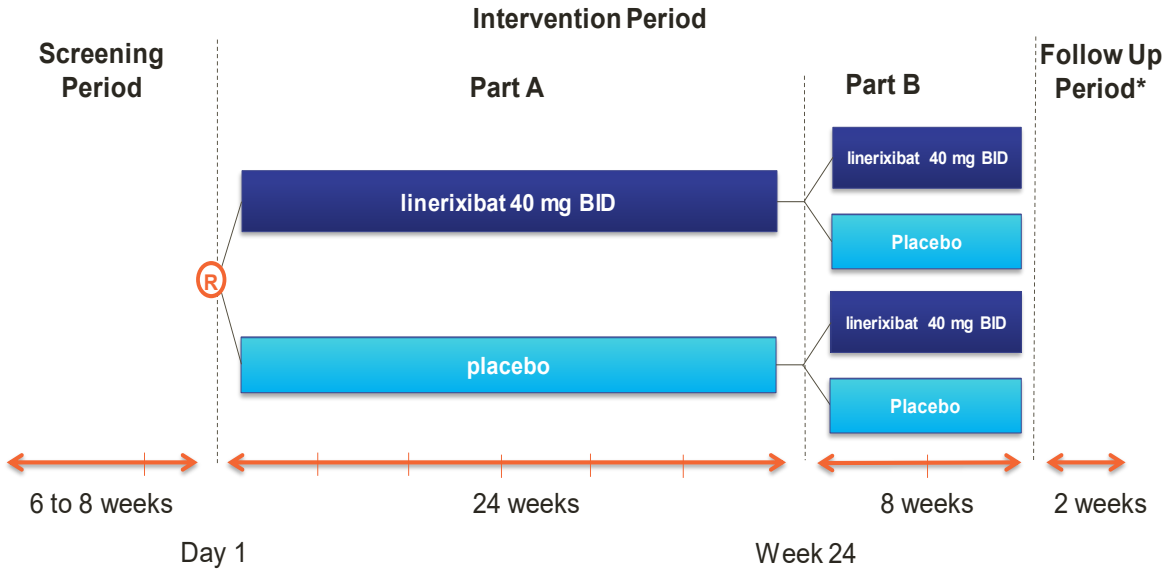
Intervention Groups and Duration:

The total duration of the study including screening, treatment and follow up phone-call (if performed) is not expected to exceed 42 weeks. Visit frequency will be approximately every 4 weeks during treatment.

- Screening: Up to 56-day screening window.
- Part A: 24 weeks treatment with either linerixibat 40 mg BID or placebo
- Part B: 8 weeks treatment with either linerixibat 40 mg BID or placebo
- Follow-up: 2 weeks (for those not enrolling in the follow-on study)

Data Monitoring / Other Committee: Yes
An Independent Data Monitoring Committee (IDMC) will perform a futility analysis of efficacy at the planned interim analysis for the study and evaluate the safety of participants.

1.2. Schema



*The follow-up period will only apply to participants who do not enrol into a follow-on study

R = Randomization

1.3. Schedule of Assessments (SoA)

	Screening (up to 56 days before Day 1)		**Intervention Period**									**ED**	**Follow-up (7 -14 days post last dose)**	**Notes E.D = Early Discontinuation/Withdrawal (as described in Section 7.2).**
			Part A							**Part B**				Where applicable country and local regulations and infrastructure allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (Please see Section 10.8).
Visit Number	1	2	3		4	5	6	7	8	9	10	11			
Day number	-56 to -42	-28 to -14	1		28	56	84	112	140	168	196	224			
Visit window (days)	NA	NA	NA		±3	±3	±3	±3	±3	±3	±3	±3			
Week number	-8 to -6	-4 to -2 (>V1 + 4Wks)	1		4	8	12	16	20	24	28	32			
Informed consent	X														
Inclusion and exclusion criteria	X		X												Recheck clinical status before randomization.
Demography	X														
Full physical exam	X														Including height and weight.
Brief physical examination			X		X	X	X	X	X	X	X	X	X		Please see Section 8.3.1; physical exams may be performed as symptom directed exams or by other means if assessment performed at locations other than the clinical site.

	Screening (up to 56 days before Day 1)		**Intervention Period**									**ED**	**Follow-up (7 -14 days post last dose)**	**Notes E.D = Early Discontinuation/Withdrawal (as described in Section 7.2).**
			Part A							**Part B**				Where applicable country and local regulations and infrastructure allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (Please see Section 10.8).
Visit Number	1	2	3		4	5	6	7	8	9	10	11			
Day number	-56 to -42	-28 to -14	1		28	56	84	112	140	168	196	224			
Visit window (days)	NA	NA	NA		±3	±3	±3	±3	±3	±3	±3	±3			
Week number	-8 to -6	-4 to -2 (>V1 + 4Wks)	1		4	8	12	16	20	24	28	32			
Medical history and prior/current conditions	X		X												Including substance usage (drugs, alcohol, tobacco and caffeine), family history of premature cardiovascular (CV) disease and PBC specific Medical History and past-PBC-related procedures. Any change in medical history since screening should be reviewed at Day 1, and a baseline stool frequency should be recorded as described in Section 7.1.3.
Background Itch Assessment	X														The investigator will ask participants to rate their overall itch severity for the 2 months preceding the screening visit as described in Section 8.2.1.1.
Urine Pregnancy test (Women of Childbearing Potential [WOCBP] only)	X		X		X	X	X	X	X	X	X	X	X		Refer to Section 8.3.5, serum pregnancy may be required locally in some locations.

	Screening (up to 56 days before Day 1)		**Intervention Period**									**ED**	**Follow-up (7 -14 days post last dose)**	**Notes E.D = Early Discontinuation/Withdrawal (as described in Section 7.2).**
			Part A							**Part B**				Where applicable country and local regulations and infrastructure allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (Please see Section 10.8).
Visit Number	1	2	3		4	5	6	7	8	9	10	11			
Day number	-56 to -42	-28 to -14	1		28	56	84	112	140	168	196	224			
Visit window (days)	NA	NA	NA		±3	±3	±3	±3	±3	±3	±3	±3			
Week number	-8 to -6	-4 to -2 (>V1 + 4Wks)	1		4	8	12	16	20	24	28	32			
Human Immunodeficiency Virus (HIV), Hepatitis B and C screening	X														
Clinical Laboratory tests	X	X	X		X	X	X	X	X	X	X	X	X		Refer to Section 10.2, Clinical laboratory tests at Visit 2 refer to liver biochemistry parameters only.
Fecal Occult Blood Test (FOBT)			X							X					Please see Section 8.3.4.2.
Exploratory Biomarkers		X	X		X	X	X	X	X	X	X	X	X		Please see Section 8.7. Sample on Day 1 should be taken prior to any study intervention administration. Assessment is not required if study treatment is permanently discontinued.
Enhanced Liver Fibrosis (ELF) Test			X							X		X			ELF may not be performed in China due to operational limitations.

	Screening (up to 56 days before Day 1)		**Intervention Period**									**ED**	**Follow-up (7 -14 days post last dose)**	**Notes E.D = Early Discontinuation/Withdrawal (as described in Section 7.2).**
			Part A							**Part B**				Where applicable country and local regulations and infrastructure allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (Please see Section 10.8).
Visit Number	1	2	3		4	5	6	7	8	9	10	11			
Day number	-56 to -42	-28 to -14	1		28	56	84	112	140	168	196	224			
Visit window (days)	NA	NA	NA		±3	±3	±3	±3	±3	±3	±3	±3			
Week number	-8 to -6	-4 to -2 (>V1 + 4Wks)	1		4	8	12	16	20	24	28	32			
Fibroscan			X							X					To be performed only where site availability permits; please see Section 8.7.1.2.
Pharmacokinetics (PK)			X			X	X	X	X	X					PK samples are required at a total of 3 timepoints, 1 sample is required prior to first study intervention administration at Visit 3 and 2 further samples will be required at any 2 additional visits between weeks 8 and 24. Assessment is not required if study treatment is permanently discontinued.
12-lead ECG	X						X			X		X	X		
Vital signs	X		X		X	X	X	X	X	X	X	X	X		
Randomization			X												
Genetic sample			X												Please see Section 8.6. Sample is optional and to be taken predose if possible. Genetic samples will not be collected in China or Israel.

	Screening (up to 56 days before Day 1)		**Intervention Period**									**ED**	**Follow-up (7 -14 days post last dose)**	**Notes E.D = Early Discontinuation/Withdrawal (as described in Section 7.2).**
			Part A							**Part B**				Where applicable country and local regulations and infrastructure allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (Please see Section 10.8).
Visit Number	1	2	3	4	5	6	7	8	9	10	11			
Day number	-56 to -42	-28 to -14	1	28	56	84	112	140	168	196	224			
Visit window (days)	NA	NA	NA	±3	±3	±3	±3	±3	±3	±3	±3			
Week number	-8 to -6	-4 to -2 (>V1 + 4Wks)	1	4	8	12	16	20	24	28	32			
Study intervention dispensing			X		X		X			X				
Study intervention administration				←==========→										Day 1 is the day on which the first study intervention administration takes place and may differ from the randomization date.
Medication diary				←==========→										Study medication diary to be completed daily throughout the study. The medication diary is not required if study treatment is permanently discontinued.
Study intervention return/compliance					X	X	X	X	X	X	X	X			
Adverse Event (AE) review				←==========→								X	X	AEs will be collected from the start of study intervention.
Serious Adverse Event (SAE) review	←==========→											X	X	
Concomitant medication review	←==========→											X	X	Including PBC-specific Medications (past and present).

	Screening (up to 56 days before Day 1)		**Intervention Period**									**ED**	**Follow-up (7 -14 days post last dose)**	**Notes E.D = Early Discontinuation/Withdrawal (as described in Section 7.2).**
			Part A							**Part B**				Where applicable country and local regulations and infrastructure allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (Please see Section 10.8).
Visit Number	1	2	3	4	5	6	7	8	9	10	11			
Day number	-56 to -42	-28 to -14	1	28	56	84	112	140	168	196	224			
Visit window (days)	NA	NA	NA	±3	±3	±3	±3	±3	±3	±3	±3			
Week number	-8 to -6	-4 to -2 (>V1 + 4Wks)	1	4	8	12	16	20	24	28	32			
Symptom Questionnaire	←==========										→	X		Symptom Questionnaire includes the itch, sleep and fatigue NRS. Please see Section 8.2.1.1.
Gastrointestinal Symptom Rating Scale			←==========								→	X		Questionnaire on GI symptoms to be completed weekly in eDiary with a seven day recall as described in Section 8.2.1.3.
PGI-C					X	X	X	X	X	X	X	X	X		Patient Global Impression of Change Questionnaire
PGI-S			X		X	X	X	X	X	X	X	X	X		Patient Global Impression of Severity
PBC-40			X		X	X	X	X	X	X	X	X	X		PBC-40 Health Related Quality of Life Scale
BDI-II			X				X			X		X	X		Beck Depression Inventory II
ESS			X				X			X		X	X		Epworth Sleepiness Scale

2. INTRODUCTION

2.1. Study Rationale

Cholestatic pruritus burdens up to three quarters of PBC patients through the course of their disease [Hegade, 2014; Hegade, 2019]. This itch due to the rare, chronic liver disease is a serious condition that causes significant impairment of day-to-day functioning, including sleep disturbance, fatigue, depression, and suicidality [Jin, 2016; Hegade, 2016; Younossi, 2000; Hönig, 2018].

Limitations of efficacy and tolerability of current treatments mean that patients are left with restricted choices. Thus, there is a continued urgent unmet medical need for new treatments for cholestatic pruritus in PBC that provide symptomatic relief and reduce the impact of pruritus on quality of life.

Linerixibat, an ileal bile acid transporter inhibitor administered as a twice daily (BID) oral tablet, has shown significant improvement in cholestatic pruritus in PBC patients in Phase 2 studies (BAT117213 and the previously mentioned GLIMMER study). Moreover, the GLIMMER study demonstrated linerixibat 40 mg BID as the minimally effective dose providing improvement on cholestatic pruritus over 12 weeks of treatment with a low rate of discontinuation due to gastrointestinal (GI) intolerability.

Primary Biliary Cholangitis-40 Questionnaire (PBC-40) is a disease-specific health-related quality of life (QoL) instrument consisting of 6 domains: social, emotional, symptoms, fatigue, itch (including an item on sleep disturbance from itch domain) and cognitive. Results from the GLIMMER study demonstrated clinically and statistically significant improvement from baseline in the social and emotional domains of PBC-40 for participants receiving 40 mg BID linerixibat. Since sleep is only a single item in PBC-40 and sleep disturbance is a major complaint of PBC patients with cholestatic pruritus, participant's sleep was also evaluated daily in the eDiary using an NRS scale and concordant improvements in itch and sleep were observed in GLIMMER. The Epworth Sleepiness Scale (ESS) has also been included to further assess the impact of itch relief on sleep and daytime somnolence.

This Phase 3 study will further investigate the efficacy and safety of 24 weeks of 40 mg BID oral linerixibat with stable background itch therapy, if applicable, for the treatment of pruritus in PBC patients with moderate to severe cholestatic pruritus (Part A), as well as assess the return of itch over 8-weeks after withdrawal of 40 mg BID oral linerixibat compared to placebo (Part B). Participants enrolled in the study can take stable background itch therapy (if applicable) at the discretion of the physician in the best interest of the patient.

2.2. Background

2.2.1. Overview of Disease

Primary biliary cholangitis is a rare, chronic autoimmune disease characterized by granulomatous inflammatory destruction of intrahepatic bile ducts leading to intrahepatic cholestasis, retention of bile acids and other toxic metabolites, and eventual cirrhosis and

liver failure. A combination of genetic risk factors and environmental exposures has been proposed for the etiology of PBC [Lindor, 2019].

The major symptoms of PBC affecting QoL are cholestatic pruritus (itch) and fatigue [Lindor, 2019, Zakharia, 2018; Younossi, 2000]. While the origin of cholestatic pruritus in PBC is still unknown, it has long been suspected that some component of bile that accumulates in serum contributes to pruritus. Patients with clinically significant pruritus fare worse than those with mild or no itch on all the QoL domains (fatigue, social, emotional, cognitive, and other symptoms) of the PBC-40, a disease specific health-related quality of life instrument [Carey, 2020].

Overall, pruritus has been reported to affect almost three quarters of PBC patients at some time during their disease, but the prevalence of pruritus at any given point in time is around 50% [Hegade, 2014; Hegade, 2019]. Recent observational studies report the prevalence of approximately 30% when restricted to moderate to severe pruritus [Hegade, 2014; Tanaka, 2016; Yagi, 2017; Carey, 2018; Hönig, 2018]. Intractable pruritus may be an indication for liver transplantation [Lindor, 2019].

In clinical practice, response rates <50% are common for most of the guideline-recommended therapies for cholestatic pruritus [Levy, 2011]. Bile acid sequestrants are recommended as first-line therapy in treatment guidelines for cholestatic pruritus in PBC, despite a limited evidence base and tolerability is often an issue [Lindor, 2019; EASL, 2017; Komori, 2014; Chengwei, 2015]. Only one therapy, cholestyramine, is approved in the United States [Questran USPI] and China for pruritus associated with partial biliary obstruction and in Europe [Questran SmPC] for pruritus associated with partial biliary obstruction and partial biliary cirrhosis. Reduction of serum bile acids through ileal bile acid transporter (IBAT) inhibition is showing promise in treating pruritus in PBC and other cholestatic conditions [Karpen, 2020].

2.2.2. Background information on the product

Linerixibat (also referred to as GSK2330672) is a soluble and selective inhibitor of the human ileal bile acid transporter (IBAT) [Wu, 2013], also known as apical sodium-dependent bile acid transporter (ASBT), that is minimally absorbed from the GI tract. Linerixibat is being developed as a novel, oral treatment for cholestatic pruritus associated with PBC.

Inhibition of the IBAT by linerixibat decreases pruritic serum bile acids through fecal elimination [Hegade, 2017]. Linerixibat has demonstrated reduction in itch and potential for improvement in sleep and health-related quality of life (QoL) in cholestatic pruritus in PBC patients in both Phase 2a (BAT117213) and GLIMMER studies as described in the below sections and in the Investigator's Brochure (IB).

2.2.3. Clinical Studies

The effect of linerixibat on cholestatic pruritus in PBC was evaluated in the BAT117213 study and the GLIMMER dose-range finding study.

BAT117213 was a randomized, double-blind, placebo-controlled 2-period cross-over trial in which linerixibat was administered as 45 mg BID for the first 3 days and increased to 90 mg BID on Day 4 of the randomized active treatment period. This study enrolled participants with severe pruritus and newly diagnosed or untreated pruritus who qualified based on disease status and clinical symptoms. Linerixibat treatment for 14 days resulted in significant reductions from baseline in itch intensity scores as measured by numerical rating scale (NRS), PBC-40 itch domain and 5-D itch scale ($p<0.0001$ for all) in both treatment sequences after linerixibat treatment [Hegade, 2017]. Compared to the double-blind placebo treatment, linerixibat reduced itch intensity significantly more in all three scales; between treatment differences were: –23% (95% CI, –1 to –45, p=0·0374) for NRS, –14% (95% CI, –1 to –26, p=0·0335) for PBC-40 itch domain, and –20% (95% CI, –7 to –34, p=0·0045) for 5-D itch. This was accompanied by a significant reduction in serum total bile acid concentrations of more than 50%, which was reversed within 2 weeks of stopping linerixibat. In contrast, there was a 12% increase in serum total bile acid concentrations after placebo dosing. In this study, linerixibat also demonstrated statistically significant improvements in the fatigue domain of PBC-40 and sleep interference following 14 days of treatment [Hegade, 2017]. In general, linerixibat was well tolerated without SAEs. An equal number of AEs were reported during placebo and study intervention treatment periods. There was a 33% incidence of diarrhea reported as an adverse event while on linerixibat vs. 5% on placebo. The individual episodes tended to be mild in severity and short lived in the majority of cases. No subjects discontinued dosing or had their dose decreased secondary to diarrhea.

The GLIMMER study was a randomized, double-blind parallel-group, dose-finding study further evaluating linerixibat for the treatment of pruritus in patients with PBC. This study assessed the efficacy, safety, and tolerability, and assessed dose and dosing regimen (once vs. twice daily). Participants must have had proven PBC, rated their itch severity as being ≥ 4 on a 0 to 10-point NRS for the majority of time during the 8 weeks prior to the screening visit, and on stable doses of ursodeoxycholic acid (UDCA) (or enrolled 8 weeks after their last dose of UDCA if not taking UDCA due to intolerance). Eligible patients were randomized based on an NRS itch score of ≥ 3. Additionally, they could continue to receive therapies including anti-histamines, rifampicin, naltrexone, naloxone, nalfurafine or sertraline for the treatment of cholestatic pruritus in PBC provided the medications were maintained at stable doses with no plan to discontinue them during the study. Concomitant use of cholestyramine, colesevelam, colestimide or colestipol was not permitted until after completion of the treatment period.

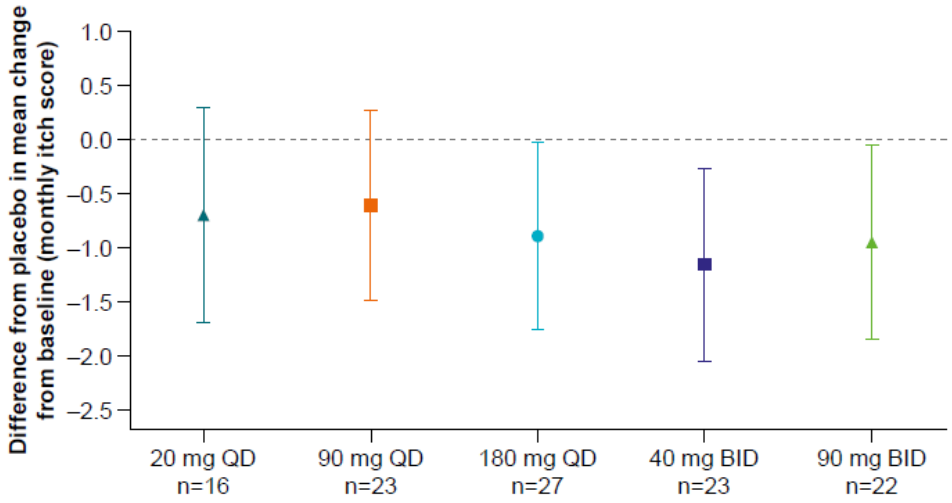
Participants were randomized to treatment with placebo or one of the five linerixibat doses of 20 mg, 90 mg, 180 mg once daily (QD), 40 or 90 mg BID for up to 12 weeks. Itch was measured morning and evening using an NRS anchored with 0 (no itching) and 10 (worst imaginable itching).

Following the Screening period, there were four study periods: a 4-week single-blind Run-in Period where all participants received placebo; a 12-week Main Study Period where participants received double-blind treatment with placebo or linerixibat, a 4-week Final Period where all participants received placebo, and a 2-week follow-up period. The 147 eligible participants were randomized based on Mean Worst Daily Itch Score (now

referred to as the Weekly Itch Score in Study 212620 [GLISTEN]) of ≥3 (averaged over the 7 days prior to randomization).

Mean pruritus intensity scores were reduced (itch improved) at the end of the Main Study Period for all treatment groups including the placebo arm (please refer to IB Section 5.4.4). Due to the potential for itch to fluctuate over time, the change from Baseline in Monthly Itch Score (worst week of the month) over the entire treatment period was used to evaluate the duration and stability of treatment effect. A mixed-effect repeated measure (MMRM) analysis of this endpoint thus utilized data across the whole 12-week Main Study period (as opposed to an analysis using a single timepoint) and resulted in a statistically significant difference from placebo for 40 mg BID (p=0.0105), 90 mg BID (p=0.0370) and 180 mg QD (p=0.0424) doses (Figure 1).

Figure 1 **Difference from Placebo in change from baseline in Monthly Itch Score over the entire 12-week treatment period (Intend To Treat [ITT] population)**

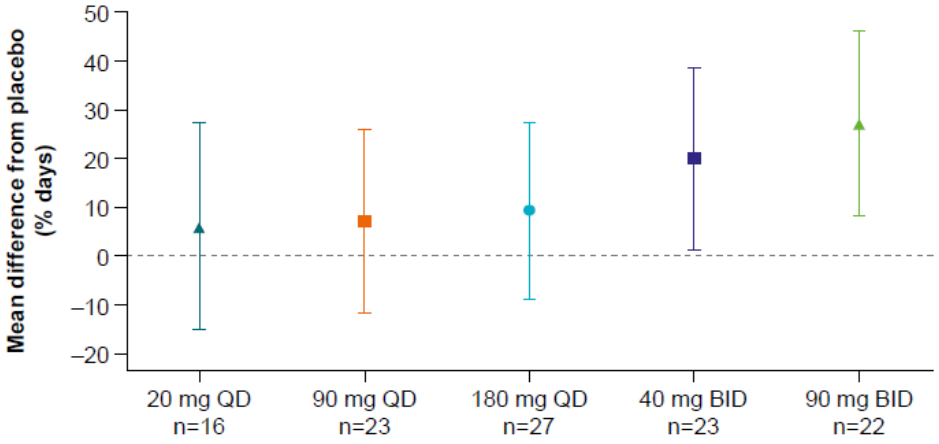


Note: Error bars show 95% Confidence Interval (CI).

Furthermore, a rapid reduction of itch was observed for the 40 mg BID and 90 mg BID dosing groups compared to placebo as early as Weeks 1 and 2 (data on file). Based on this observation, a secondary endpoint assessing change in Weekly Itch Score at Week 2 will be evaluated in the current study.

In addition, within person change using the responder definition (defined as ≥2-point improvement in mean worst daily itch score [now referred to as Weekly Itch Score in the current 212620 (GLISTEN) study] from baseline) provides interpretation for the primary endpoint in terms of clinical meaningfulness of the result. Percentage of itch responder days also favored BID dosing, with a mean increase of 20% for 40 mg BID and 27% for 90 mg BID groups relative to placebo (Figure 2).

Figure 2 Mean difference from placebo in percentage itch responder days during 12 weeks' treatment (ITT population)



Note: Error bars show Standard Error (SE).

Of note, among the total study population approximately 29% (42/147) had prior history of treatment with bile acid binding resins and 29% (42/147) of participants were receiving concomitant itch therapy during the study. Neither prior treatment with bile acid binding resins nor concomitant treatment with pruritus therapy during the study were significant after accounting for treatment groups in an analysis of covariates.

Impact on health-related QoL was also evident following treatment with linerixibat. Improvement on sleep interference was highly correlated to improvement on itch score across all treatment groups (R=0.84, data on file).

All arms including placebo showed significant improvement from baseline in the itch domain of PBC-40 but only the 40 mg BID dose demonstrated significant improvements from baseline in the PBC-40 social and emotional domains.

The most frequently reported drug-related AEs across all treatment groups were diarrhea and abdominal pain, with diarrhea demonstrating an increase of incidence with increasing dose (placebo 8%, 20 mg QD 31%, 90 mg QD 48%, 180 mg QD 59%, 40 mg BID 39%, 90 mg BID 64%). Diarrhea and abdominal pain were also the AEs most frequently leading to study drug discontinuation across all treatment groups (10 participants and 5 participants, respectively). The discontinuation incidence due to diarrhea was lower in the 40 mg BID group (4%) compared to the 90 mg BID (14%) and 180 mg QD (19%) treatment groups. Diarrhea was mostly mild to moderate in severity, there were no SAEs related to diarrhea and no case of dehydration during the treatment period were observed.

There were 3 SAEs which were all considered not related to study treatment (lumbar spinal stenosis 90 mg QD; lower respiratory tract infection 20 mg QD; constipation 180 mg QD).

No notable change from Baseline or difference from placebo was observed for Enhanced Liver Fibrosis (ELF) tests, liver function tests (LFTs), bone biochemistry or liposoluble

vitamins across the treatment arms. There were no clinically significant patterns of abnormal vital sign measurements, ECG changes, or clinical laboratory findings observed.

Overall, the 40 mg BID dose demonstrated significant improvement in pruritus over 12 weeks of treatment, as well as significant change from baseline in the social and emotional domains of PBC-40. Gastrointestinal tolerability data also favored 40 mg BID dosing over higher doses.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of linerixibat may be found in the IB.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product [GSK2330672/linerixibat]		
• Gastrointestinal effects including diarrhea, abdominal pain and abdominal discomfort.	• Animal studies including altered bowel motions (see the IB, Section 4.5). • AEs in humans including diarrhea and loose stools (see the IB, Section 5.3). • Diarrhea adverse events were seen in studies with PBC participants and cholestatic pruritus (BAT117213 and GLIMMER) as described in Section 2.2.3 and the IB, Section 5.3.3.2. • Abdominal pain events were reported in healthy participants and in studies with PBC participants with cholestatic pruritus (BAT117213 and GLIMMER) as described in Section 2.2.3 and the IB, Section 5.3.3.2.	• Exclusion of participants with current clinically significant diarrhea in the Investigator's medical opinion (see Section 5.2). • Monitoring/stopping criteria for participants experiencing diarrhea have been provided as found in Section 7.1.3. • Study aids providing guidance to investigators for management of diarrhea will be provided in the Study Reference Manual (SRM).
• Potential gallstones due to interruption of enterohepatic recirculation of bile acids.	• A single SAE of acute cholecystitis (imaging confirmed cholelithiasis) was reported in GSK study 200185 in a Type 2 diabetes (T25D) participant (see the IB, Section 5.3.3.1). • A phenome-wide association study (PheWAS) conducted by GSK under the United Kingdom Biobank Ethics and Governance Framework, using data from a large cohort (379,337 participants from the	• Exclusion of participants with current symptomatic cholelithiasis or inflammatory gallbladder disease (cholecystitis) (see Section 5.2).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	UK Biobank) suggested an association between genetically determined impairment of the enterohepatic recirculation of bile acids with an increased risk of gallbladder disease and cholecystectomy, but not with colorectal cancer [Campbell, 2018]. An additional pheWAS performed in up to 2.5 million European ancestry (EUR) 23andMe cohort participants identified significant associations among 82,913 participants with a history of gallstones for two IBAT Lack of Function (LOF) variants with experimentally validated effects on SLC10A2 function [McLaughlin, 2020].	
• Hypertriglyceridemia due to interruption of enterohepatic recirculation of bile acids.	• Slight increases in triglycerides were seen in T2D participants in study 201351 (see the IB, Section 5.3).	• Lipid profiles will be monitored throughout the study as at the timepoints listed in Section 1.3.
• Increase in alanine aminotransferase (ALT).	• Transient elevations in alanine aminotransferase (ALT) of up to 3x upper limit of normal (ULN) have been observed in 4 healthy participants (see the IB, Section 5.3). • Liver increased monitoring criteria (increase ALT >2 x baseline and ALT> 3 x ULN) were reached in 7 PBC participants in the GLIMMER study (see the IB, Section 5.3).	• Stopping/monitoring rules for liver chemistry have been implemented as described in Section 7.1.1. • Liver enzymes will be monitored throughout the study at the timepoints listed in Section 1.3.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• In the GLIMMER study, one participant in the linerixibat 90 mg BID group met the liver stopping criteria for ALT levels (reported as an AE of abnormal liver test) 60 days after receiving linerixibat. This event resolved after a duration of 98 days. The investigator noted that the AE of abnormal liver test could have been related to study medication and study medication was permanently discontinued. The participant had also experienced a non-serious AE of tooth abscess approximately 6 weeks prior, which resulted in tooth extraction and associated dental infection and was treated with amoxicillin and metronidazole antibiotics. Based on the information, there is a possibility that the concomitant antibiotics and painkillers may have contributed to the abnormal LFTs (see the IB, Section 5.4.3).	
• Increased risk of colon cancer in association with increased fecal excretion of bile acids	• Although a theoretical association between increased colonic bile acids and colorectal cancer has been postulated there is no direct evidence of causation between bile acids and the development of colon cancer [Acosta, 2014]. • Two large pheWAS studies in 379,337 and up to 2.5 million European ancestry participants respectively, did not suggest an association between genetically determined impairment of the enterohepatic recirculation of bile acids (loss of function IBAT variants, SLC10A2) with an increased risk of	• FOBTs will be collected at the timepoints shown in the SoA (see Section 1.3) as described in Section 8.3.4.2. • Stopping criteria for participants diagnosed with colon cancer at any point have been provided as found in Section 7.1.6.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	colorectal cancer [Campbell, 2018, McLaughlin, 2020]. These findings were also supported by a genome -wide association study (GWAS) in 58,131 European ancestry cases [Huyghe, 2019]. The genetic findings were consistent with published long-term follow-up of participants with ileal bypass surgery, which did not support an effect of enterohepatic circulation on colon cancer risk [Buchwald, 1990]. • No reports of colon cancer (or similar events) have been reported in the linerixibat clinical program (see IB, Section 6.3.2.2). • Currently, the data suggests that there is no increase in risk of colorectal cancer in patients receiving linerixibat for cholestatic pruritus in patients with PBC (see IB, Section 6.3.2.2).	

2.3.2. Benefit Assessment

There may be a number of potential benefits of participating in this study including:

- Potential improvement in symptoms of pruritus associated with PBC during intervention.
- Medical evaluations/assessments associated with study procedures that assess participant's PBC (e.g., physical examinations, laboratory assessments).
- Contribution to the process of developing new therapies for the treatment of pruritus associated with PBC.
- Potential opportunity to participate in a long-term study of linerixibat as defined in Section 6.7.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with linerixibat are justified by the anticipated benefits that may be afforded to participants with PBC.

3. OBJECTIVES AND ENDPOINTS/ESTIMANDS

Itch will be recorded by participants twice daily using an eDiary as described in Section 8.2.1.1. A 0-10 NRS will be used, where 0 represents no itching and 10 the worst imaginable itching. Every morning the participant will record the worst itch experienced the night before and every evening, the participant will record the worst itch experienced that day. The itch scores for any day, week, and month will then be determined as follows:

- **Worst Daily Itch Score:** the worst of the two scores recorded daily will be considered the score for that day
- **Weekly Itch Score** (WIS) (formerly referred to as Mean Worst Daily Itch Score [MWDI])**:** the average of the Worst Daily Itch Scores in one week
- **Monthly Itch Score:** the worst Weekly Itch Score for that month (i.e., worst week score of the 4 weeks)

Cholestatic pruritus has a negative impact on health-related QoL for PBC patients. The PBC-40 is a disease-specific QoL instrument consisting of 6 domains: social, emotional, symptoms, fatigue, itch (including an item on sleep disturbance from itch domain) and cognitive. Results from the GLIMMER study demonstrated significant improvement from baseline in the social and emotional domains of PBC-40 for participants receiving 40 mg BID linerixibat. Therefore, this study will further evaluate the effect of linerixibat on PBC-40 domains. Since sleep is only a single item in PBC-40 and sleep disturbance is a major complaint of PBC patients, participant's sleep will also be evaluated using the daily eDiary. Participants will record a sleep interference score each morning using a 0-10 NRS, where 0 represents no sleep interference and 10 represents complete sleep interference. For each week, the average of the Daily Sleep Score will be used to calculate the Weekly Sleep Score (formerly referred to as Mean Daily Sleep Score). The

Monthly Sleep Score is the worst Weekly Sleep Score for that month (i.e., worst week score of the 4 weeks).

Objectives*	**Endpoints**
Primary	
To investigate the effect of treatment with oral linerixibat compared with placebo on itch in PBC patients with cholestatic pruritus over 24 weeks (Part A)	• Change from Baseline in Monthly Itch Scores over 24 weeks using a 0-10 numerical rating scale (NRS)
Secondary	
To evaluate the early effects of oral linerixibat compared to placebo on itch in PBC patients with cholestatic pruritus (Part A)	• Change from baseline in Weekly Itch Score at Week 2
To characterize the effects of treatment with oral linerixibat compared with placebo on health related QoL (Part A)	• Change from Baseline in Monthly Sleep Score as measured by 0-10 NRS over 24 weeks • Change from Baseline in PBC-40 domain scores at Week 24
To evaluate the effects of 24 weeks of treatment with oral linerixibat compared to placebo on itch response rates in PBC patients with cholestatic pruritus (Part A)	• Responder defined as achieving a ≥2-point reduction from Baseline in the Monthly Itch score at Week 24. • Responder defined as achieving a ≥3-point reduction from Baseline in the Monthly Itch score at Week 24. • Responder defined as achieving a ≥4-point reduction from Baseline in the Monthly Itch score at Week 24.
To investigate the treatment effect of oral linerixibat compared with placebo on Patient's Global Impression of Severity (PGI-S) and Patient's Global Impression of Change (PGI-C) throughout the treatment period (Part A)	• Change from baseline in Patient's Global Impression of Severity (PGI-S) over 24 weeks • PGI-C over 24 weeks
To evaluate the effects of treatment with linerixibat on markers of PBC disease activity and progression (Part A)	• Change from baseline in ALP at Week 24 • Change from baseline in bilirubin at Week 24

Objectives*	**Endpoints**
Safety	
• To evaluate the safety of oral linerixibat compared with placebo (Part A and Part B)	Clinical assessments including, but not limited to: • Adverse Events (AEs) and Serious Adverse Events (SAEs) • Vital signs • 12-lead Electrocardiogram (ECG) • Clinical laboratory evaluation (including liver chemistry panel and fasting lipids)
• **Exploratory**	
• To evaluate the gastrointestinal (GI) tolerability of oral linerixibat compared with placebo on gastrointestinal symptoms (Part A and Part B)	• Change from Baseline in Gastrointestinal Symptom Rating Scale (GSRS) over time
• To evaluate the effects of oral linerixibat compared to placebo on the percentage of itch response days (Part A)	• Percentage of days participant achieves a ≥2 point reduction from Baseline in the Worst Daily Itch score over 24 weeks. • Percentage of days participant achieves a ≥3 point reduction from Baseline in the Worst Daily Itch score over 24 weeks. • Percentage of days participant achieves a ≥4 point reduction from Baseline in the Worst Daily Itch score over 24 weeks.
• To investigate the improvement, maintenance, or return of itch (Part B)	• Change from Baseline (Part A) in Weekly Itch Score at 8 weeks • Change from Baseline (Part B) in Monthly Itch Score over 8 weeks (maintenance)
• To investigate the improvement, maintenance, or decline of health-related quality of life (QoL) and other patient-reported outcomes (Part B)	• Change from Baseline in o PBC-40 domain scores at 8 weeks o Monthly Sleep Score at 8 weeks o Monthly Fatigue Score at 8 weeks o Epworth Sleepiness Scale at 8 weeks o BDI-II at 8 weeks o PGI-S at 8 weeks • PGI-C at 8 weeks

Objectives*	Endpoints
• **Exploratory (continued)**	
• To evaluate the effects of oral linerixibat compared with placebo on exploratory biomarkers (Part A and Part B)	• Change from Baseline in concentrations of exploratory biomarkers including: o Serum C4 o Total serum bile acids o Autotaxin o Fibroblast Growth Factor-19 (FGF-19)
• Explore the effect of bile acid binding resins on linerixibat Pharmacodynamics (PD) (Part A and Part B)	• Linerixibat serum biomarkers including: o Serum C4 o Total serum bile acids o Autotaxin o FGF-19
• To characterize the PK in PBC participants (Part A)	• Determination of PK parameters by population PK analysis.
• To evaluate the effect of linerixibat compared to placebo on non-invasive markers of liver fibrosis (where available) (Part A and Part B, if applicable)	• Change from Baseline (Part A) in Enhanced Liver Fibrosis (ELF) at Week 24 • Change from Baseline (Part B) in ELF at Week 8 • Change from Baseline in Transient Elastography (Fibroscan) at Week 24
• To further characterize the effects of oral linerixibat compared with placebo on symptoms and health-related quality of life (Part A)	• Change from Baseline in Epworth Sleepiness Scale (ESS) over 24 weeks • Change from Baseline in Beck Depression Inventory-II (BDI-II) at 24 weeks • Change from Baseline in Monthly Fatigue Score as measured by 0 – 10 NRS over 24 weeks.

*Linerixibat refers to linerixibat with stable background itch therapy if applicable. Placebo refers to placebo with stable background itch therapy if applicable.

3.1. Primary Estimand

Unless otherwise specified, all primary and secondary study objectives will be assessed using estimands defined with the following common elements in terms of population, treatment comparison and approach for managing intercurrent events.

Population	• PBC patients with cholestatic pruritus
Treatment	• Linerixibat + background itch therapy if applicable • Placebo + background itch therapy if applicable

Intercurrent events	• Permanent treatment discontinuation, disruptions in treatment or treatment delays unrelated to the COVID-19 pandemic: addressed with treatment policy strategy, i.e., regardless of the intercurrent event occurring. • Permanent treatment discontinuation, disruptions in treatment or treatment delays related to the COVID-19 pandemic: addressed with hypothetical strategy, i.e., the outcomes impacted by the COVID-19 related intercurrent events will be discarded • Change in background itch therapy or use of rescue medication: addressed with treatment policy strategy, i.e., regardless of the intercurrent event occurring

3.2. Summary Measures

Endpoint	Summary Measure
Primary objective	
Change from Baseline in Monthly Itch Scores over 24 weeks using a 0-10 NRS	Difference in means averaged over 24 weeks between treatment groups
Secondary objectives	
Change from baseline in Weekly Itch Score at Week 2	Difference in means between treatment groups
Change from Baseline in Monthly Sleep Score as measured by 0-10 NRS over 24 weeks	Difference in means averaged over 24 weeks between treatment groups
Responder defined as achieving a ≥2-point reduction from Baseline in the Monthly Itch score at Week 24	Difference in proportions between treatment groups
Responder defined as achieving a ≥3-point reduction from Baseline in the Monthly Itch score at Week 24	Difference in proportions between treatment groups
Responder defined as achieving a ≥4-point reduction from Baseline in the Monthly Itch score at Week 24	Difference in proportions between treatment groups
Change from Baseline in PBC-40 domain scores at Week 24	Difference in means between treatment groups
Change from baseline in PGI-S over 24 weeks	Difference in means averaged over 24 weeks between treatment groups
PGI-C over 24 weeks	Difference in means averaged over 24 weeks between treatment groups
Change from baseline in ALP at Week 24	Difference in means between treatment groups

Endpoint	Summary Measure
Change from baseline in bilirubin at Week 24	Difference in means between treatment groups

Summary measures for Part B are not included as these objectives are exploratory. For further details, please see Section 9.4.

3.3. Supplementary Estimand

A supplementary estimand for the primary objective will be defined to assess the hypothetical treatment effect of linerixibat compared to placebo in the absence of intercurrent events including treatment discontinuation, disruptions in treatment or treatment delays, changes in itch therapy or use of rescue. In this case all Daily Itch Score data impacted by the intercurrent events will be discarded (see Section 9.4 for further details).

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase 3, multicenter, 2-part (Part A and Part B), randomized, double-blind, placebo-controlled study in PBC patients with moderate to severe pruritus. Part A will evaluate the efficacy, safety, and impact on health-related quality of life of linerixibat with background itch therapy, if applicable, compared with placebo with background itch therapy, if applicable, over 24 weeks, while Part B will assess the return of itch over 8 weeks after withdrawal of linerixibat. Participants may be treatment naïve, have had prior itch therapy and/or may take stable background itch therapy at the discretion of the physician in the best interest of the patient or rescue medication where applicable.

This study will consist of four periods:

- Screening Period (up to 56 days)

At Screening Visit 1 (Visit 1), screening assessments will be performed as described in the Schedule of Assessments (SoA) (Section 1.3). This will include a baseline itch evaluation in which the participant will be asked to rate their overall itch severity in the 2 months preceding screening as described in Section 8.2.1.1. Participants will then enter the screening period during which participants must complete a symptom questionnaire in an electronic Diary (eDiary) for eligibility purposes which include itch and sleep NRS scores as defined in Section 8.2.1.1.

Participants must also attend a second screening visit (Visit 2) to take place at least 4 weeks after Visit 1, for further assessment of liver biochemistry. This is to ensure stability of liver disease and for participant safety and eligibility purposes as described in Section 8.3.4.1.

- Intervention Period: Part A (Day 1 through Week 24)

Eligible participants will be randomized in a 1:1:1:1 ratio to receive linerixibat 40 mg BID in Part A and Part B, linerixibat 40 mg BID in Part A and placebo in Part B, placebo in Part A and Part B, or placebo in Part A and linerixibat 40 mg BID in Part B.

Randomization will be stratified by:

- Severity of pruritus based on Monthly Itch Score for the 28 days preceding randomization:
    - Moderate: ≥ 4 and < 7
    - Severe: ≥ 7
- Concomitant cholestatic pruritus treatment regimen (definitions of cholestatic pruritus treatments can be found in the main protocol text):
    - Bile acid binding resin-containing regimen
    - Regimen that does not contain bile acid binding resins
    - No cholestatic pruritus treatment.

    Bile acid binding resins include cholestyramine, colesevelam, colestimide and colestipol. Other cholestatic pruritus medications include antihistamines, fibrates, rifampicin, naltrexone, naloxone, nalfurafine, pregabalin, gabapentin or selective serotonin reuptake inhibitors (SSRIs). Please see further information on concomitant medications in Section 6.9.

The region (US or rest of the world) and site categorized by whether the visits will be conducted fully remotely will serve as an administrative stratification factor. The primary analysis will not adjust for this administrative stratification factor. Further details will be provided in the SAP.

The primary analysis will be performed when all randomized participants have completed the Part A intervention period (up to Week 24/Visit 9), as described in Section 9.4. The blinding strategy is described in Section 6.4. Part A is completed when the Week 24 Visit (Visit 9) is completed.

- Intervention Period: Part B (Week 24 through Week 32)

Participants who had initially been taking linerixibat in Part A will either continue on linerixibat or switch to placebo at Week 24 for Part B. Participants who had been taking placebo in Part A will either continue on placebo or switch to linerixibat at Week 24 for Part B.

Part B is completed at the completion of Week 32 Visit (Visit 11).

- Follow up (approximately 2 weeks)

Participants who complete treatment in Part A and Part B will be offered the opportunity to take part in a separate long-term follow-on study as described in Section 6.7. Participants who do not enter the follow-on study or are discontinued from study treatment but remain in the study will complete a follow-up telephone call approximately 7-14 days after the last dose of linerixibat.

The total expected duration of study participation for each participant is approximately 40-42 weeks.

Where applicable country and local regulations allow, some or all of the participant visits may be conducted remotely or via a virtual trial platform. Home healthcare services also may be utilized to support these activities where local regulations and infrastructure allow.

Approximately 230 total participants with PBC and moderate to severe cholestatic pruritus are expected to be randomized into this study. Participants receiving concomitant bile acid binding resins may comprise up to approximately 15% of the overall total study population.

Based on GLIMMER (201000) study, it is expected that at least 20% of participants in the study will be receiving concomitant itch therapy and/or have had prior itch therapy; patients entering the study have moderate to severe itch and as such these patients have not adequately responded to or are intolerant to available standard of care.

An Independent Data Monitoring Committee (IDMC) will be utilized to evaluate futility for the interim analysis planned for the study (please see Section 9.5). Further detail on the IDMC will be provided in a separate charter.

4.2. Scientific Rationale for Study Design

4.2.1. Rationale for Study Blinding and Placebo Control

This is a Phase 3, placebo-controlled study with a 24-week double-blind Part A, followed by an 8-week double-blind Part B. Previous studies of IBAT inhibitors in PBC patients have demonstrated that patient-reported itch may show some improvement on placebo treatment [Hegade, 2017; Mayo, 2019]. A placebo arm is employed in the study to help determine the true clinical effect of linerixibat relative to background cholestatic pruritus treatment.

4.2.2. Rationale for Stratification Factors

In order to balance the baseline itch score, treatment assignment for Randomization at Day 1 will be stratified according to the Monthly Itch Score during the 28 days before Day 1, using the categories: **Moderate**: Monthly Itch score ≥ 4 and < 7; **Severe**: Monthly Itch Score≥ 7.

Concomitant use of stable treatments for cholestatic pruritus will be allowed (see Section 6.9.1), consistent with published guidelines by American Association for the Study of Liver Diseases (AASLD) [Lindor, 2019], European Association for the Study of the Liver [EASL, 2017], Ministry of Health, Labor and Welfare of Japan [Komori, 2014] and guidelines in China [Chengwei, 2015]. In order to balance the use of treatments for cholestatic pruritus, randomization will also be stratified by concomitant cholestatic pruritus treatment regimen (bile acid binding resin-containing regimen, regimen that does not contain bile acid binding resins, and no cholestatic pruritus treatment). Bile acid binding resins include cholestyramine, colesevelam, colestimide and colestipol.

Other cholestatic pruritus medications include antihistamines, fibrates, rifampicin, naltrexone, naloxone, nalfurafine, pregabalin, gabapentin or SSRIs. Participants receiving concomitant bile acid binding resins may comprise up to 15% of the overall Phase 3 study population.

4.2.3. Rationale for Part B

The Intervention Period will start with Part A (Day 1 through Week 24) followed by Part B (Week 24 through Week 32). Eligible participants will be randomized in a 1:1:1:1 ratio to receive linerixibat 40 mg BID in Part A and Part B, linerixibat 40 mg BID in Part A and placebo in Part B, placebo in Part A and Part B, or placebo in Part A and linerixibat 40 mg BID in Part B. Therefore, participants who received placebo in Part A will either continue on placebo or switch to linerixibat at Week 24 for Part B. Participants who had received linerixibat in Part A will either continue on linerixibat or switch to placebo at Week 24 for Part B.

Based on results of the GLIMMER data, it is expected that participants switched from linerixibat in Part A to placebo in Part B will have some return of their itch. The current 8-week randomized-withdrawal in Part B allows evaluation of what occurs once linerixibat is removed compared to those who are maintained on placebo treatment in regard to itch, sleep, health-related QoL, and safety.

4.2.4. Rationale for Concomitant Medications

Participants may be receiving concomitant therapy with UDCA or fibrates for treatment of PBC or with standard of care therapies for cholestatic pruritus, including bile acid binding resins, fibrates, rifampicin, naltrexone, naloxone, nalfurafine, pregabalin, gabapentin or SSRIs. Any of these therapies, as well as other medications that may affect itch such as opioids, systemic corticosteroids, or antihistamines that may be prescribed for other indications, must be stable, defined as no initiation, discontinuation, or dose changes within 8 weeks of Screening, during the Screening period and throughout the Intervention (treatment) period of the study, including both Part A and Part B (Please see Section 6.9.1). This is to ensure that evaluation of linerixibat's effect on pruritus is not confounded by changes in background therapies that may affect itch.

Eligible participants who are not receiving any standard of care therapies for cholestatic pruritus may participate in the study. For these participants only, if worsening pruritus develops then rescue medication (cholestyramine) may be permitted, provided they have been in the study for at least 12 weeks, a duration that was acceptable during the GLIMMER trial, and meet additional itch criteria (see Section 6.9.3). Participants who are receiving background cholestatic pruritus therapy are not eligible for rescue medication and, changes in their cholestatic pruritus medications (initiation, discontinuation, or change in dose) at any time during the study will be considered a protocol violation as described in Section 6.9.3.

Obeticholic acid (OCA) use is not permitted at any time during the study due to its potential to confound assessment of efficacy and safety. OCA is approved for use in a subset of PBC participants with an inadequate response to or intolerance to UDCA [Ocaliva US Prescribing Information, and EU SmPC, 2021], and is associated with a dose

dependent exacerbation in pruritus leading to treatment discontinuation in 1–10% of participants [EASL, 2017]. In Study 213688 evaluating pharmacokinetic drug-drug interaction with 5 and 10 mg OCA, linerixibat 40 mg BID demonstrated a protocol-defined meaningful reduction in total-OCA concentration. It is not recommended to co-administer linerixibat with OCA (IB, Section 6.4.4).

4.2.5. Rationale for Use of Itch Numerical Rating Scale as the Primary Endpoint

There are no well-established physical or physiological markers of treatment activity of pruritus associated with cholestatic liver disease that can be observed or measured. The rating of itch is subjective, and each participant is likely to have a distinct response to treatment for cholestatic pruritus. The aim of treatment with linerixibat is to provide the symptomatic relief of pruritus associated with primary biliary cholangitis. Therefore, patient-reported outcomes (PRO) are the best way to measure a treatment effect. Both the BAT117213 and the GLIMMER study reflected this, where individual participant responses clearly showed rapid and significant improvement of pruritus following linerixibat treatment using multiple PRO assessments [Hegade, 2017; data on file].

The Symptom Questionnaire, which includes the itch, sleep and fatigue NRS items (described in Section 8.2.1.1), was developed by GSK with input from patients with PBC and psychometricians to detect the severity and variability of pruritus and associated symptoms, as well as the potential effects of treatment with the current standard of care on these symptoms. The itch and sleep NRS items assess symptoms that are relevant, important to, and well understood by PBC patients, and the patients are able to select responses that best reflect their disease experiences. NRS scales are widely used as a measure of severity as they are clear and simple and effective at measuring single constructs [Gries, 2017]. An external validation study was completed to collect quantitative data to assess the psychometric properties of the Mean Worst Daily Score (now referred to as the Weekly Itch Score), PBC-40, and Symptom Questionnaire and GSRS (GSK Health Outcomes Study 212144). The study along with analysis of the GLIMMER study provided psychometric validation of the PRO measures (0-10 Worst Itch NRS item, Symptom Questionnaire, and the weekly version of the PBC-40) with input from PBC-related pruritic study subjects (data on file).

4.2.6. Rationale for Questionnaires

Cholestatic pruritus in patients with PBC is a serious condition that causes significant impairment of day-to-day functioning, including fatigue, sleep disturbance, depression, and suicidality [Jin, 2016; Hegade, 2016; Younossi, 2000; Hönig, 2018]. Participants will complete questionnaires in both Part A and Part B of the study in order to assess the impact on these parameters. The PBC-40 is a patient-derived, disease specific health-related quality of life measure developed and validated for use in PBC [Jacoby, 2005] as described in Section 8.2.1.2.

Since depressive symptoms are prevalent in PBC patients [Shaheen, 2018] the BDI-II will assess symptoms of depression as described in Section 8.2.1.5.

Cholestatic pruritus often interferes with sleep therefore participants will rate their sleep NRS in the eDiary and the ESS will assess daytime sleepiness as described in Section 8.2.1.4.

GI symptoms are the most commonly reported adverse events associated with linerixibat. The GSRS as described in Section 8.2.1.3 will be used to systematically evaluate gastrointestinal symptoms. Management of GI symptoms should be based on adverse event reports (see Section 7.1.3).

4.2.7. Patient Input into Study Design

A small group of 5 patients with PBC were interviewed to gain insights on key study design elements from the perspective of a potential study participant. Patients provided feedback on the placebo-controlled design and follow-on study and how those may impact their interest in participating, their ability to maintain daily diaries, take study intervention daily, and complete the other assessments; overall study duration, and eligibility criteria.

The patients provided feedback that more clarity was needed about excluded medications and stable background medication requirements. Patients also stated that it should be clarified that background medications would still be permitted throughout the study. This feedback has been incorporated into this protocol (as defined in Section 6.9.1) and will be incorporated along with other operational aspects as part of the SRM.

4.3. Justification for Dose

The dose to be included in this 24-week study will be linerixibat 40 mg BID based on the efficacy and tolerability results of the GLIMMER study and kinetic-pharmacodynamic (K-PD) modelling. In the GLIMMER study, doses of 20 mg once daily (QD), 90 mg QD, 180 mg QD, 40 mg BID, and 90 mg BID were evaluated over a 12-week, double-blind period. When comparing the mean change from baseline in the Monthly Itch Score over the 12-week main study period, the doses of 40 mg and 90 mg BID and 180 mg QD were statistically different than placebo. The 40 mg BID dose trended with the greatest difference compared to placebo in Mean Worst Daily Itch score when considering the worst week of the month (Monthly Itch Score) as compared to 90 mg BID and 180 mg QD. Only 40 mg BID dose demonstrated significant improvements from baseline in the PBC-40 social and emotional domains. In addition to the dose-dependent decrease in Mean Worst Daily Itch scores, biomarkers of target engagement (serum C4 and FGF-19) measured in GLIMMER demonstrated a greater response with BID dosing as compared to QD dosing.

There was a dose-dependent relationship with gastrointestinal-related adverse events with a greater rate of permanent discontinuation and poorer tolerability at the higher doses of study intervention (180 mg QD and 90 mg BID) compared to 40 mg BID. Common gastrointestinal-related AEs, including diarrhea, abdominal pain, nausea, and vomiting, all trended to favor the 40 mg BID dose as compared to the higher doses. The most frequently reported AE was diarrhea, which was mostly mild to moderate, there were no reported SAEs associated with diarrhea and no case of dehydration during the treatment period. There were no clinically significant consequences of diarrhea. These results

support the use of 40 mg BID in Phase 3. Further details on dose rationale are available in the IB.

4.4. End of Study Definition

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

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit. For participants that will enroll into a follow-on study this last visit is Week 32 or completion of any required follow-up. If the participant will not enroll in a follow-on study, this would include completion of the follow-up phone call as shown in the SoA (see Section 1.3) or any required follow-up.

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:

Sex and Age

1. Male and female participants must be between 18 to 80 years of age inclusive, at the time of signing the informed consent.

   Note: if country/site age requirements for consent differ, the more stringent (e.g., higher age) restriction will be required for that country/site.

Type of Participant and Disease Characteristics

2. Participants who have proven PBC, as demonstrated by historically having at least 2 of the following:
   - Documented history of sustained increased ALP levels greater than ULN first recognized at least 6 months prior to the Screening Visit (Note: Sustained ALP elevations at the time of Screening is not required, recognizing that the ALP may have decreased after initiation of UDCA therapy).
   - Documented positive anti-mitochondrial antibody (AMA) titer (>1:40 titer on immunofluorescence or M2 positive by enzyme linked immunosorbent assay [ELISA] or by an alternative validated assay) or PBC-specific antinuclear antibodies (antinuclear dot and/or nuclear rim positive).
   - Liver biopsy (documented at any time in the past) consistent with PBC.
3. Participants who, during the Screening period, record their daily itch score by entering at least 40 of the 56 required itch entries, with an entry on at least 4 days in each week, during the 4-week period immediately preceding Randomization at Day 1

and have a Monthly Itch Score of ≥4 (i.e., at least 1 of the 4 Weekly Itch Scores must be ≥4), and no Weekly Itch Score can be <3 for any other week.

Contraceptive/Barrier Requirements

4. Contraceptive/Barrier Requirements (applicable for female participants only): A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

   - Is a woman of non-childbearing potential (WONCBP)

   OR

   - Is a woman of childbearing potential (WOCBP) and using an acceptable contraceptive method as described in Section 10.4 during the study intervention period (at a minimum until 4 weeks after the last dose of study intervention). The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive urine pregnancy test (or serum as required by local regulations) within 7 days before the first dose of study intervention, see Section 8.3.5, Pregnancy Testing.

  Note: If a serum pregnancy test is required by local regulations, sample collection must be arranged before Visit 3 to ensure the result confirming eligibility can be available before randomization.

  - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.
- 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.

Note: Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

5. Capable of giving signed informed consent as described in Section 10.1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Total bilirubin >2.0 x ULN using the average of two baseline measures.

   Note: Total bilirubin > 2x ULN but < 3x ULN is acceptable if bilirubin is fractionated and direct bilirubin is < 35%.

2. Screening ALT > 6x ULN in a single baseline measure or ALT > 5x ULN using the average of two baseline measures.

3. Participants with abnormal liver biochemistry (ALT, aspartate aminotransferase [AST], ALP, or total bilirubin) during the Screening period (at Visit 1 or Visit 2) and the variance between these two samples for the abnormal parameter is >40%.

   Note: Variance will be calculated as the absolute value of [(Sample 1- Sample 2)/average of Sample 1 and Sample 2) x100]. Sample 1 and Sample 2 must be collected ***at least 4 weeks apart****.*

   If variance of >40% is seen between Visit 1 and 2 samples, an additional sample may be taken and the variance between the additional sample (third sample) and the Screening (Visit 1) sample must be ≤ 40%.

4. Screening estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

5. History or presence of hepatic decompensation (e.g., variceal bleeding, hepatic encephalopathy or ascites).

6. Presence of viral hepatitis B (HBsAg positive) or C (anti-HCV positive and RNA detected) infection, primary sclerosing cholangitis (PSC), alcoholic liver disease and/or confirmed hepatocellular carcinoma or biliary cancer.

7. Infection with human immunodeficiency virus (HIV).

8. Current clinically significant diarrhea in the Investigator's medical opinion.

9. Active inflammatory ileal disease according to Investigator´s clinical judgment.

10. Current symptomatic cholelithiasis or cholecystitis. (Participants with history of cholecystectomy ≥12 weeks before screening may be eligible for enrolment at the discretion of the investigator.)

11. Current diagnosis of primary skin disorders with itch as a characteristic feature (e.g., atopic dermatitis, psoriasis).

12. Primary sleep disorders such as but are not limited to sleep apnea, narcolepsy, hypersomnia.

13. Any current malignancies (including hematologic and solid malignancies).

14. History of bariatric surgery with ileal bypass at any time, or any bariatric surgery performed in the past 3 years.

15. Any current uncontrolled psychiatric condition.

16. Any current medical condition (e.g., senility or dementia), which may affect the participant's ability to comply with the protocol specified procedures.

Prior/Concomitant Therapy

17. Initiation, discontinuation or change in dose of UDCA in the 8 weeks prior to Screening. (Participants may join the study on stable doses of UDCA, but no initiation, discontinuation, or change in dose is permitted until completion of the Treatment Periods.)
18. Use of obeticholic acid: within 8 weeks prior to Screening. (Participants may not initiate or restart during the study, please see Section 6.9.2.)
19. Initiation, discontinuation, or change in dose of fibrates at any time during the 8 weeks prior to Screening. (Participants may join the study on stable doses of these medications, but no initiation, discontinuation, or change in dose is permitted until completion of the Treatment Periods.)
20. Initiation, discontinuation, or change in dose of any of the following in the 8 weeks prior to Screening: bile acid binding resins, rifampicin, naltrexone, naloxone, nalfurafine, pregabalin, gabapentin, sertraline or other SSRIs. (Participants may join the study on stable doses of these medications, but no change in dose nor addition of new treatment for cholestatic pruritus is permitted during the study.)

    Note: Dosing of linerixibat and bile acid binding resins should be staggered by at least 4 hours.
21. Initiation, discontinuation or change in dose of opioids, regardless of indication, in the 8 weeks prior to Screening. (Participants may join the study on stable doses of these medications).
22. Initiation, discontinuation or change in dose of colchicine, methotrexate, azathioprine, or systemic corticosteroids in the 8 weeks prior to Screening.

    Note: If a change in dose in any of these medications is anticipated during the course of the study, the participant should be excluded.
23. Initiation, discontinuation, or change in dose of antihistamines used for the treatment of itching the 8 weeks prior to Screening.

    Note: Antihistamines used acutely for indications other than itch (e.g., for acute allergic reactions) are permitted.
24. Administration of any other IBAT inhibitor in the 12 weeks prior to screening.
25. Any planned procedures intended to treat cholestatic pruritus such as nasobiliary drainage or ultraviolet light therapy from Screening and throughout the study.

Prior/Concurrent Clinical Study Experience

26. Current enrolment or participation within the 8 weeks before start of the Screening, in any other clinical study involving an investigational study treatment.

Diagnostic assessments

27. QTc >480 msec

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. It is either machine-read or manually over-read.

The specific formula used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study and should be the only QT correction formula used during the study. In other words, several different formulas cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.

Other Exclusions

28. History of sensitivity or intolerance to the study treatment or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation in the study.
29. Subjects with moderate (or greater) alcohol consumption defined as one standard drink per day for women and two drinks per day for men; whereby one standard drink is equivalent to: 12 oz beer (5% alcohol); 5 ounces of wine (12% alcohol),or 1.5 ounces of 80 proof spirits (40% alcohol).

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

There are no specific dietary restrictions required for participation in the study. Laboratory samples should be taken in a fasted state; no food is permitted 6 hours prior to sample collection, though water, study interventions and other medications are permitted.

Dosing of study intervention should be taken at least 30 minutes before food or beverage (other than water) for both the morning and evening doses to ensure optimal efficacy.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants should abstain from alcohol for 24 hours prior to laboratory samples being taken and should not consume one standard drink or more per day for women and two drinks or more per day for men whereby one standard drink is equivalent to 12 oz beer (5% alcohol), 5 oz of wine (12% alcohol), or 1.5 oz of 80 proof spirits (40% alcohol).

5.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. For the duration of the study, until final follow up, participants are encouraged to refrain from changing their activity beyond that which they normally perform.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in to 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 SAEs. Information on prior and current treatment for cholestatic pruritus may also be collected for screen failures to provide information on/insight into the treatment history of the PBC population with pruritus.

In the case of COVID-19 diagnosis during the Screening period, the decision whether to continue screening the participant will be at the discretion of the investigator.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time at the Investigator's discretion. The participant may be rescreened one additional time in consultation with the GSK Medical Monitor. The second rescreening must be approved in writing by the GSK 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.

The interval between screening visits for the same participant should be a minimum of 1-week. Rescreened participants should be assigned a new participant number for every screening/rescreening event. Previously assigned participant numbers are to be recorded in the participants' electronic CRF (eCRF).

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of definitions. Linerixibat is not yet authorized in any region.

6.1. Study Intervention(s) Administered

Study Intervention Name	GSK2330672/linerixibat	Placebo
Dose Formulation	CCI film coated tablet	CCI film coated tablet
Unit Dose Strength(s)	40 mg tablets	N/A
Dosage Level(s)	1 tablet taken twice daily	1 tablet taken twice daily

Study Intervention Name	GSK2330672/linerixibat	Placebo
Route of Administration	Oral	Oral
Use	Experimental	Placebo comparator
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor

6.2. Preparation/Handling/Storage/Accountability

- 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 and only authorized site staff may supply or administer study intervention. Please refer to Section 10.8.4 for home healthcare permissions.
- All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled 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).
- Participants will be instructed to commence study treatment with the evening dose on the day that study treatment is received.
- Further guidance and information for the final disposition of unused study intervention are provided in the SRM.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- 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.
- The contents of the Study Interventional label will be in accordance with all applicable regulatory requirements. If allowed by country regulation/ethics, study intervention (including rescue study medication) can be shipped from the

investigational site, depot, or appropriately designated facility to the participant's home address. Used and/or unused IMP can also be collected from the participant's home address to the return/destruction location. The process for this shipment must be agreed with GSK who will provide operational details if this service is available.

6.3. Assignment to Study Intervention

All participants will be centrally assigned to randomized study intervention using an IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

Study intervention will be dispensed at the study visits as summarized in the SoA.

Returned study intervention should not be re-dispensed to the participants.

6.4. Blinding

This is a double-blind study in which participants, investigators, site personnel (including site pharmacists), and the Sponsor are blinded to study intervention.

The primary analysis will be performed when all randomized participants have completed the Part A intervention period (up to Week 24/Visit 9), as described in Section 9.4; at which point the study will become partially unblinded (core sponsor team unblinded, site blinded). GSK personnel involved in direct communication with the study sites/investigators continuing on Part B of GLISTEN will remain blinded to the randomized treatment assignment of individual participants in the study. The results of the primary analysis will not be disseminated to site personnel, investigators (except for the one investigator signatory of the clinical study report (CSR), under confidentiality), or study participants until the study (including Part B) is fully completed and the study is fully unblinded. All efforts will be taken to protect site facing sponsor personnel and site personnel from unblinding, which is described in a separate blinding plan. No impact on trial integrity is expected.

Individual participant-level, de-identified (not associated with participant number), and unblinded exploratory biomarker (TSBA) and tolerability data (AEs of diarrhea and GSRS scores) will be analyzed prior to unblinding the study for population K-PD model development. Independent sponsor programmers and clinical pharmacology modeling and simulation (CPMS) analysts will have access to actual randomization and dosing information. In addition to the dosing information and pharmacodynamic (PD) endpoint records, variables to be investigated as predictive covariates in the K-PD models such as demographics, concomitant medication data, safety laboratory data, and exploratory biomarker concentrations (e.g. C4, FGF-19, autotaxin) at one or more timepoints (e.g., prior to the final analysis) throughout the study will be made available. Individuals unblinded early will have no involvement in the study conduct including any analysis of blinded PRO data described in Section 9.4.5. Procedures are described in a separate blinding plan, and no impact on trial integrity is expected.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention for the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours of this occurrence. The date and reason why the blind was broken must be recorded.

A participant will be withdrawn from study intervention if the participant's intervention code is unblinded by the investigator or treating physician, however the participant will be asked to remain in the study and complete all remaining study visits. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.5. Study Intervention Compliance

- When participants self-administer study intervention(s) at home, they will be required to document administration of study treatment in a daily eDiary. Compliance with study treatment will be assessed by the number of returned tablets confirmed by site staff at each visit and supported by the medication eDiary data. Compliance will be documented in the source documents and eCRF. Deviations that impact overall compliance with the prescribed dosage regimen should be recorded.
- A record of the quantity of linerixibat dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.6. Dose Modification

No modification of individual participant's study intervention dose is permitted.

6.7. Continued Access to Study Intervention after the End of the Study

The sponsor will not provide treatment after the end of the study. However, participants who complete treatment in Part A and Part B will be given the opportunity to take part in an open-label, long-term follow-on study assessing safety and tolerability (and efficacy in participants transferring from this study), where linerixibat will be provided in an open-label manner. This follow on study is expected to continue for approximately four years

until study end, linerixibat can be lawfully made available to participants, or the study is terminated.

Participants who wish to take part in this or any further follow-on studies must provide separate consent to those studies and meet the study-defined eligibility criteria.

6.8. Treatment of Overdose

For this study, any dose of linerixibat greater than 180 mg (greater than 4 tablets) per day will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until linerixibat can no longer be detected systemically.
3. Obtain a plasma sample for PK analysis within 24-72 hour from the date of the last dose of study intervention 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.
5. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.9. Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant has received in the 12 weeks prior to screening, is receiving at the time of enrolment or receives during the study must be recorded in the eCRF along with:

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

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

6.9.1. Permitted Medications

Details concerning reasons for taking medications **must be recorded in the eCRF for all concomitant medications** whether prescription or non-prescription, including topical agents.

Guidance for permitted agents that may be used in the study population, provided all details are recorded in the eCRF, are provided below, however this list is not exhaustive and further concomitant medications should be discussed with the Medical Monitor:

- **Colchicine, methotrexate, azathioprine, or systemic corticosteroids:** If there is a clinical need to start one of these medications during the study, it should be discussed with the medical monitor wherever possible. During Follow-Up Period systemic corticosteroids may be permitted.

- **Anti-diarrheals**: Participants experiencing diarrhea, in consultation with the Investigator, may take anti-diarrheal treatments (loperamide or suitable local alternative as agreed by the Medical Monitor) obtained over the counter. Use of these treatments and their effect will be recorded at each review of concomitant medications (please see Section 7.1.3).

Concomitant therapy for PBC or any medications that may affect itch as shown below are permitted but **must be stable prior to Screening and throughout the Screening and Treatment Periods (i.e. no treatments in these categories may be initiated, discontinued or dose changed in the 8 weeks prior to Screening and throughout the study).**

- **UDCA:** Participants may be enrolled in the study on UDCA provided the dosing regimen is consistent with product labelling. Deviations from product labelling are permitted if medically necessary as judged by the Investigator. The UDCA dosing regimen must remain stable during the study

- **Bile acid binding resin medications:** Dosing of bile acid binding resin medications such as cholestyramine, colesevelam, colestipol or colestimide **should be altered so that dosing is separated from the study intervention (linerixibat) by at least 4 hours** for the duration of study participation.

- **Rifampicin, naltrexone, naloxone, nalfurafine, gabapentin, pregabalin:** Use of these agents is permitted during the study.

- **Fibrates:** Use of these agents is permitted during the study.

- **Selective Serotonin Reuptake Inhibitors (SSRIs):** Use of these agents is permitted during the study.

- **Opioid Medications:** Use of these agents is permitted during the study.

- **Antihistamines (topical or systemic):** Antihistamines may not be initiated for the treatment of itch, but antihistamines used regularly in the two months before screening may be continued without change in dose. Antihistamines used acutely for indications other than itch (e.g. for treatment of acute allergic reactions) may be initiated, discontinued, or dose changed as needed.

6.9.2. Prohibited Medications

Other IBAT inhibitors: Use of any IBAT inhibitor except for the study intervention, is not permitted at any time during the study.

Obeticholic acid: Use is not permitted at any time during the study. Obeticholic acid should not have been used for at least 8-weeks prior to the screening visit.

6.9.3. Rescue Medication

Rescue medication is permitted only for participants who are not receiving background cholestatic pruritus treatment when entering the study. If a participant reports experiencing worsening itch and requests rescue therapy, it may be considered only after 12 weeks of randomized treatment. Rescue medication may be considered if either of the following criteria are met:

1. Monthly itch score at or after Week 12 (Visit 6) has increased by at least 2 points compared to baseline AND is ≥ 7

OR

2. For participants with a baseline Monthly Itch Score > 8 Monthly itch score at or after Week 12 (Visit 6) is 10

Once these criteria have been satisfied, the investigator may offer treatment with cholestyramine to the participant per treatment guidelines. Any use of rescue medications will be recorded in the eCRF.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

No replacement is planned for participants who discontinue/withdraw from the study.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. In all cases, the participant should be encouraged to discuss any potential study intervention discontinuation with the investigator prior to stopping study intervention.

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, behavioral, compliance or administrative reasons as described in Section 7.2. If study intervention is permanently discontinued following randomization and before the scheduled follow up, participants should not be withdrawn from the study and should complete the remaining scheduled visits and all required assessments, including the patient-reported Symptom Questionnaire and all other PRO assessments. Exploratory biomarkers, PK, and medication diaries are not required to be completed for participants remaining on the study but withdrawn from study treatment. Participants who have been withdrawn from

study treatment but will remain in the study will not be required to complete an Early Discontinuation Visit but should complete a follow-up phone call 7-14 days after last dose of study treatment.

If the participant is withdrawing from the study, they will be encouraged to complete Early Discontinuation Visit (please refer to Section 1.3, SoA) before their last dose of study intervention if possible. Table 1 below outlines the scenarios for participant discontinuation and the assessments required to be performed.

Table 1 Scenarios for Participant Discontinuation

Discontinuing Study Treatment but will remain on the study	Follow up phone call 7-14 days after last dose of study treatment; continue scheduled visits as planned. Early Discontinuation Visit is not required to be performed.
Withdrawing from Study	Early Discontinuation Visit conducted as soon as possible after withdrawal decision, and follow-up phone call 7-14 days after last dose of study treatment. Note: If an Early Discontinuation Visit is completed between 7 and 14 days after last dose of study treatment, additional follow-up phone calls are not required

7.1.1. Liver Chemistry Monitoring/Discontinuation Criteria

Liver chemistry increased monitoring and stopping criteria have been designed to assure participants' safety and evaluate liver event etiology.

Participants will be informed on the signs and symptoms of potential liver injury such as abdominal pain, nausea, vomiting, loss of appetite, dark yellow urine, yellow eyes, or skin, or persistent fatigue, and report such symptoms immediately to the study center, even after the study has been concluded. The monitoring/discontinuation criteria outlined in the following sections should be used for participant monitoring.

7.1.1.1. Increased monitoring:

Increased safety monitoring is required under the circumstances listed below. The baseline defined below is described in Section 8.3.4.1.

- Participants with normal baseline liver indices who develop elevations of any of the following:

  - ALT ≥3x ULN
  - AST ≥3x ULN
  - Total bilirubin ≥2x ULN
  - ALP ≥2x ULN and GGT ≥2x ULN

- Participants with abnormal baseline liver indices who develop elevations of any of the following:

  - ALT ≥2x baseline
  - AST ≥2x baseline
  - Total bilirubin ≥1.5x baseline
  - ALP ≥2x baseline and GGT ≥2x baseline

In the event of abnormal laboratory parameters as described above, repeat testing should be performed within 48-72 hours. If there are persistent elevations upon repeat testing of any of the criteria defined above, then close observation (see Section 7.1.1.3), and study intervention discontinuation should be considered (see Section 7.1.1.2).

7.1.1.2. Stopping criteria

Study intervention will be stopped (permanently or temporarily) for a participant if any of the following stopping criteria are met:

- AST ≥8x ULN
- ALT ≥8x ULN
- ALT ≥3x baseline and ≥5x ULN
- AST ≥3x baseline and ≥5x ULN
- *ALT≥3x ULN and INR > 1.5 and the participant is not receiving anticoagulants (if normal at baseline)*
- *AST ≥3x ULN and INR > 1.5 and the participant is not receiving anticoagulants (if normal at baseline)*
- *ALT≥2x BL and INR > 1.5 and the participant is not receiving anticoagulants (if abnormal at baseline)*
- *AST ≥2x BL and INR > 1.5 and the participant is not receiving anticoagulants (if abnormal at baseline)*
- Total bilirubin ≥2x baseline and ≥1.5x ULN
- Total bilirubin ≥3x ULN
- ALP ≥2x ULN and GGT ≥2x ULN (if normal at baseline) or ALP ≥2x baseline and GGT ≥2x baseline (if abnormal at baseline) AND either: total bilirubin ≥2x baseline and ≥2x ULN, or direct bilirubin ≥2x baseline and ≥2x ULN, or new or worsening of liver-related symptoms*.

- If there are liver chemistry elevations which, in the opinion of the investigator, are not attributable to the participant's underlying PBC, or if there is worsening liver chemistry associated with appearance of new liver-related symptoms.

*Liver-related symptoms, which may typically be associated with drug-induced liver injury, include fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, worsening pruritus and/or eosinophilia [>5%].

When liver stopping criteria are met, the study intervention should be immediately discontinued. Additional procedures and safety follow up will be required (see Section 10.6, Appendix 6) and close observation should be implemented (see Section 7.1.1.3).

The GSK Medical Monitor must be notified within 24 hours of learning of the abnormality to confirm the participant's study intervention cessation and follow-up.

Upon completion of the liver safety follow-up, restart of study intervention (where there is a clear underlying non-Drug Induced Liver Injury [DILI] cause for the event) may be considered as outlined in Section 7.1.9.1.

In all instances where study intervention is stopped due to meeting protocol-specified liver stopping criteria or investigator concern about possible deterioration in liver function, a formal adjudication of causality will be requested from the Hepatotoxicity Safety Panel. Details of this panel and the process of review will be provided in a separate charter.

7.1.1.3. Close Observation

If elevations persist upon repeat testing for participants who meet monitoring criteria or any participants who meet stopping criteria, the investigator should consult the medical monitor and the following ongoing monitoring should be performed:

- Liver function tests (including AST, ALT, ALP, and direct bilirubin) should be taken two to three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study intervention has been discontinued and the subject is asymptomatic.
- Obtaining additional tests to evaluate liver function, including international normalized ratio (INR) as appropriate.
- Obtain a more detailed history of symptoms and prior or concurrent diseases.
- Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; Non-alcoholic Steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtain a history of exposure to environmental chemical agents.

7.1.2. Hepatic Encephalopathy

Study intervention should be discontinued if the participant develops new clinically overt hepatic encephalopathy as per investigator clinical assessment against the published Westhaven 1-4 criteria [Vilstrup, 2014]. Under these circumstances, the liver event form should be completed in the eCRF, and the participant should be assessed for potential precipitants of encephalopathy.

Study intervention can only be considered for restart following discussion with the Medical Monitor if an alternative (non-liver-related) cause of cognitive dysfunction is diagnosed and the episode is fully resolved and, in the investigator's opinion unlikely to recur.

7.1.3. Diarrhea Management Criteria and Stopping Criteria

Diarrhea is an anticipated pharmacologic effect of linerixibat due to the increase in bile acid concentration in the colon and may be clinically similar to bile acid diarrhea. The most common clinical characteristics of bile acid diarrhea are loose (rarely watery) stools, stools without blood, and stools that are associated with urgency.

Participants will be informed about diarrhea and will be instructed to contact the investigator if, at any time during the study, they are experiencing diarrhea that impacts their daily activities. In this study, the Common Terminology Criteria for Adverse Events (CTCAE), currently in version 5, will be used to quantitate the severity of diarrhea as well as the standard AE intensity grading defined in Section 10.3.4. This standard tool was initially developed by the National Cancer Institute.

When study participants are experiencing diarrhea that is impacting their daily activities, investigators should instruct participants to use anti-diarrheal (loperamide or suitable local alternative as agreed by the Medical Monitor) for treatment (Details to be provided separately). Management of diarrhea with loperamide (or suitable local alternative as agreed by the Medical Monitor) following inhibition of IBAT has been previously described in the literature [Key, 2020] which supports its use in this study.

7.1.3.1. Determination of diarrhea severity

Diarrhea severity is determined in the context of normal stool frequency. At baseline, participants will be asked to describe their normal daily stool count and if they are currently experiencing diarrhea that is impacting their daily activities. This baseline stool frequency will be recorded for reference and calculation of diarrhea severity if needed and as described in the SRM.

Participants should be asked about their experience with diarrhea at each visit as part of ongoing AE/SAE review. Diarrhea will be considered an AE of special interest (AESI) and will be recorded on a specific AESI eCRF page. AESIs are described in Section 8.4.7.

Diarrhea severity will be assessed using the standard criteria in Section 10.3.4 and using CTCAE 5 criteria (as found in Table 2) in reference to their baseline stool frequency as

mentioned above. For Activities of Daily Living (ADL) please see Section 10.9, Appendix 9.

Table 2 CTCAE 5 Severity Scale for Diarrhea

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in frequency and/or loose or watery bowel movements.					

Diarrhea should be managed as detailed in Section 7.1.3.2 and further details will be provided in the SRM.

7.1.3.2. Stopping Criteria for Diarrhea (Grade 3 or 4)

The criteria for decisions to permanently or temporarily discontinue study are shown in Table 3, as determined by the CTCAE criteria mentioned in Section 7.1.3.1, Determination of diarrhea severity.

Table 3 Study Intervention Actions for Severe Diarrhea (CTCAE 5 criteria)

Study Intervention action	Symptom Severity
Temporary Discontinuation	Grade 3 diarrhea
Permanent Discontinuation	≥ Grade 4 diarrhea

Participants who have study intervention temporarily discontinued will be managed as clinically indicated until the participant returns to no more than Grade 2 diarrhea symptoms (i.e., ≤6 stools per day above baseline); at which time the study intervention may be restarted.

Study intervention may be permanently discontinued, at the investigator's discretion.

7.1.4. QTc Stopping Criteria

The same QT correction formula must be used for each individual participant to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.

- For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the same formula must continue to be used for that participant for all QTc data being collected for data analysis.

Safety ECGs and other non-protocol specified ECGs are an exception. The QTc should be based on a single QTc value of an ECG obtained over a brief (e.g., 5-10 minute) recording period. If an automated reading is not available, the ECG should be manually

over-read by the investigator or adequately trained physician. A participant who meets either of the criteria based on the single ECG reading will be withdrawn from study intervention:

- QTc ≥530 msec **AND/OR** increase from baseline of QTc >60 msec

7.1.5. Renal Stopping Criteria

A participant's study intervention will be discontinued if the confirmed eGFR is <30 mL/min/1.73m^2 based on the CKD-EPI equation at any time during the study.

The investigator should consult with designated sponsor personnel regarding the potential for restarting study intervention. If medical input is required, the Medical Monitor will be consulted for guidance.

7.1.6. Diagnosis of Colon Cancer

Participants who are diagnosed with colon cancer at any point in the study will be permanently discontinued from study intervention.

7.1.7. Pregnancy

Female participants who become pregnant during the study should discontinue study intervention immediately.

7.1.8. Temporary Discontinuation due to AEs

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention (see Section 10.3, Appendix 3).

The investigator will make an assessment of intensity for each AE reported during the study as described in Section 10.3, Appendix 3.

For diarrhea AEs only, an assessment should also be made using the CTCAE v5 criteria as described in Section 7.1.3.1.

In cases where participants discontinue study intervention due to an AE, the investigator should consult with the Medical Monitor to determine the appropriate evaluation and guidance on whether study intervention may be re-started.

7.1.9. Restart of Study Intervention

7.1.9.1. Study Intervention Restart after Meeting Liver Stopping Criteria

Restart refers to resuming study intervention following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, restart is

not permitted following liver stopping event when the underlying cause was alcohol-related hepatitis.

Approval by GSK for participants to restart study intervention may be considered where:

- Investigator requests consideration for study intervention restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5x baseline and ALT <3x ULN).
- Possible study intervention-induced liver injury has been excluded by the principal investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia).
- There is no evidence of alcohol-related hepatitis.
- IRB/IEC approval of study intervention restart must be obtained, as required.
- The participant is informed of any associated risks of restart and a separate ICF for study intervention restart is signed by the participant

- **If restart of study intervention is approved by GSK in writing:**

- The participant must be provided with a clear description of the possible benefits and risks of study intervention administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the study intervention restart. Documentation of informed consent must be recorded in the study file.
- Study intervention must be administered at the dose specified by GSK.
- Participants approved by GSK for restart of study intervention must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If participant meets protocol-defined liver chemistry stopping criteria after study intervention restart, study intervention should be permanently discontinued.
- GSK Medical Monitor, and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be informed of the participant's outcome following study intervention restart.
- GSK must be notified of any adverse events.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request for any reason (or without providing any reason).
- A participant may be discontinued/withdrawn at any time at the discretion of the investigator for the occurrence of any condition that, in the opinion of the Investigator, significantly jeopardizes the wellbeing and safety of the participant (including serious or intolerable AE that prevents the participant from continuing

with study participant). Discontinuation/withdrawal may also occur at the discretion of the investigator for any behavioral or compliance reasons. It is expected that these situations will be uncommon.

- At the time of discontinuation from the study, if possible, an early termination visit should be conducted as soon as possible, as shown in the SoA (Section 1.3). 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.
- All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analysis. 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 may be withdrawn from study intervention but encouraged to continue participation in the study (including collection of PRO/eDiary data) as described in Section 7.1.

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 timings are summarized in the SoA (see Section 1.3).
- Protocol waivers or exemptions are not allowed
- Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (at the discretion of the investigator). The site may work with GSK to use a centrally appointed home nursing vendor for conduct of study assessments. Please refer to Section 10.8 for further details on home healthcare availability.
- 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 (Section 1.3), 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.
- Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel.
- 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.

8.1. Administrative Procedures

8.1.1. Collection of demographic data

Demographic data such as year of birth, sex, race, and ethnicity will be recorded in the participant's eCRF.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.2. Efficacy Assessments

An eDiary will be used to electronically collect a number of PROs as described in this section. All participants will receive sufficient training on PRO completion using electronic devices.

The SoA (Section 1.3) defines the timepoints and visits at which PROs are to be collected.

8.2.1. Patient Reported Outcomes (PROs)

8.2.1.1. Symptom Questionnaire/eDiary

A symptom questionnaire will be used to measure impact of linerixibat on itch, sleep, and fatigue as described below. In addition, the eDiary will prompt participants to record whether they are taking the study treatment, and details of any missed doses.

Itch Numerical Rating Scale (NRS)

Itch will be assessed throughout this study using an NRS scale. At the screening visit (Visit 1) itch severity will be assessed retrospectively based on participant recall. The participant will be asked to rate their overall itch severity in the 2 months preceding screening to establish whether their baseline itch is severe enough prior to entering the screening period.

Following the Screening Visit (Visit 1), participants will enter the Screening period and begin completing the eDiary to establish their baseline itch for eligibility purposes. The eDiary is to be completed twice each day; once in the morning and once in the evening. Participants will score the severity of their itching using the same scale described above. The NRS recorded in the morning will characterize the worst itch experienced during the night-time, whilst the NRS recorded in the evening will characterize the worst itch experienced during the day-time hours.

During the screening period, participants must complete at least 40 of the 56 itch entries, with an entry on at least 4 days in each week, in the 28 days immediately preceding the Randomization visit on Day 1. For the 28 days prior to Randomization, the Monthly Itch Score must be ≥4 (i.e., at least 1 of the 4 Weekly Itch Scores must be ≥4), and no Weekly Itch Score can be <3 for any other week. Please see exclusion criteria in Section 5.2.

After randomization, participants will continue to complete the symptom questionnaire in the eDiary throughout the study and will be completed twice each day; once in the morning and once in the evening approximately at the time of study intervention dosing.

Sleep Interference and Fatigue NRS

Participants will be asked to score the severity of how itch interfered with their sleep using an NRS from 0 to 10 where 0 represents no sleep interference and 10 is complete sleep interference according to the SoA (Section 1.3). The sleep NRS is recorded once daily in the morning.

Participants will also be asked to score their fatigue using an NRS from 0 to 10 where 0 represents no fatigue and 10 represents the worst possible fatigue. The fatigue NRS is recorded once daily in the evening.

8.2.1.2. PBC-40 Health Related Quality of Life Scale

The PBC-40 is a patient-derived, disease specific health-related quality of life measure with data to support its validity in PBC [Jacoby, 2005]. The PBC-40 assesses a variety of symptoms including itch, fatigue, memory and concentration and impact on social life and daily living. The PBC-40 was developed and validated with a 4 week recall period, which was modified to a recall period of "the past 7 days" to ensure more accurate recall of the impacts associated with PBC pruritus in the GLIMMER study. The revised recall period version has undergone cognitive interviewing and has been validated in a blinded interim analysis of GLIMMER and an external validation study (data on file). This revised PBC-40 will be used in this study at the timepoints specified in the SoA (Section 1.3).

8.2.1.3. Gastrointestinal Symptom Rating Scale (GSRS)

The GSRS is a validated scale that will be assessed for all participants at the timepoints indicated in the SoA (see Section 1.3). The GSRS assesses 15 items combined in to five symptom clusters, representing reflux, abdominal pain, indigestion, diarrhea, and constipation and will assess gastrointestinal symptoms experienced by participants over the preceding 5 to 7 days [Svedlund, 1988].

8.2.1.4. Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS) is a self-administered questionnaire that assesses daytime sleepiness. The ESS is comprised of 8 questions with respondents rating on a 4-point scale (0-3) their usual chances of having dozed off or fallen asleep while engaged in eight different activities that differ widely in their somnificity. The total ESS score (the sum of 8 item-scores, range 0-24) gives an estimate of a more general characteristic, the person's average sleep propensity (ASP), across a wide range of activities in their daily lives [Johns, 2002]. The higher the ESS score, the higher that person's ASP in daily life, or their 'daytime sleepiness'. These ESS item-scores provide estimates of eight different situational sleep propensities (SSP) for that person [Johns, 1994; Johns, 2010].

General cut-points for sleepiness severity are: 0-5 Lower Normal Daytime Sleepiness; 6-10 Higher Normal Daytime Sleepiness; 11-12 Mild Excessive Daytime Sleepiness; 13-15 Moderate Excessive Daytime Sleepiness; 16-24 Severe Excessive Daytime Sleepiness.

The ESS will be administered at the timepoints specified in the SoA (Section 1.3).

8.2.1.5. Beck Depression Inventory (BDI-II)

The Beck Depression Inventory (BDI-II) is a 21-item questionnaire used to assess the intensity of depression in clinical and normal patients. The questionnaire will be administered at the timepoints specified in the SoA (Section 1.3).

8.2.1.6. Patient's Global Impression of Severity (PGI-S)

This questionnaire will be used to understand how participant's itch score over the past week using the 0-10 NRS relates to overall participant-reported itch severity. The primary role of the PGI-S is as an anchor for the psychometric analysis of the Itch NRS. The PGI-S uses a 5-level response scale and will be collected at the timepoints specified in the SoA (Section 1.3).

8.2.1.7. Patient's Global Impression of Change (PGI-C)

This questionnaire will be used to understand how the participant's daily itch score using the 0-10 NRS relates to overall participant-reported change in itch severity. The primary role of the PGI-S is as an anchor for the psychometric analysis of the Itch NRS. The PGI-C comprises a 7-level response scale to evaluate the participant's assessment of change since baseline and a dichotomous (Yes/No) question on whether the change is considered meaningful by the participant. The PGI-C will be collected at the timepoints specified in the SoA (Section 1.3).

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- In cases where visits may be performed at locations other than a trial site, such as by a home healthcare provider, physical exams may be performed as symptom directed exams or by other means as agreed with the investigator. Please refer to Section 10.8 for home healthcare activities.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

- Temperature, pulse rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with 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).

- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded.

8.3.3. Electrocardiograms (ECGs)

- Single 12-lead ECGs 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. Refer to Section 7.1.4 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- ECGs will be reviewed locally by the investigator or an adequately trained physician.

8.3.4. Clinical Safety Laboratory Assessments

- Clinical Safety Laboratory Assessments are performed at the relevant laboratories provided in the List of Clinical Laboratories.
- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- 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 clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual/Study Reference Manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests 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), then the results must be recorded.
- All available liver function tests (including liver enzymes, ALP, GGT, INR, total and direct bilirubin, CPK, LDH, and albumin) done by local laboratories must be recorded in the eCRF.
- All local laboratory results for Liver Event/other safety follow-up must be recorded in the eCRF.

8.3.4.1. Baseline Liver Biochemistry/Variance During Screening

Given that participants may have abnormal screening values for liver biochemistry, baseline serum AST, ALT, ALP, and total bilirubin (TB) values will be established using an average of two sets of laboratory values obtained at least 4 weeks apart. If both values (Sample 1 and Sample 2) are within normal range, no further assessment is required.

Variance will be calculated as the absolute value of [(Sample 1- Sample 2)/average of Sample 1 and Sample 2) x100].

In order to ensure stability of liver disease and for participant safety, if any of the four liver parameters is above ULN in either Sample 1 or Sample 2, the variance between the two samples for the abnormal parameter(s) should be ≤ 40%. Should the variance between the two samples be > 40%, a third measure (Sample 3) may be obtained prior to the randomization visit. These participants would be eligible for enrollment provided the variance between Samples 1 and 3 for the parameter(s) is ≤ 40%. The baseline value will, therefore, be established using the average of Samples 1 and 2 or in the event that a third measure was obtained, the average of Samples 1 and 3.

8.3.4.2. Fecal Occult Blood Test (FOBT)

FOBT will be obtained at the timepoints outlined in Section 1.3 (SoA) in line with risk monitoring as described in Section 2.3.1.

Participants with a positive FOBT should be referred to their healthcare provider for follow up according to local standard of care.

8.3.5. Pregnancy Testing

- Refer to Section 5.1, Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) will be conducted at all on-treatment visits for women of child bearing potential during study intervention period.
- Pregnancy testing (urine or serum as required by local regulations) will be conducted for women of child bearing potential at the end of relevant systemic exposure.
- 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 participation in the study.

8.3.6. Study Safety Monitoring

- Participant safety will be continuously monitored by the GSK Medical Monitor, and the designated Safety Lead (or delegate) throughout the study. Pertinent findings and conclusions are shared with the product's Safety Review Team (SRT) for review of the overall benefit risk profile of the product.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of AEs or SAEs can be found in Section 10.3.

All events meeting permanent stopping criteria described in Section 7.1 except for pregnancy will be recorded as a (S)AE.

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, are considered related to the study intervention or the study, that caused the participant to discontinue the study intervention (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

- All SAEs will be collected from the signing of the ICF until the last scheduled visit, follow-up phone call (if performed), or completion of any required follow-up in the study (if applicable), whichever is later, at the time points specified in the SoA (Section 1.3).
- All AEs will be collected from the start of intervention until the last scheduled visit, the follow-up phone call (if performed), or completion of any required follow-up in the study (if applicable), whichever is later, at the time points specified in the SoA (Section 1.3).
- If a participant is found to have met increased monitoring or stopping criteria at Week 32 requiring additional follow-up after being enrolled in the follow-on study 212358 (LLSAT), AEs and SAEs that occur after the Week 32 Visit will be recorded as follows:
    - AEs and SAEs considered by investigator to be part of the safety event requiring additional follow-up in GLISTEN: Record in GLISTEN eCRF.
    - AEs and SAEs that are considered by investigator NOT to be part of the safety event requiring additional follow-up in GLISTEN: Record in LLSAT eCRF.
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions not as AEs.
- 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 information on 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, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

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.

8.4.3. 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, and non-serious AEs of special interest (as defined in Section 10.3, Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting), 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, Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an 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, IRB/IECs, and investigators.
- An investigator who receives an investigator safety report describing an 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.
- 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.

8.4.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the final follow up visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant's pregnancy. 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.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.5. 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 intervention immediately but will be encouraged to continue to attend study visits and undergo assessments.

8.4.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.4.7. Adverse Events of Special Interest

Adverse events of special interest for this study include:

- Diarrhea reported as an AE
- Elevated ALT reported as a Liver Event

AESIs will be recorded on separate AESI forms within the eCRF in addition to the AE/SAE eCRFs.

8.4.8. Participation Card

The investigator (or designee) must provide the participant with a “participant card” containing information about the clinical study. The participant must be instructed to

always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/ caregiver/ family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back up.

8.5. Pharmacokinetics

Whole blood samples will be collected for measurement of plasma concentrations of linerixibat as specified in the SoA (Section 1.3).

- 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. In addition, PK sample collection and/or analysis may be terminated when sufficient data has been collected, and any remaining samples may be discarded if not required.
- Dosing instructions for visits at which PK assessments are drawn will be specified in the SRM.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples collected for analyses of linerixibat plasma concentration 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 plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.
- Intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6. Genetics

A blood and/or saliva sample for deoxyribonucleic acid (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 and/or saliva 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 Section 10.5 for information regarding genetic research. Details on processes for collection and shipment of these samples will be found in a separate laboratory manual.

8.7. Biomarkers

Blood samples will be collected to measure the levels exploratory biomarkers, including markers of bile acid synthesis and re-uptake (total serum bile acids, autotaxin, serum C4 and FGF-19). Biomarker sample collection and/or analysis may be terminated when sufficient data has been collected, and any remaining samples may be discarded if not required.

The levels of biomarkers in PBC subjects at baseline, the effect of linerixibat treatment on biomarker levels and impact of background therapies (e.g. bile acid binding resins) will be assessed. Samples will be collected according to the schedule described in the SoA (see Section 1.3) and as detailed in the laboratory manual provided separately to sites.

GSK may store samples for up to 15 years after the end of the study to achieve study objectives (please see China specific requirements in Section 10.7.1). Additionally, with participants consent, samples may be used for further research by GSK or others such as universities or other companies to contribute to the understanding of PBC, cholestatic pruritus, other diseases or the development of related or new treatments or research methods. Further research will only be conducted in countries where permitted by local regulation and guidelines.

8.7.1. Biomarkers of Disease Progression

Disease progression can occur even when patients are receiving adequate treatment (e.g., UCDA), with a risk of liver-related complications. In GLIMMER, results demonstrated that linerixibat does not result in an increase in plasma ALP confirming the lack of detrimental impact on PBC itself or clinically relevant interaction between linerixibat and UDCA (for more details see IB, Section 5.2.2).

However, in order to continue to assess the hallmarks of PBC progression over a longer period, serum surrogate markers of liver fibrosis and liver function, ELF, and transient elastography (TE) utilizing Fibroscan will be obtained at timepoints outlined in Section 1.3. In addition, investigators are advised to implement hepatocellular carcinoma screening for patients with cirrhosis according to standard of care and country guidelines and/or local practices. Any liver biopsies that may be performed during the course of the study will be collected in the eCRF pages.

8.7.1.1. Enhanced Liver Fibrosis Test (ELF)

Blood samples for the ELF should be obtained at timepoints outlined in Section 1.3 (SoA). These samples may not be collected from participants in China due to operational or logistical difficulties.

8.7.1.2. Fibroscan

Transient Elastography (TE) using Fibroscan should be performed at timepoints outlined in Section 1.3 (SoA). This is applicable only for sites that where Fibroscan is available and is performed regularly.

9. STATISTICAL CONSIDERATIONS

Unless otherwise specified, all objectives/endpoints/hypotheses compare treatment with oral linerixibat with background itch therapy, if applicable, against placebo with background itch therapy, if applicable. Hereafter this comparison will be referred to as "linerixibat vs placebo".

9.1. Statistical Hypotheses

9.1.1. Primary endpoint

The primary objective is to investigate the superiority of 24 weeks of treatment with oral linerixibat compared with placebo on itch in PBC patients with cholestatic pruritus. The primary endpoint is Change from Baseline in Monthly Itch Scores over 24 weeks using a 0-10 numerical rating scale (NRS). The primary estimand is the difference in means between linerixibat and placebo in the change from baseline in itch score over 24 weeks in PBC patients with cholestatic pruritus. For details of intercurrent events, see Section 9.4. The primary analysis will be a mixed model approach based on Monthly Itch score over 24 weeks (Weeks 4, 8, 12, 16, 20, and 24). The primary hypothesis is that linerixibat reduces itch score over 24 weeks compared to placebo. A negative change from baseline (or reduction) represents an improvement in itch.

The null hypothesis (H_0) assumes that there is no difference in the reduction of itch score over 24 weeks between linerixibat and placebo groups. The alternate hypothesis (H1) assumes that there is difference in the reduction of itch score over 24 weeks between linerixibat and placebo groups.

The overall significance level for the primary endpoint analysis is set at the two-sided 0.05 level.

9.1.2. Secondary endpoints

Formal multiplicity-controlled testing will be conducted for the key secondary endpoints of change from baseline in Weekly Itch Score (WIS) at Week 2, change from baseline in Monthly Sleep Score over 24 weeks, as well as responder endpoint defined as achieving ≥2, ≥3, and ≥4-point reduction from Baseline in the Monthly Itch Score at Week 24. Additional testing not multiplicity controlled will be conducted for other secondary endpoints including change from baseline in PBC-40 domain score at Week 24, change from baseline in PGI-S over 24 weeks, PGI-C over 24 weeks, change from baseline in ALP at Week 24, and Change from baseline in bilirubin at Week 24.

A step-down/hierarchical approach will be used to test the following key secondary endpoints if statistical significance is achieved for the primary endpoint:

- Change from Baseline in WIS at Week 2
- Change from Baseline in Monthly Sleep Score over 24 weeks
- Responders defined as achieving a ≥2-point reduction from Baseline in the Monthly Itch score at Week 24.

- Responders defined as achieving a ≥3 -point reduction from Baseline in the Monthly Itch score at Week 24.
- Responders defined as achieving a ≥4 -point reduction from Baseline in the Monthly Itch score at Week 24.

These tests will be conducted sequentially at a 5% two-sided significance level. Other secondary endpoints will also be tested but outside this formal hierarchy.

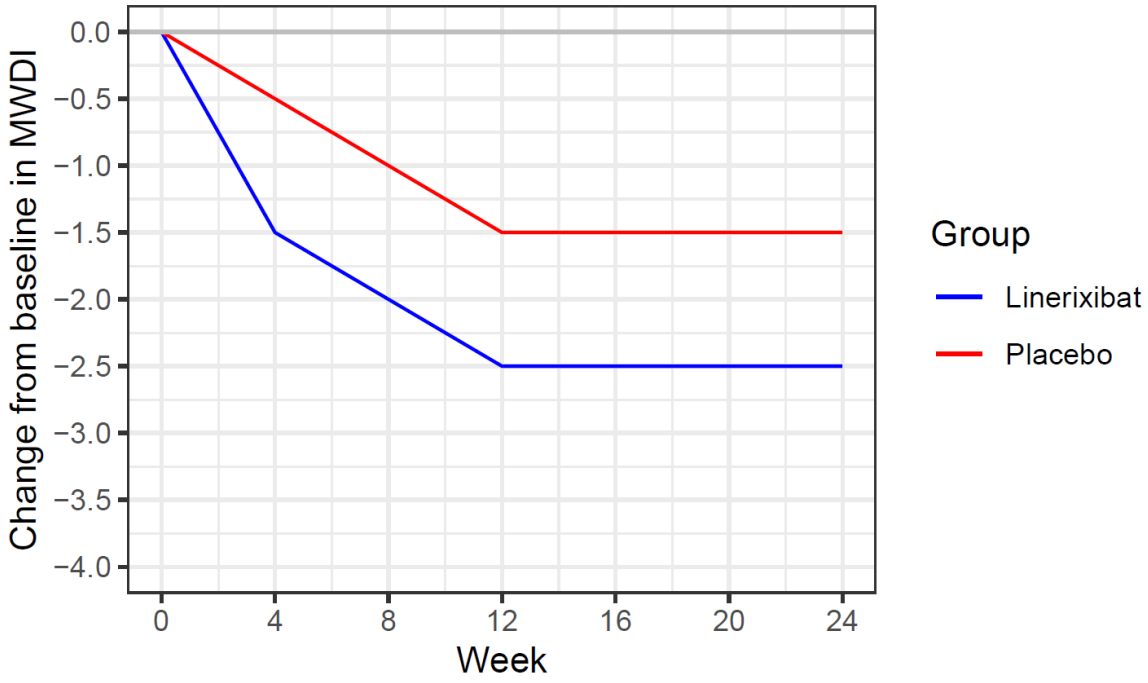
9.2. Sample Size Determination

Approximately 230 participants (115 per group) who pass the screening eligibility criteria will be randomized in a 1:1 ratio to linerixibat or placebo groups. The sample size of 230 was obtained and evaluated assuming that 10% of participants discontinue from the study at random and the data from the discontinuation week through week 24 are missing. This sample size allows approximately 90% power for a two-sided test with an alpha level of 0.05 when the expected overall difference in change from baseline in Monthly Score across 24 weeks is ~-0.9 (based on BAT117213 and GLIMMER data) between the linerixibat and placebo groups (assuming a between subject standard deviation [SD] of 2.07 for both groups based on GLIMMER data).

9.2.1. Sample size assumptions

Change from baseline in the WIS was simulated for each week from week 1 to week 24 after randomization. It was assumed that the mean change from baseline in the WIS of placebo group reaches its plateaued effect size of -1.5 by week 12 in a linear relationship against treatment week. It was also assumed that delta between linerixibat and placebo reaches plateau of -1 by week 4 in a linear relationship against treatment week, and the mean change from baseline in the WIS of linerixibat group is the sum of placebo and delta as shown in Figure 3.

Figure 3 Expected Change from Baseline in MWDI*



* MWDI now referred to as the Weekly Itch Score (WIS).

The expected weekly means are listed in Table 4 below.

Table 4 Expected Change from Baseline in Weekly Itch Score (WIS)

Group	N	Expected Change from Baseline in WIS by Week (week 1 – week 11)	Expected Change from Baseline WIS (Week 12 - 24)	Dropout Rate
Placebo	115	{-0.125, -0.250, -0.375, -0.500, -0.625, -0.750, -0.875, -1.000, -1.125, -1.250, -1.375}	-1.5	10%
Linerixibat	115	{-0.375, -0.750, -1.125, -1.500, -1.625, -1.750, -1.875, -2.000, -2.125, -2.250, -2.375}	-2.5	10%

For each iteration of simulation, change from baseline data for each week was generated for 115 subjects per group using a truncated multivariate normal distribution within the interval of [-10, 10] with the mean vectors presented above. The variance covariance matrix was assumed to have a compound symmetry (CS) structure with standard deviation of 2.25 and correlation of 0.85 which corresponds to a between subjects SD of ~2.07 and a within subject SD of ~0.87, based on the GLIMMER data.

The rates of study withdrawal that resulted in missing values from withdrawals for placebo group and linerixibat 40 mg BID group after randomization were 1/36 and 1/23,

respectively, in the GLIMMER study. Therefore, it was expected to have ~10% study withdrawal rate for each arm and the study withdrawal can occur at any week after randomization. Missing data was assumed to be missing at random in the simulation.

Simulations were based on planned visits at week 4, 8, 12, 16, 20, and 24. For visit on week 4, the worst change from baseline in WIS from week 1 to 4 was reported as the change from baseline in Monthly Itch Score. Similarly, the change from baseline in Monthly Itch Scores were obtained for other visits. Mixed model repeated measure analysis was then applied to change from baseline in Monthly Itch Scores and the model included treatment, visit, and treatment by visit interaction as fixed effect. The comparison of active and placebo arms was based on the simple average of LS means of all visits, i.e., the main effect of treatment averaged across the 6 visits with equal weight at each visit.

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Screening	All participants who sign the ICF
Enrolled	All participants who sign the ICF and pass screening (meet the eligibility criteria)
ITT Population	This population will comprise all randomized participants. Participants in the ITT Population will be classified according to the treatment as randomized.
Non-bile acid binding resin ITT (Intent to Treat) Population	The Non-bile acid binding resin ITT Population is a subset of the ITT population who are not receiving concomitant bile acid binding resin therapy at randomization (e.g., cholestyramine).
Safety	All randomized participants who take at least 1 dose of study intervention. Participants will be analyzed according to the treatment they actually received.

9.4. Statistical Analyses

The primary statistical analysis to assess the primary, secondary, and safety objectives will be performed when all randomized participants have completed the Part A intervention period (up to Week 24/Visit 9). In addition, available data for exploratory endpoints in Part A and Part B will be analyzed as part of this primary statistical analysis. By the time the last participant completes the Part A intervention period, it is anticipated that the majority of participants will have also completed the Part B intervention period (Week 24 through Week 32). Therefore, all available Part B data will also be assessed and reported as part of the primary statistical analysis.

A final analysis will then be performed when all participants have completed the Part B intervention period, and the follow-up period, if applicable. This analysis will include complete Part B data and the full data for exploratory endpoints in Part A for which full datasets were not available at the time of the primary analysis.

The statistical analysis plan will be finalized prior to database lock (DBL) 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.

9.4.1. General Considerations

The study will test at a 5% two-sided significance level the null hypotheses listed previously in Section 9.5.

9.4.2. Primary and Secondary Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	The primary objective is to evaluate the treatment effect of linerixibat compared to placebo on itch over 24 weeks. The primary hypothesis is that linerixibat reduces itch score over 24 weeks compared to placebo. A negative change (or reduction) from baseline in monthly itch score averaged over 24 weeks represents an improvement in itch. The Monthly Itch Score, based on a 0-10 NRS, will be determined from the worst weekly average available for the month. A week will have a Weekly Itch Score if at least 4 days in the week have a score. Otherwise, the Weekly Itch Score for the week will be missing. If one or more weekly scores is missing, then the worst of the non-missing weekly scores is selected as the worst for that month. If no week scores are available for a month, the Month Itch Score will be missing. The following intercurrent events have been considered for the evaluation of the primary endpoint of Monthly Itch Score: o Permanent treatment discontinuation, disruptions in treatment, treatment delays unrelated to the COVID-19 pandemic, addressed with treatment policy strategy o Permanent treatment discontinuation, disruptions in treatment, treatment delays related to the COVID-19 pandemic, addressed with hypothetical strategy o Change in background itch therapy or use of rescue medication, addressed with treatment policy strategy The summary measure will be mean difference between treatment groups. The primary analysis will be a mixed model for repeated measures (MMRM) of

Endpoint	Statistical Analysis Methods
	change from baseline in Monthly Itch score over the 24-week treatment period. The model will include main effects for treatment, visit (Weeks 4, 8, 12, 16, 20, and 24), concomitant use of itch medications at baseline, and baseline itch severity as continuous as well as treatment by visit interaction and baseline by visit interaction. An unstructured covariance structure will be assumed; if this does not converge then CS will be used, followed by an autoregressive [AR] covariance structure if CS does not converge. The change from baseline over 24-week treatment period will use a treatment policy strategy for the intercurrent events unrelated to the COVID-19 pandemic, in which data following intercurrent events will be included as available and participants will be classified according to assigned treatment (regardless of treatment actually received) according to ITT principles. For intercurrent events related to the COVID-19 pandemic, hypothetical strategy will be used. The outcomes impacted by the COVID-19 related intercurrent events will be discarded, and the MMRM then fitted. This assumes that unobserved outcomes of subjects who withdrew from the study or who experienced a COVID-19 related intercurrent event are missing at random (MAR). Full details will be provided in the Statistics Analysis Plan. A sensitivity analysis will be conducted to evaluate the impact of the MAR assumption on the conclusions of the primary analysis if the primary endpoint is significant in favor of linerixibat. In this sensitivity analysis, a tipping point approach will be used. This is akin to progressive stress-testing to assess how severe departures from the MAR assumption must be in order to change the overall conclusion of the primary analysis. Missing data will first be imputed for all visits under the MAR assumption, and then a shift will be applied. This will be repeated until the result is no longer statistically significant. The plausibility of the set of assumptions required for conclusions to change provides context for the interpretation of the trial results. The tipping point analysis will be two-dimensional, which allows assumptions about the missing outcomes on the two arms to vary independently and includes scenarios where dropouts on linerixibat have worse outcomes than dropouts on

Endpoint	Statistical Analysis Methods
	placebo. Full details will be provided in the Statistics Analysis Plan. As a supplementary estimand for the primary objective, the hypothetical treatment effect of linerixibat will be compared to placebo in the absence of any intercurrent events. Hypothetical strategy will be applied to all the intercurrent events defined above, including treatment discontinuation, disruptions in treatment or treatment delays, changes in itch therapy or use of rescue medication. The outcomes impacted by the intercurrent events will be discarded, and the MMRM then fitted. This assumes that unobserved outcomes of subjects who withdrew from the study or who experienced an intercurrent event are MAR. The main analytical approach will also be repeated using the non-bile acid binding resin ITT population. Any participant taking bile acid binding resin as the background itch therapy at baseline will be excluded from the non-bile acid binding resin ITT population and any data from these excluded participants will not contribute to the analysis.
Secondary	<u>Change from baseline in Weekly Itch Score at Week 2</u> The change from baseline WIS at Week 2 will be evaluated. Similar to the primary estimand framework, treatment policy strategy will be used for the intercurrent events unrelated to the COVID-19 pandemic, whereas hypothetical strategy will be used for the intercurrent events related to the COVID-19 pandemic. Change from baseline WIS at Week 1 and 2 will be analyzed by a MMRM model including baseline itch severity as a continuous covariate, treatment, week (Weeks 1 and 2), concomitant use of itch medications at baseline, treatment by week interactions, and baseline by week interaction as fixed effects. The comparison at Week 2 will be estimated from the MMRM model. • <u>Change from Baseline in Monthly Sleep score over 24 weeks:</u> Change from baseline in Monthly Sleep score over 24 weeks will be evaluated.

Endpoint	Statistical Analysis Methods
	Similarly, treatment policy strategy will be used for the intercurrent events unrelated to the COVID-19 pandemic, whereas hypothetical strategy will be used for the intercurrent events related to the COVID-19 pandemic. Change from baseline of Monthly Sleep score averaged over 24 weeks will be analyzed using a repeated measure mixed model including baseline Monthly Sleep score as covariate, treatment, visit, concomitant use of itch medications at baseline, treatment by visit interaction, and baseline by visit interaction as fixed effects. <u>Responder defined as achieving a ≥2-point reduction from baseline in the Monthly Itch score at Week 24;</u> <u>Responder defined as achieving a ≥3-point reduction from baseline in the Monthly Itch score at Week 24;</u> <u>Responder defined as achieving a ≥4-point reduction from baseline in the Monthly Itch score at Week 24:</u> The proportion of participants who are responders at Week 24 will be evaluated. Similarly, treatment policy strategy will be used for the intercurrent events unrelated to the COVID-19 pandemic, whereas hypothetical strategy will be used for the intercurrent events related to the COVID-19 pandemic. Data impacted by a COVID-19 related intercurrent event will be discarded and multiple imputation will be applied to impute itch data using available data for all subjects. The imputed data will then be used to derive the responder endpoint. The summary measure will be the difference in responder rates between linerixibat and placebo groups, analyzed using a stratified analysis with Cochran-Mantel-Haenszel (CMH) weights, adjusting for baseline itch severity and concomitant use itch medications. • <u>Change from Baseline in PBC-40 domain scores at week 24:</u> Change from baseline in the domain scores of PBC-40 at week 24 will be evaluated. Similarly, treatment policy strategy will be used for the intercurrent events

Endpoint	Statistical Analysis Methods
	unrelated to the COVID-19 pandemic, whereas hypothetical strategy will be used for the intercurrent events related to the COVID-19 pandemic. Change from baseline in the domain scores of PBC-40 -over 24 weeks will be analyzed using a mixed model including baseline domain scores of PBC-40 as covariate, treatment, visit , concomitant use of itch medications at baseline, treatment by visit interaction, and baseline by visit interaction as fixed effects. The comparison at Week 24 will then be estimated from the MMRM model. <u>Change from baseline in PGI-S over 24 weeks</u> Change from baseline in PGI-S over 24 weeks will be evaluated. Similarly, treatment policy strategy will be used for the intercurrent events unrelated to the COVID-19 pandemic, whereas hypothetical strategy will be used for the intercurrent events related to the COVID-19 pandemic. Change from baseline in PGI-S averaged over week 24 will be analyzed using a mixed model including baseline PGI-S as covariate, treatment, visit, concomitant use of itch medications at baseline, treatment by visit interaction, and baseline by visit interaction as fixed effects. <u>PGI-C over 24 weeks</u> Change from baseline in PGI-C over 24 weeks will be evaluated. Similarly, treatment policy strategy will be used for the intercurrent events unrelated to the COVID-19 pandemic, whereas hypothetical strategy will be used for the intercurrent events related to the COVID-19 pandemic. Change from baseline in PGI-C averaged over week 24 will be analyzed using a mixed model including treatment, visit, concomitant use of itch medications at baseline, and treatment by visit interaction as fixed effects. <u>Change from baseline in ALP at Week 24</u> Change from baseline in ALP at Week 24 will be evaluated. Similarly, treatment policy strategy will be used for the intercurrent events unrelated to the COVID-19 pandemic, whereas hypothetical strategy will be used for the intercurrent events related to the COVID-19 pandemic. Change from baseline in ALP -

Endpoint	Statistical Analysis Methods
	over 24 weeks will be fitted by a mixed model including baseline ALP as covariate, treatment, visit, concomitant use of itch medications at baseline, treatment by visit interaction, and baseline by visit interaction as fixed effects. The comparison at Week 24 will be estimated from the MMRM model. <u>Change from baseline in bilirubin at Week 24</u> Change from baseline in bilirubin at Week 24 will be evaluated. Similarly, treatment policy strategy will be used for the intercurrent events unrelated to the COVID-19 pandemic, whereas hypothetical strategy will be used for the intercurrent events related to the COVID-19 pandemic. Change from baseline in bilirubin -over 24 weeks will be fitted by a mixed model including baseline bilirubin as covariate, treatment, visit, concomitant use of itch medications at baseline, treatment by visit interaction, and baseline by visit interaction as fixed effects. The comparison at Week 24 will be estimated from the MMRM model.

9.4.3. Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Safety	Overall safety evaluations will be descriptive using the Safety Population. Graphical and tabular displays will be presented to facilitate safety data review. AEs and SAEs will be summarized, sorted by system organ class and preferred term assigned by MedDRA, and presented as number and percent by treatment group. Additional summaries of AEs leading to discontinuation of study intervention and study intervention related AEs will also be generated. AESI including diarrhea and elevated ALT reported as a liver event will be presented separately. Change from baseline for laboratory values including liver chemistry panel and for ECG values will be summarized by visit and treatment group. In addition, the number and percentage of participants with values outside the potential clinical importance range will also be summarized.

Endpoint	Statistical Analysis Methods
	All vital sign data and change from baseline will be summarized by visit and treatment group. For systolic and diastolic blood pressure and heart rate, the number and percentage of participants with values of potential clinical importance will be summarized by treatment group. Criteria for potential clinical importance will be specified in the statistical analysis plan (SAP).

9.4.4. Exploratory Endpoint(s)

Details of analysis methods to be used for exploratory endpoints, including the endpoints for part B, are provided in the SAP.

9.4.5. Other Analyses

Blinded PRO data (Itch NRS, PGI-S, PGI-C) from the ITT population will be accessed during study conduct to establish a clinically meaningful within-patient change threshold or range of thresholds for the Itch NRS, specifically as it relates to change in scores at Week 24. Following FDA guidance [FDA, 2023], both distribution-based and anchor-based methods will be used for determining clinically meaningful within-patient change. An external vendor will be used to conduct these analyses, the details of which are provided separately.

9.5. Interim Analysis

The study has a planned futility analysis to be conducted after approximately 100 participants reach 24 weeks of treatment (or discontinued early). The analysis will be overseen by an IDMC with non-binding futility guidelines as documented in the IDMC Charter. The study may be terminated following this analysis if the probability of demonstrating clinical efficacy based on observed data is too low to support continuing or following the safety review if the overall risk-benefit is assessed to be unfavorable. In the event of the study being discontinued, GSK processes will be followed to ensure the best interests and the safety of the participants. The trial will not be stopped for early benefit at this point and no alpha-spend is incurred.

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, IB, and other relevant documents (e.g., advertisements, PRO) 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.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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), European Medical Device Regulation 2017/745 for clinical device research (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 and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations (CFR) 50, local regulations, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- 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
- Participants who are rescreened are required to sign a new ICF

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about linerixibat or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have linerixibat approved for medical use or approved for payment coverage.

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

In case of unexpected pregnancy, participant must be informed that Personal Information such as date of birth and sex of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4. Recruitment Strategy

A competitive recruitment strategy is utilized for this study. Prior to selecting a site for inclusion in the study, data may be gathered to understand the number of participants that might be enrolled from the current patient population and existing networks.

Supportive materials (if permitted locally and approved by the appropriate Ethics Committee or equivalent), such as leaflets and flyers may also be prepared and provided in digital format by recruitment third parties for use by investigator sites to provide information and awareness to participants and other healthcare providers/patient advocacy groups. These may be provided as paper printouts, which may be displayed in clinics or at patient events or provided to interested parties.

A digital GLISTEN website and pre-screener tool may be created in certain countries in accordance with local regulations to provide information and awareness on the trial in a digital format, as well as enable digital prescreening of participants and establish a connection with investigator sites for further screening activities as applicable. This will only be implemented where permitted locally and once all applicable Ethics Committee approvals are in place.

10.1.5. 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.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- 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.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

10.1.6. Committee Structure

10.1.6.1. Safety Review Team (SRT)

An SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

10.1.6.2. Independent Data Monitoring Committee

An IDMC will perform a futility analysis of efficacy at the planned interim analysis for the study and evaluate the safety of participants. Details of the structure and function of the IDMC, and analysis plan for IDMC reviews, are outlined in the IDMC Charter.

10.1.7. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- 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. GSK will also provide the investigator with the full summary of the study results including a summary of trial results understandable to laypersons.
- The investigators are encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this study 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 study participants are used to maximum effect in the creation of knowledge and understanding.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- 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.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or 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 physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided separately to investigators.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- 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 including definition of study critical data items and processes (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. Detailed information about study data collection and management process including systems used can be found in the Data Management Plan or equivalent.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- 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 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.

10.1.9. 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 reported on the CRF or entered 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 and its origin can be found in the Source Data Acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring 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.

10.1.10. Study and Site Start and Closure

First Act of Recruitment

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

The first participant's first visit (FSFV) will be the study start date.

Study/Site Termination

GSK or 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- Total number of participants included earlier than expected
- 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 subject and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication Policy

- The results of this study may be published in peer reviewed scientific literature and/or presented at scientific meetings.
- 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 multicenter 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 5 will be performed by the central laboratory unless medically necessary as judged by the Investigator in consultation with the GSK Medical Monitor or designee.

Local laboratory results are only required if the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time if possible.

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.

Investigators must document their review of each laboratory safety report.

Table 5 Protocol Required Safety Laboratory Tests

Laboratory Assessments	**Parameters**		
Hematology	Platelet Count Red Blood Cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin (MCH) %Reticulocytes	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Coagulation	Prothrombin Time (PT) / International Normalized Ration (INR)		
Clinical Chemistry[1]	Blood Urea Nitrogen (BUN) Bicarbonate Creatinine eGFR (CKD-EPI) Potassium Sodium Calcium Glucose (fasting)[2] Total Cholesterol (fasting) [2] Direct Low Density Lipoprotein (LDL) Cholesterol (fasting) [2] Direct High Density Lipoprotein (HDL) Cholesterol (fasting) [2] Triglycerides (Fasting) [2]	Alanine Aminotransferase (ALT) Aspartate Aminotransferase (AST) Alkaline phosphatase (ALP) Gamma Glutamyl Transferase Total and direct bilirubin Total Protein Albumin	
Other	Vitamins A, D, E and K Fecal Occult Blood Test (FOBT)		

Laboratory Assessments	**Parameters**
Biomarkers	Enhanced Liver Fibrosis (ELF)[3], Serum C4, FGF-19. Autotaxin, Total Serum Bile Acids
Pregnancy testing	• Highly sensitive urine (Serum if required locally) human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[5]
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)

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.
2. Laboratory samples should be taken fasted (water, study intervention and other medications are permitted) for all visits.
3. ELF may not be performed in China due to limitations in testing.
4. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.3. Appendix 3: AEs and SAEs: 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 Meeting 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 intervention- intervention 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. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT 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 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

An SAE is defined as any serious adverse event that, at any dose:
a. Results in death
b. 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (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.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

An SAE is defined as any serious adverse event that, at any dose:
• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)
g. Other situations: • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

10.3.4. 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.
- 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 required form.
- 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.

Diarrhea AEs will also be assessed based on the CTCAE criteria as defined in Section 7.1.3.1.

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.

Assessment of Causality

- 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 submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Follow-up of pregnancies

- Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the paper pregnancy follow-up report and the AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Follow-up of AE and SAE
• Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such. • Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in Section 8.4.5.

10.3.5. 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) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • 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 GSK Medical Monitor by telephone. • Contacts for SAE reporting can be found in the Study Reference Manual.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the case management group. • 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 data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the Study Reference Manual.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- 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-estrogen 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.
- Permanent sterilization methods (for the purpose of this study) include:
    - 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, gonadal dysgenesis), 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.

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.

10.4.2. Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS) [b]
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** *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- 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 • *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.*
• **Effective Methods[d] That Are Not Considered Highly Effective** *Failure rate of ≥ 1% per year when used consistently and correctly.*
Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
Male or female condom with or without spermicide[e]
Cervical cap, diaphragm, or sponge with spermicide

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

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.
d. Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.
e. Male condom and female condom should not be used together (due to risk of failure from friction).

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 and/or saliva sample will be collected for DNA analysis
- DNA samples will be used for research related to linerixibat or PBC, cholestatic pruritus and related diseases. They may also be used to develop tests/assays including diagnostic tests related to linerixibat, other IBAT inhibitors and PBC or cholestatic pruritus. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate)
- Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to linerixibat or study interventions of this class to understand the study disease or related conditions.
- The results of genetic analyses may be reported in the CSR 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 linerixibat or study interventions of this class or indication continues but no longer than the data retention period of the study or other period as per local requirements.

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

Procedures When Liver Stopping Criteria are Met

The procedures listed below are to be followed if a participant meets any of the liver chemistry stopping criteria defined in Section 7.1.1.

Immediately withdraw the participant from study intervention (see Section 7.1.1.2).

Make every reasonable attempt to have the participant return to the clinic within 24-72 hrs. for repeat liver chemistries and additional testing.

Notify the GSK Medical Monitor or designee within 24 hours of learning of the abnormality to confirm the participant's study intervention cessation and follow-up.

Complete the "Safety Follow-Up Procedures" listed below.

Complete the liver event eCRFs. If the event also meets the criteria of an SAE, the SAE data collection tool will be completed separately with the relevant details.

Upon completion of the liver safety follow-up, the participant should remain in the study, restart of study intervention (where there is a likely non-DILI cause for the event) might be considered upon discussion with medical monitor (see Section 7.1.9.1).

Monitor participants at least weekly until liver chemistries (ALT, AST, ALP, TB, PT/INR) resolve, stabilize or return to within baseline values and the subject is asymptomatic.

Additional Safety Follow-Up Procedures for participants who meet any of the liver stopping criteria:

Viral hepatitis serology including:

- Hepatitis A Immunoglobulin (IgM) antibody;
- Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
- Hepatitis C RNA;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Hepatitis E IgM antibody.

Blood sample for PK analysis, obtained within 12 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to blood sample draw on the eCRF. 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 included in the SRM.

Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

Serum and plasma samples for biomarkers of liver injury

Fractionate bilirubin, if total bilirubin ≥2xULN.

Assess eosinophilia.

Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) as relevant on the AE eCRF.

Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications eCRF.

Record alcohol use on the Liver Events eCRF.

The following are required for participants who meet liver stopping criteria for both ALT and total bilirubin:

Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).

Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week).

Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

The Liver Imaging and/or Liver Biopsy eCRFs are also to be completed if these tests are performed.

10.7. Appendix 7: Country-Specific Requirements

10.7.1. China

10.7.1.1. Biomarkers and Exploratory Laboratory Samples

For China, collection of all exploratory biomarker samples (Serum C4, FGF-19, Autotaxin, Total Serum Bile Acids) will be contingent on agreements with China regulatory (HGRAC). Depending on the agreements with the China regulatory and ethics committees, all or some of these biomarkers will be made optional for participants from China.

These exploratory biomarkers are all biomarkers of bile acid synthesis and reuptake and will be analyzed to help inform about the pharmacodynamics of linerixibat.

In addition, the optional genetics sample described in Section 8.6, ELF and Fibroscan as described in Section 8.7.1.2 will be contingent on agreements with HGRAC. ELF and serum acetaminophen Adduct HPLC assay for liver event testing may not be performed in China due to operational or logistical difficulties.

For any biological samples taken, samples will be analyzed and stored within China according to local storage and retention regulations and requirements.

Further research as described in Section 8.6 and Section 8.7 will not be applicable for samples from China.

10.7.1.2. Visit 9 Questionnaire

A questionnaire consisting of four questions will be administered to participants in China in order to support PRO validation for participants in China. Three of the questions have categorical based responses with one question open for free text response. The questionnaire is to be administered to participants from China at Visit 9 (end of Part A).

10.7.1.3. China Schedule of Assessments (SoA)

	Screening (up to 56 days before Day 1)		**Intervention Period**									**ED**	**Follow-up (7 -14 days post last dose)**	**Notes E.D = Early Discontinuation/Withdrawal (as described in Section 7.2).**
			Part A							**Part B**				Where applicable country and local regulations and infrastructure allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (Please see Section 10.8).
Visit Number	1	2	3		4	5	6	7	8	9	10	11			
Day number	-56 to -42	-28 to -14	1		28	56	84	112	140	168	196	224			
Visit widow (days)	NA	NA	NA		±3	±3	±3	±3	±3	±3	±3	±3			
Week number	-8 to -6	-4 to -2 (>V1 + 4Wks)	1		4	8	12	16	20	24	28	32			
Informed consent	X														
Inclusion and exclusion criteria	X		X												Recheck clinical status before randomization.
Demography	X														
Full physical exam	X														Including height and weight.
Brief physical examination			X		X	X	X	X	X	X	X	X	X		Please see Section 8.3.1; physical exams may be performed as symptom directed exams or by other means if assessment performed at locations other than the clinical site.

	Screening (up to 56 days before Day 1)		**Intervention Period**									**ED**	**Follow-up (7 -14 days post last dose)**	**Notes E.D = Early Discontinuation/Withdrawal (as described in Section 7.2).**
			Part A							**Part B**				Where applicable country and local regulations and infrastructure allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (Please see Section 10.8).
Visit Number	1	2	3	4	5	6	7	8	9	10	11			
Day number	-56 to -42	-28 to -14	1	28	56	84	112	140	168	196	224			
Visit widow (days)	NA	NA	NA	±3	±3	±3	±3	±3	±3	±3	±3			
Week number	-8 to -6	-4 to -2 (>V1 + 4Wks)	1	4	8	12	16	20	24	28	32			
Medical history and prior/current conditions	X		X											Including substance usage (drugs, alcohol, tobacco and caffeine), family history of premature cardiovascular (CV) disease and PBC specific Medical History and past-PBC-related procedures Any change in medical history since screening should be reviewed at Day 1, and a baseline stool frequency should be recorded as described in Section 7.1.3.
Background Itch Assessment	X													The investigator will ask participants to rate their overall itch severity for the 2 months preceding the screening visit as described in Section 8.2.1.1.

	Screening (up to 56 days before Day 1)		**Intervention Period**									**ED**	**Follow-up (7 -14 days post last dose)**	**Notes E.D = Early Discontinuation/Withdrawal (as described in Section 7.2).**
			Part A							**Part B**				Where applicable country and local regulations and infrastructure allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (Please see Section 10.8).
Visit Number	1	2	3		4	5	6	7	8	9	10	11			
Day number	-56 to -42	-28 to -14	1		28	56	84	112	140	168	196	224			
Visit widow (days)	NA	NA	NA		±3	±3	±3	±3	±3	±3	±3	±3			
Week number	-8 to -6	-4 to -2 (>V1 + 4Wks)	1		4	8	12	16	20	24	28	32			
Urine Pregnancy test (Women of Childbearing Potential [WOCBP] only)	X		X		X	X	X	X	X	X	X	X	X		Refer to Section 8.3.5, serum pregnancy may be required locally in some locations.
Human Immunodeficiency Virus (HIV), Hepatitis B and C screening	X														
Clinical Laboratory tests	X	X	X		X	X	X	X	X	X	X	X	X		Refer to Section 10.2, Clinical laboratory tests at Visit 2 refer to liver biochemistry parameters only.
Fecal Occult Blood Test (FOBT)			X							X					Please see Section 8.3.4.2.

	Screening (up to 56 days before Day 1)		**Intervention Period**									**ED**	**Follow-up (7 -14 days post last dose)**	**Notes E.D = Early Discontinuation/Withdrawal (as described in Section 7.2).**
			Part A							**Part B**				Where applicable country and local regulations and infrastructure allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (Please see Section 10.8).
Visit Number	1	2	3		4	5	6	7	8	9	10	11			
Day number	-56 to -42	-28 to -14	1		28	56	84	112	140	168	196	224			
Visit widow (days)	NA	NA	NA		±3	±3	±3	±3	±3	±3	±3	±3			
Week number	-8 to -6	-4 to -2 (>V1 + 4Wks)	1		4	8	12	16	20	24	28	32			
Exploratory Biomarkers		X	X		X	X	X	X	X	X	X	X	X		Please see Section 8.7. Sample on Day 1 should be taken prior to any study intervention administration. Assessment is not required if study treatment is permanently discontinued.
Enhanced Liver Fibrosis (ELF) Test			X							X		X			ELF may not be performed in China due to operational limitations.
Fibroscan			X							X					To be performed only where site availability permits; please see Section 8.7.1.2.

	Screening (up to 56 days before Day 1)		**Intervention Period**									**ED**	**Follow-up (7 -14 days post last dose)**	**Notes E.D = Early Discontinuation/Withdrawal (as described in Section 7.2).**
			Part A							**Part B**				Where applicable country and local regulations and infrastructure allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (Please see Section 10.8).
Visit Number	1	2	3	4	5	6	7	8	9	10	11			
Day number	-56 to -42	-28 to -14	1	28	56	84	112	140	168	196	224			
Visit widow (days)	NA	NA	NA	±3	±3	±3	±3	±3	±3	±3	±3			
Week number	-8 to -6	-4 to -2 (>V1 + 4Wks)	1	4	8	12	16	20	24	28	32			
Pharmacokinetics (PK)			X			X	X	X	X	X				PK samples are required at a total of 3 timepoints, 1 sample is required prior to first dose of study treatment at Visit 3 and 2 further samples will be required at any 2 additional visits between weeks 8 and 24. Assessment is not required if study treatment is permanently discontinued.
12-lead ECG	X						X			X		X	X		
Vital signs	X		X		X	X	X	X	X	X	X	X	X		
Randomization			X												
Study intervention dispensing			X		X		X			X					
Study intervention administration				←==========							==========→			Day 1 is the day on which the first study intervention administration takes place and may differ from the randomization date.

	Screening (up to 56 days before Day 1)		**Intervention Period**									**ED**	**Follow-up (7 -14 days post last dose)**	**Notes E.D = Early Discontinuation/Withdrawal (as described in Section 7.2).**
			Part A							**Part B**				Where applicable country and local regulations and infrastructure allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (Please see Section 10.8).
Visit Number	1	2	3	4	5	6	7	8	9	10	11			
Day number	-56 to -42	-28 to -14	1	28	56	84	112	140	168	196	224			
Visit widow (days)	NA	NA	NA	±3	±3	±3	±3	±3	±3	±3	±3			
Week number	-8 to -6	-4 to -2 (>V1 + 4Wks)	1	4	8	12	16	20	24	28	32			
Medication diary				←==========→										Study medication diary to be completed daily throughout the study. The medication diary is not required if study treatment is permanently discontinued.
Study intervention return/compliance					X	X	X	X	X	X	X	X			
Adverse Event (AE) review				←==========→								X	X	AEs will be collected from the start of study intervention.
Serious Adverse Event (SAE) review	←==========→											X	X	
Concomitant medication review	←==========→											X	X	Including PBC-specific Medications (past and present).
Symptom Questionnaire	←==========→											X		Symptom Questionnaire includes the itch, sleep and fatigue NRS. Please see Section 8.2.1.1.

	Screening (up to 56 days before Day 1)		**Intervention Period**									**ED**	**Follow-up (7 -14 days post last dose)**	**Notes E.D = Early Discontinuation/Withdrawal (as described in Section 7.2).**
			Part A							**Part B**				Where applicable country and local regulations and infrastructure allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (Please see Section 10.8).
Visit Number	1	2	3		4	5	6	7	8	9	10	11			
Day number	-56 to -42	-28 to -14	1		28	56	84	112	140	168	196	224			
Visit widow (days)	NA	NA	NA		±3	±3	±3	±3	±3	±3	±3	±3			
Week number	-8 to -6	-4 to -2 (>V1 + 4Wks)	1		4	8	12	16	20	24	28	32			
Gastrointestinal Symptom Rating Scale			←==========→										X		Questionnaire on GI symptoms to be completed weekly in eDiary with a seven day recall as described in Section 8.2.1.3.
PGI-C					X	X	X	X	X	X	X	X	X		Patient Global Impression of Change Questionnaire
PGI-S			X		X	X	X	X	X	X	X	X	X		Patient Global Impression of Severity
PBC-40			X		X	X	X	X	X	X	X	X	X		PBC-40 Health Related Quality of Life Scale
BDI-II			X				X			X		X	X		Beck Depression Inventory II
ESS			X				X			X		X	X		Epworth Sleepiness Scale
Visit 9 Questionnaire										X					

10.7.2. Israel

10.7.2.1. Genetics

For Israel, due to operational challenges, sample collection for optional genetic research described in Section 8.6 and Section 10.5 will not be performed.

10.7.3. France

This appendix includes all applicable requirements of French Public Health Code/specific local GSK requirements and identified, item per item, the mandatory modifications or additional information to the study protocol.

10.7.3.1. Concerning the Selection of Study Population and Withdrawal Criteria

The following vulnerable subject populations will be excluded; minors, protected subjects, adult subjects not in condition to express their consent, subjects deprived of liberty, subjects receiving psychiatric cares, subjects hospitalized in a Health and Social Establishment for other purpose than the participation to the study.

A subject will be eligible for inclusion in this study if he/she is either affiliated to or beneficiary of a social security category (French Public Health Code law L.1121-8-1). (exception for a participant to a non-interventional study or to a participant to an interventional study if authorised by the Ethics Committee). It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject:

- is either affiliated to or beneficiary of a social security category
- has got an authorisation by the Ethics Committee.

10.7.3.2. Concerning the Study Governance Considerations

- In section "Regulatory and Ethical Considerations, including the Informed Consent Process" of study protocol; Concerning the process for informing the subject and/or his/her legally authorized representative, the following text is added:

  French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the subject and/or his/her legally authorized representative written consent. It also contains a reference to the authorisation of ANSM and the approval from the French Ethics Committee.

- Concerning the management of the Patient Informed Consent Forms, the following text is added:

  French Patient Informed Consent Form is in duplicate (triplicate for minor subject). The first page of the Patient Informed Consent Form is given to the investigator. The copy is kept by the patient or legally authorized representative.

- Notification to the Hospital Director

In accordance with Article L1123-13 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-69).

- Information to the Hospital Pharmacist

In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g., included in the IB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial

- Ethnic Origin

In accordance with the data privacy regulation, the ethnic origin, as any personal data, can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- Testing of Biological Samples

In accordance with the French Public Health Code law – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

10.7.3.3. Concerning the DATA MANAGEMENT

The following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the data privacy regulation, each of these people aforesaid has a right of access, correction and opposition on their own data through GSK (Clinical Operations Department).

10.7.3.4. Concerning Data Privacy

In accordance with the applicable data privacy regulation, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction, or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with one of the methodology of reference (MR-001) or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with GSK in accordance with the legal provisions.

10.8. Appendix 8: Home Healthcare/Remote Activities

10.8.1. Overall Rationale for this Appendix

This protocol appendix outlines measures to be considered for any country/site where home healthcare options may be implemented for participants as permitted by country and local regulations and infrastructure.

Activities may be performed remotely either to ensure study continuity during periods of significant challenge (e.g., pandemic, conflict), or if partial or fully remote study activities are permitted locally to support participant burden with visit scheduling.

Where required due to study continuity issues, clinical investigators should document in participant notes appropriately how restrictions related to the event led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local regulatory guidance). Missing protocol required data/visits due to study continuity issues should be noted in participant notes and recorded as a protocol deviation.

The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare, and rights, and promote data integrity.

10.8.2. Home Healthcare Provisioning

If allowed by country regulation/ethics, study assessments may be conducted remotely at some visits during this study, the details of which are provided separately. Remote activities for these applicable visits, such as those described in the below section, can be conducted by a home healthcare professional either as arranged and overseen by the investigator site or by a sponsor delegated third party such as CCI, which has been contracted to perform these activities in many countries if requested using virtual technologies (telemedicine, secure video conferences, phone calls, or a web portal and/or mobile application).

In addition, a fully remote metasite, wherein all visits are conducted fully remotely will be implemented with CCI, where permitted by regulation/ethics.

10.8.3. Protocol Defined Procedures/Visits

- It is the responsibility of the investigator or designee to inform GSK when remote assessments are required and occur and to document in the source notes.
- Measurement of vital signs and weight, as well as conduct of a brief physical exam may be conducted remotely. In some cases, brief physical exams may be performed as symptom directed exams or by other means as agreed with the investigator.
- Clinical safety laboratory sampling, PK, biomarkers and genetic sampling and processing may all be conducted remotely by a home healthcare professional. Ancillary materials for the above laboratory sampling may also be shipped direct to the participant's home address from the investigational site/depot or delegated third party. Collected laboratory samples can also be collected direct from the participant's home address to the central laboratory.
- The process for laboratory sample shipments must be agreed with GSK if performed by the clinical site or details can be provided if performed by an agreed third party.
- Additional unscheduled safety assessments such as routine blood sampling may be performed at the discretion of the Investigator including in the participant's home, if deemed necessary Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If visits to a site/home are not feasible, then medical evaluation may take place by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress. GSK will be accountable for working with third party vendors to ensure the site has the required equipment, training and support for this model and should be notified as soon as possible by the investigator that the service is required.
- As part of this model, study visits may be completed on a virtual platform that connects participants to their investigators and study teams through either a study-issued smartphone or participant's own device (BYOD) model. This technology may be used in combination with visits from mobile study personnel (e.g. mobile nurses) to participants' homes for various lab collections and designated study procedures.
- The study investigator is responsible for ensuring that the identification, management, and reporting of AEs and SAEs are completed in accordance with the protocol and applicable regulations. AEs are first reported by participants to the investigator/study team or may be identified by the study team during interactions with the participants via telemedicine encounters. In addition, mobile nurses may identify AEs as well and report them to the investigator for evaluation. Additionally, AEs may be identified from lab reports, imaging or ECG reports, and other records. As determined by the investigator, the appropriate medical intervention, therapeutic intervention, and/or support measures are

instituted, as necessary. Participants can also request a timely secure videoconference with the investigator and/or site staff.

- The participant should be informed of the plan and any potential risks associated with the virtual medium and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

- **Note**: If the Investigator wishes to conduct a trial visit at a location that has not been previously assessed by GSK, it is the investigator's responsibility to identify an adequate alternate location and to notify GSK of the alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, is well-equipped to perform study procedures and covered by an adequate insurance. Furthermore, the investigator should have sufficient oversight to ensure that the staff at the alternate location are trained to perform study procedures.

10.8.4. Study Intervention(s)

- If allowed by country regulation/ethics, then study intervention (including rescue study medication and ancillary supplies related to Investigational Medicinal Product (IMP) administration) can be shipped direct-to-participant (DTP) from the investigational site or delegated third party, as arranged by the sponsor, to the participant's home address. The process for this shipment must be agreed with GSK who will provide the relevant documentation and links to courier sites required to ensure shipments are adequately temperature controlled (if required) throughout transportation.
- Used and/or unused IMP can also be collected from the participant's home address to the return/destruction location, either the investigational site or agreed location of destruction. The process for this shipment must be agreed with GSK who will provide operational details if this service is available.
- Staff at each clinical study center or the home healthcare professional (if provided by sponsor delegated third party) will be responsible for supply of study intervention according to procedures detailed in the SRM. No special procedures for the safe handling of study intervention are required.
- The Principal Investigator assumes Good Clinical Practice (GCP) responsibilities for IMP handling and the medical control for dispensing to participants. Site Staff should document the dispensing in the Dispensing/Accountability Logs adding a comment that this was a DTP dispensing.
- Compliance with study intervention administration will be verified through observation by study staff or trained home healthcare professionals if performed by sponsor delegated third party.
- In some cases, trial participants who no longer have access to investigational product or the investigational site may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment).

10.8.5. Data Management/Monitoring

- If on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by local regulations and the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure subject privacy.
- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing the eDC platform (Veeva CDMS) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK.

10.9. Appendix 9: Activities of Daily Living (ADLs)

Basic ADLs*	Instrumental ADLs**
1. Bathing	1. Using the telephone
2. Dressing	2. Shopping
3. Toileting	3. Doing housework
4. Transferring	4. Doing laundry
5. Maintaining continence	5. Preparing meals
6. Feeding	6. Driving
	7. Taking medications
	8. Managing money

*Basic ADLS: self-care activities that an individual must accomplish in order to remain self-sufficient
**Instrumental ADLs: higher-level activities that individuals must perform or have help with to remain independent in their homes

10.10. Appendix 10: Abbreviations, Definitions of Terms, and Trademarks

ABBREVIATION	DEFINITION
AASLD	American Association for the Study of Liver Diseases
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMA	Anti-mitochondrial antibody
AR	Autoregressive
ASBT	Apical Sodium-Dependent Bile Acid Transporter
ASP	Average Sleep Propensity
AST	Aspartate Aminotransferase
BDI-II	Beck Depression Inventory-II
BID	Bis in die (twice daily)
BUN	Blood Urea Nitrogen
C4	7-α-hydroxy-4-cholesten-3-one
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials

ABBREVIATION	DEFINITION
COVID-19	SARS-CoV-2 Virus
CPK	Creatine Phosphokinase
CPMS	Clinical Pharmacology Modeling and Simulation
CRF	Case Report Form
CS	Compound Symmetry
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
CV	Cardiovascular Disease
DBL	Database Lock
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic Acid
DoR	Delegation of Responsibilities
DTP	Direct to Participant
EASL	European Association for the Study of the Liver
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Early Discontinuation
eDiary	Electronic Diary
eGFR	Estimated Glomerular Filtration Rate
ELF	Enhanced Liver Fibrosis
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
ESS	Epworth Sleepiness Scale

ABBREVIATION	DEFINITION
FDA	Food and Drug Administration
FGF-19	Fibroblast Growth Factor-19
FOBT	Fecal Occult Blood Test
FSFV	First Subject, First Visit
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
GSK	GlaxoSmithKline
GSRS	Gastrointestinal Symptom Rating Scale
GWAS	Genome-wide Association Study
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B
hCG	Human chorionic Gonadotropin
HCV	Hepatitis C
HDL	High Density Lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
IBAT	Inhibitor of the Human Ileal Bile Acid Transporter
ICF	Informed Consent Form

ABBREVIATION	DEFINITION
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intend to Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IWRS	Interactive Web Response System
K-PD	Kinetic-Pharmacodynamic
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LOF	Loss of Function
MAR	Missing at Random
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
mg	Milligram
MMRM	Mixed Model Repeated Measure
MSDS	Material Safety Data Sheet

ABBREVIATION	DEFINITION
MWDI	Mean Worst Daily Itch (now referred to as Weekly Itch)
NASH	Nonalcoholic Steatohepatitis
NRS	Numerical Rating Scale
OCA	Obeticholic Acid (Ocaliva)
PBC	Primary Biliary Cholangitis
PBC-40	Primary Biliary Cholangitis-40 Health Related Questionnaire
PD	Pharmacodynamics
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PheWAS	Phenome-wide Association Study
PI	Principal Investigator
PK	Pharmacokinetics
PRO	Patient Reported Outcome
PSC	Primary Sclerosing Cholangitis
PT	Prothrombin Time
QD	Quaque die (once daily)
QoL	Quality of Life
QTcB	QT interval Bazett's Formula
QTcF	QT interval Fredericia's Formula
QTL	Quality Tolerance Limit
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

ABBREVIATION	DEFINITION
SD	Standard Deviation
SDR	Source Document Review
SDV	Source Data Verification
SE	Standard Error
SoA	Schedule of Assessments
SRM	Study Reference Manual
SSP	Situational Sleep Propensities
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2D	Type 2 Diabetes
TB	Total Bilirubin
UDCA	Ursodeoxycholic Acid
UK	United Kingdom
ULN	Upper Limit of Normal
WBC	White Blood Cell
WIS	Weekly Itch Score (formerly referred to as Mean Worst Daily Itch [MWDI] Score)
WOCBP	Women of Childbearing Potential
WONCBP	Women of non-Childbearing Potential
WSS	Weekly Sleep Score (formerly referred to as Mean Daily Sleep Score)

Term	Definition
Adverse drug reaction	An adverse event where a causal relationship between a medicinal product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. a. In the context of a clinical trial, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition).
Background therapy	Type of medicinal product administered to each of the clinical trial participant, regardless of randomization group, to treat the indication that is the object of the study. Background treatment is generally considered to be the current standard care for the particular indication. In these trials, the IMP is given in addition to the background treatment and safety efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared with an active comparator or with placebo plus background treatment.
Blinding	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In a double-blind study, the participant, the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the intervention assignment.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Term	Definition
Comparator	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
Direct-from-Participant Shipments	Home pickup of collected biological specimens, or pickup and return of unused/partially used/expired trial materials for return to investigator site.
Direct-to-Participant Shipments	Shipping of Investigational Product, lab kits, devices, etc., to the participant's residence under secure and controlled conditions.
eDiary	Electronically registered patient data and automated data entries on, for example, a handheld mobile device, tablet or computer.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Home Healthcare Services	Deployment of mobile health care professional(s) (nurses or phlebotomists) to perform study activities remotely.
Investigational Product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

Term	Definition
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Pharmacogenomics	The ICH E15 Guidance for Industry defines pharmacogenomics as the "Study of variation of DNA and RNA characteristics as related to drug or treatment response." Pharmacogenetics, a subset of pharmacogenomics, is "the study of variations in DNA sequence as related to drug response." Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g., mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (PK, safety, efficacy or effectiveness, mode of action). Proteomic and metabolomic biomarker research is not pharmacogenomics.

Term	Definition
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit	This term refers to the visit conducted in the place other than the study site.
Rescue medication	Medicines identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Standard of care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. 1. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant. Note: “Study intervention” and “study treatment” are used interchangeably unless otherwise specified.
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).

Term	Definition
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
SUSAR	Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting.
Telemedicine	The use of electronic information and telecommunications technologies (both video-based and audio-only) to facilitate remote health care delivery, participant and professional health-related education, public health and health administration.
Virtual visit	This term refers to study visits conducted using multimedia or technological platforms.

TRADEMARK INFORMATION

Trademarks of the GSK group of companies
None

Trademarks not owned by the GSK group of companies
Enhanced Liver Fibrosis
Fibroscan
Ocaliva
Questran

10.11. Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [03-ISR-01]: 24-MAR-2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Introduction of country-specific requirement for Israel.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Assessments (SoA)	Note added to indicate that sample for optional genetic research will not be collected in Israel.	In line with study strategy
New Section 10.7.2 Israel	Country-specific requirement for Israel added: sample collection for optional genetic research will not be performed.	In line with study strategy

Amendment [03]: 02-SEP-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Inclusion of additional stopping criteria, liver biochemistry triggers for monitoring of drug induced cholestatic liver injury and clarifications on exclusion criteria.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis	Text amended referring to questions within the PBC-40 questionnaire	Clarification of question domains

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis	Addition of text related to administrative stratification factors	Addition of text for clarification purposes in alignment with SAP.
Section 1.1. Synopsis	IDMC reference text amended to include safety monitoring of patients in the study	Clarification of text
Section 2.1.	Text amended referring to questions within the PBC-40 questionnaire	Clarification of question domains
Section 2.3.1. Risk Assessment	Addition of reference to abdominal pain in relation to gastrointestinal effects including diarrhea	Added for alignment with Investigator's Brochure
Section 3. Objectives and Endpoints/Estimands	Text amended referring to questions within the PBC-40 questionnaire	Clarification of question domains
Section 4.1. Overall Design	Addition of text related to administrative stratification factors	Addition of text for clarification purposes in alignment with SAP.
Section 5.2. Exclusion Criteria	Text added to clarify that participants with positive COVID-19 tests will also be excluded from the study	Text amended in line with updated guidance
Section 5.2. Exclusion Criteria	Text amended to clarify alcohol restriction requirements for the study	Text amended in line with regulatory feedback

Section # and Name	Description of Change	Brief Rationale
Section 5.4. Screen Failures	Text clarified that screen failures do not ultimately enrol in the study	Clarification of text
Section 6.1. Study Intervention(s) Administered	Changes to colour of tablet and clarification of dosage level text	Correction of text
New Section 6.3.1. Unblinding Procedures	Addition of text indicating unblinding procedures	Clarification of text
6.4. Study Intervention Compliance	Clarification that deviations will be recorded for impacted compliance	Clarification of text
Section 7.1.1.1. Increased Monitoring	Liver monitoring/stopping criteria amended	Text amended in line with regulatory feedback
Section 7.1.1.2. Stopping Criteria	Additional ALP criteria added	Text amended in line with regulatory feedback
Section 7.1.1.3 Close Observation	Additional ALP test added	Text amended in line with regulatory feedback
Section 7.1.3. Diarrhea Management Criteria and Stopping Criteria	Removal of text requiring participant request for anti-diarrheal treatment	Clarification of text
New Section 7.1.5. Renal Stopping Criteria	Added stopping criteria related to renal function	Text added in line with regulatory feedback
New Section 7.1.6. Diagnosis of Colon Cancer	Added stopping criteria related to diagnosis of colon cancer	Text added in line with regulatory feedback
Section 7.2. Participant Discontinuation/Withdrawal from the Study	Text added to clarify occasions for	Clarification of text

Section # and Name	Description of Change	Brief Rationale
	discontinuation by the investigator	
Section 8.6.1. Biomarkers of Disease Progression	Text added to include expectation of screening for hepatocellular carcinoma	Text added in line with regulatory feedback
Section 9.1.2. Secondary endpoints	Text amended in relation to additional testing	Clarification of statistical approach
Section 9.4.2. Primary and Secondary Endpoint(s)	Text clarified with regards to how imputed data impacted by COVID-19 will be addressed	Clarification of text
New Section 9.4.5. Other Analyses	Text added to clarify approach to validation of PRO data	Clarification of text
Section 10.1.5.1. Independent Data Monitoring Committee	Text amended to clarify that safety of participants will be evaluated at IDMC	Clarification of text

Amendment [02]: 12-JUL-2021

This amendment was considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study

Overall Rationale for the Amendment:

Clarification of text and correction of typographical errors across the document

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Assessments	Removal of Visit Number, Day Number and Week Number	Administrative error corrected for clarification: Follow up phone calls are not linked to a specific visit
Section 1.3. Schedule of Assessments	Text added to clarify that 3 total pharmacokinetic samples are required for the study	Additional text added for clarification purposes
Section 3: Objectives and Endpoints/Estimands	Removal of word "with" from exploratory endpoint #2	Correction of typographical error
Section 3.1. Primary Estimand	Text amended to clarify analysis of intercurrent event data	Text clarified to describe how to discard data impacted by intercurrent events
Section 1.1 Synopsis Section 3.3. Supplementary Estimand	Text amended to clarify analysis of intercurrent event data	Text clarified to describe how to discard data impacted by intercurrent events
Section 1.1 Synopsis Section 4.1. Overall Design	Text added to clarify circumstances for follow up phone call	Text added to clarify that follow up phone calls should also be performed after study treatment withdrawal
Section 5.1. Inclusion Criteria	Text added to clarify additional validated assays may be used in Inclusion Criteria #2	Text added to align with local requirements of different validated assays used for diagnosis of PBC
Section 5.1. Inclusion Criteria	Removal of "not" from inclusion criteria #4	Correction of typographical error for clarification purposes
Section 4.2.4 Rationale for Concomitant Medications Section 6.8.3. Rescue Medication	Correction of term "intolerable" to "worsening"	Text has been amended to clarify conditions in which rescue medication can be considered

Section # and Name	Description of Change	Brief Rationale
Section 7.1. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	Additional text added to clarify circumstances of follow-up phone call	Text added to clarify that follow up phone calls should also be performed after study treatment withdrawal
Section 7.1.3.1. Determination of Diarrhea Severity	Text removed indicating diarrhea that is interfering with the participant's daily activities will be considered an AESI	Text removed to clarify that all diarrhea will be considered an AESI
Section 7.1.7.1. Study Intervention Restart after Meeting Liver Stopping Criteria	Removal of text referring to identified genetic markers for liver injury	Text removed as not applicable for this study
Section 8.1.1.5 Beck Depression Inventory (BDI-II)	Removal of administrative text	Text removed to clarify that questionnaires do not need to be completed during the visit
Section 8.2.4. Clinical Safety Laboratory Assessments	Removal of text referring to dose modification	Text removed as dose modification is not applicable for this study
Section 8.3.1. Time Period and Frequency for Collecting AE and SAE Information	Additional text added to clarify that AEs and SAEs will be collected until the follow up phone call or the final scheduled GLISTEN visit	Text added to clarify the duration of AE and SAE collection in relation to follow-up phone call (if applicable)

Section # and Name	Description of Change	Brief Rationale
Section 8.3.5. Pregnancy	Removal of text requiring female partners of male participants requiring consent for pregnancy reporting	Text was originally included in error, text has been removed as not necessary for study based on very low estimated exposure via semen in female partners of male participants due to minimal systemic absorption of linerixibat. Additionally, linerixibat was not genotoxic and was not associated with developmental toxicity in definitive embryofetal development studies in rats and rabbits or effects on female fertility and early embryonic development in rats at large exposure multiples.
Section 8.5. Genetics	Removal of "and destruction"	Removed due to inconsistency, details of destruction is not provided in the laboratory manual
Section 9.4.2. Primary and Secondary Endpoint(s)	Text modified to clarify handling of data impacted by intercurrent event	Text clarified to highlight how data impacted by intercurrent events will be handled
Section 9.4.3.: Safety Endpoint (s)	Text removed and clarified regarding analysis of AESI and safety data	Text clarified and further safety analyses will be specified in the Statistical Analysis Plan
Section 10.2 Appendix 2: Clinical Laboratory Tests	Duplicated "Calcium" removed	Removed as duplicated in error
Section 10.3.5. Reporting of SAE to GSK	Removal of text requiring investigator to document causality review in eCRF within 72 hours.	Text has been removed as eCRF review within 72 hours is no longer required

Section # and Name	Description of Change	Brief Rationale
Section 10.6. Appendix 6: Liver Safety: Required Actions and Follow-Up Assessments	Text added to clarify that acetaminophen adduct assay should only be performed where available	Text clarified as assay not currently available in some locations
Section 10.7. Appendix 7: Country-Specific Requirements	Text added to clarify that acetaminophen adduct assay will not be performed in China	Text clarified as additional Adduct HPLC assay not currently available in China
New Section 10.7.2 Visit 9 Questionnaire	Additional questionnaire added	Additional questionnaire added to supplement PRO validation for participants in China
New section 10.7.3 China Schedule of Assessments	China specific Schedule of Assessment added	Schedule of Assessments added for clarity for China participants

Amendment [01] 01-MAR-2021

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Change to AE grading criteria and change in randomization strategy.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	References to re-randomization or randomized withdrawal replaced with description of randomization in to 4 different arms at Week 1	Randomization strategy has changed so that treatment assignment for Part A and Part B occurs at Day 1
Section 1.2 Schema	Schema updated to reflect randomization at Week 1 only	Randomization strategy has changed so that treatment assignment for Part A and Part B occurs at Day 1

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Assessments	Randomization removed at Week 24, and note removed indicating that randomization could occur earlier than Week 24	Randomization strategy has changed so that treatment assignment for Part A and Part B occurs at Day 1
Section 1.3 Schedule of Assessments	Note added that Symptom Questionnaire will also contain fatigue NRS.	Fatigue NRS omitted from original protocol in error.
Section 2.1. Study Rationale	References to randomized withdrawal removed	Randomization strategy has changed so that treatment assignment for Part A and Part B occurs at Day 1
Section 3 Objectives and Endpoints/Estimands	Addition of exploratory endpoint for fatigue	Fatigue NRS omitted from original protocol in error.
Section 4.1 Overall Design	References to re-randomization and randomized withdrawal replaced with description of randomization in to 4 different arms at Day 1	Randomization strategy has changed so that treatment assignment for Part A and Part B occurs at Day 1
Section 4.2.2. Rationale for Stratification Factors	Reference to Randomization at Week 24 removed	Randomization strategy has changed so that treatment assignment for Part A and Part B occurs at Day 1
Section 4.2.3. Rationale for Part B	Reference to Re-Randomization removed from heading title and text amended to reflect randomization only at Day 1	Randomization strategy has changed so that treatment assignment for Part A and Part B occurs at Day 1
Section 4.2.5 Rationale of Using Itch Numerical Rating Scale as Primary Endpoint	Description of symptom questionnaire clarified that it includes itch, sleep and fatigue NRS	Fatigue NRS omitted from original protocol in error.

Section # and Name	Description of Change	Brief Rationale
Section 5.2. Exclusion Criteria	Exclusion Criteria #2 updated to reflect that assessment is relative to the average baseline measure	Update required for consistency with other sections detailing liver biochemistry baseline.
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	References to re-randomization at Week 24 removed	Randomization strategy has changed so that treatment assignment for Part A and Part B occurs at Day 1
Section 6.4. Study Intervention Compliance	Clarification that compliance is measured using participant eDiary, and not just by counting returned tablets	Compliance should be tracked using eDiary
Section 6.8.2. Prohibited Medications	OCA restricted from 8 weeks from baseline	Updated for consistency with Exclusion Criteria #20.
Section 7.1.3. Diarrhea Management Criteria and Stopping Criteria	Note added that diarrhea AEs should be graded against the standard grading as well as CTCAE v5	All AEs should be assessed using existing guidance as described in Appendix 3. AEs for diarrhea should also be assessed using CTCAE v5 criteria.
Section 7.1.3.1	Text added to clarify that diarrhea AEs should be graded against the standard criteria in Appendix 10.3.4	All AEs should be assessed using existing guidance as described in Appendix 3. AEs for diarrhea should also be assessed using CTCAE v5 criteria.
Section 7.1.6 Temporary Discontinuation due to AEs	Specific text to CTCAE v5 criteria removed, and cross referenced to other relevant sections.	Only AEs for diarrhea should be assessed using CTCAE v5 criteria, all other AEs should be assessed using existing guidance as described in Appendix 3.
Section 8.1.1.1 New Sub-heading: Symptom Questionnaire	Clarification text added that fatigue NRS and missed doses of study treatment is included with symptom diary	Fatigue NRS omitted from original protocol in error. Compliance should be tracked using eDiary

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1.1.2 Sleep Interference Questionnaire NRS	Clarification text added that fatigue NRS is included with symptom diary	Fatigue NRS omitted from original protocol in error.
Section 8.5. Genetics	Additional saliva option added	Flexibility to sample type added
Section 9.2.1. Sample Size Assumptions	Figure 3 Updated	Figure 3 updated to reflect linerixibat in a blue color
Section 10.2 Appendix 2: Clinical Laboratory Tests	Indirect LDL Cholesterol and Indirect HDL Cholesterol removed	Tests removed as not required
Section 10.3.4. Recording and Follow-Up of AE and SAE	Assessment of Intensity: Grading criteria amended from CTCAE v5 to standard mild/moderate/severe grading.	Only AEs for diarrhea should be assessed using CTCAE v5 criteria, all other AEs should be assessed using existing guidance as described in Appendix 3
Section 10.5 Appendix 5 Genetics	Additional saliva option added	Flexibility to sample type added

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