TITLE PAGE

Protocol Title: A randomized, double-blind, multi-dose, placebo-controlled study to evaluate the efficacy, safety and tolerability of GSK2330672 administration for the treatment of pruritus in patients with primary biliary cholangitis.
(**GLIMMER**: **G**SK2330672 tria**L** of **I**BAT inhibition with **M**ultidose **M**easurement for **E**valuation of **R**esponse).

Protocol Number: 201000 / 02

Short Title: Dose response study of GSK2330672 for the treatment of pruritus in patients with primary biliary cholangitis.

Compound Number: GSK2330672

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
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Medical Monitor Name and Contact Information can be found in the Study Reference Manual.

Regulatory Agency Identifying Number(s): IND Number: 130391; EudraCT Number: 2016-002416-41

Approval Date: 06-DEC-2017

SPONSOR SIGNATORY

PPD

06 DEC 2017

Dr Stuart Kendrick MA BM BCh PhD FRCP (UK)
Project Physician Lead

Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	*06-Dec-2017*
Amendment 1	*15-Nov-2016*
Original Protocol	*26-Aug-2016*

Amendment 2: 06-Dec-2017

Overall Rationale for the Amendment: To increase access to the trial for participants who will more closely reflect the intended treatment population of PBC patients while maintaining safety, to clarify some existing criteria and information, to make administrative changes, and to correct minor typographical and grammatical errors

Section # and Name	Description of Change	Brief Rationale
2. Schedule of Activities	Addition of footnote 11 that in the event of a **confirmed** baseline (run-in) failure, blood, urine, ECG, and Trial Slate assessments are not required	To minimize assessments that will not contribute to primary and secondary end points
2. Schedule of Activities	Addition of footnote 12 that highlights that randomization occurs at Visit 3	To point out that criteria for randomization are evaluated at Visit 3
3.3.1 Risk Assessment	Under "Investigational Product (GSK2330672)," first bullet point entitled "Gastrointestinal effects including diarrhea," the mitigation strategy has changed from "Exclusion of participants with current symptomatic inflammatory bowel disease or malabsorption syndromes" to "Exclusion of participants with current diarrhea."	To clarify that only diarrhea constitutes an exclusion criterion
4. Objectives and Endpoints	First exploratory endpoint, second bullet: time to worsening itch assessment changed to Weeks 17-20	To correct an error that incorrectly stated that time to worsening of itch would be assessed during Weeks 21-24
5.4 Scientific Rationale for Study Design, 7.7.1 Prohibited Medications, 7.7.2 Permitted Medications	Added the phrase, "…and during the Follow Up Period" to indicate when addition of or changes to certain medications may be made	To clarify that addition of and changes to restricted medications during Screening, the Initial Study Period, and the Main Study Period may be made during the Follow Up Period in addition to the Final Study Period
6.1 Inclusion Criteria	Revision of inclusion criterion 2, bullet 2 to read, "antinuclear dot *and*/*or* nuclear rim" instead of "antinuclear dot *and* rim"	To clarify that a potential participant may be positive for one or both PBC-specific antinuclear antibodies
6.1 Inclusion Criteria	Clarification in inclusion criterion 3 that "majority of time" means "more than half of the days, as recalled by the participant"	To define more specifically the recall period for itch severity that a participant must experience in order to be considered for the study
6.1 Inclusion Criteria	Clarification in inclusion criterion 3 that periods of low itch or no itch are acceptable as long as the worst daily itch score is ≥4 on the majority of days	To improve clarity and consistency of protocol implementation at screening, ensuring a population with moderate to severe itch on average is enrolled

Section # and Name	Description of Change	Brief Rationale
6.2 Exclusion Criteria	Revision of exclusion criterion 1 to permit potential participants with a screening total bilirubin up to 2xULN to participate	The trial population will more closely reflect the intended treatment population.
6.2 Exclusion Criteria	Revision of exclusion criterion 2 to permit potential participants with a screening ALT up to 6xULN to participate	The trial population will more closely reflect the intended treatment population.
6.2 Exclusion Criteria	Revision of exclusion criterion 5 to permit potential participants who have other hepatic conditions in addition to PBC to participate. PBC must be the dominant liver injury in the Investigator's opinion.	The trial population will more closely reflect the intended treatment population. Actively replicating viral hepatitis B and C and confirmed hepatocellular or biliary cancer remain exclusions, as does history of hepatic decompensation.
6.2 Exclusion Criteria	Revision of exclusion criterion 6 to clarify that only current diarrhea is an exclusion	The trial population will more closely reflect the intended treatment population.
6.2 Exclusion Criteria	• Revision of exclusion criterion 9 to permit potential participants to take previously-excluded immunosuppressant medications provided the medications have been at a stable (i.e., unchanged) dose for at least 2 months prior to the screening visit • Addition of a note beneath the newly revised exclusion criterion 9 that reads, "Note: If a change in dose in any of these medications is anticipated during the course of the study, the participant should be excluded. *[Rationale: Limited evidence indicates these drugs*	• The trial population will more closely reflect the intended treatment population. • The requirement for dose stability as detailed in the "note" that follows exclusion criterion 9 will minimize the risk that immunosuppressant medications could influence the secondary endpoint of change in ALP.

Section # and Name	Description of Change	Brief Rationale
	may alter disease progression in some PBC patients.]"	
6.2 Exclusion Criteria	Addition of exclusion criterion 14: "Administration of any other IBAT inhibitor in the 3 months prior to screening [Rationale: Effects of another IBAT inhibitor may influence pruritus.]"	To ensure a thorough washout period for the use of another IBAT inhibitor well before possible administration of GSK2330672 to avoid confounding effects
6.2 Exclusion Criteria	Revision of previous exclusion criterion 15, which in Amendment 02 is criterion 16, to permit potential participants with QTc up to 480 msec, regardless of the presence of bundle branch block, to participate	The trial population will more closely reflect the intended treatment population.
6.3 Criteria for Randomization	Revision of final paragraph to explain that participants who fail randomization criteria will be considered baseline (run-in) failures, and that the way to access the eligibility criteria is explained in the Study Reference Manual	To clarify how participants who fail randomization will be categorized within the trial data and to inform the reader how to access the eligibility information for a participant
6.5 Screen and Baseline Failures	Change of title of section from "Screen Failures" to "Screen and Baseline Failures"	To emphasize the differences between "screen failures" and "baseline failures" within the study
6.5.1 Screen Failures	Addition of Section 6.5.1	To clarify the differences between "screen failures" and "baseline failures" within the study
6.5.1 Screen Failures	Addition of permission to re-screen participants who potentially become eligible as a result of a protocol amendment	The trial population will more closely reflect the intended treatment population. Rescreening is only permitted where the participant would have met all the eligibility requirements of the amended protocol at the time of the first (original) screening visit. The rescreened participants must meet all the eligibility requirements at the time of the rescreening (subsequent

Section # and Name	Description of Change	Brief Rationale
		screening) visit to become eligible. Rescreening is only permitted once for each relevant amendment.
6.5.2 Baseline (Run-In Failures)	Addition of Section 6.5.2 to differentiate screen failures from baseline failures	• To clarify the differences between "screen failures" and "baseline failures" within the study • To clarify what assessments are required at Visit 3 when a baseline failure has been confirmed in order to minimize burden to a participant who will not complete the entire study
7.7 Concomitant Therapy	• Addition of "topical agents including topical corticosteroids" to the list of medicines that must be recorded within the eCRF • Addition of "(including any topical medications and rescue therapy) to the "Note" in this section	• To clarify that use of topical medications must be accounted for within the eCRF • To clarify that topical medications and rescue therapy used during the Final Study Period and reported in the Follow Up Telephone Contact will be recorded within the eCRF
7.7.1 Prohibited Medications	Deletion of immunosuppressant medications which are now permitted at stable doses according to the revised exclusion criterion 9 (Section 6.2)	To ensure consistency with the revised exclusion criterion
7.7.1 Prohibited Medications	Addition of other IBAT inhibitors as a prohibited medication	To ensure consistency with the new exclusion criterion 14
7.7.2 Permitted Medications	Addition of the sentence, "All use of any concomitant medications, including topical agents, must be recorded within the eCRF."	To clarify that topical agents may be used and to emphasize that all concomitant medications must be recorded within the eCRF
7.7.2 Permitted Medications	Under "UDCA;" "Rifampicin, naltrexone, naloxone, nalfurafine, or sertraline;" and "Bezafibrate or fenofibrate;" the words "…and the Follow Up	To clarify that during *both* the Final Study Period *and* the Follow Up Period use of these particular agents may be permitted

Section # and Name	Description of Change	Brief Rationale
	Period" were inserted after, "During the Final Study Period."	
7.7.2: Permitted Medications	Addition of "Colchicine, methotrexate, azathioprine, or systemic corticosteroids may be used as long as the dose has remained stable for 2 months prior to screening and that no change in dose is anticipated for the duration of the study. 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."	The trial population will more closely reflect the intended treatment population.
7.7.3 Rescue Therapy	The words, "…and the Follow Up Period" were inserted after the phrase "During the Final Study Period" in the first sentence	To clarify that during *both* the Final Study Period *and* the Follow Up Period use of these particular agents may be permitted
7.7.3 Rescue Therapy	Clarification that use of rescue therapy should be recorded in the eCRF	To emphasize that rescue therapy, like any other therapy given during the trial, should be recorded in the eCRF
8.1.1 Liver Chemistry Stopping Criteria	Change of the section title from "Liver Chemistry Stopping Criteria" to "Liver Chemistry ***Increased Monitoring and*** Stopping Criteria"	To clarify that this section contains both the increased monitoring and stopping criteria, and to emphasize that these criteria are different from each other
8.1.1 Liver Chemistry Increased Monitoring and Stopping Criteria	• Insertion of Table 4 heading for **Liver Chemistry Criteria for Increased Monitoring**; addition of an action column, and simplification of the table format • Insertion of Table 5 heading for **Liver Chemistry Criteria for Stopping Study Treatment**; addition of	• To provide easier identification of the Tables within the protocol and provide clarity on follow-up actions • To ensure in this population with abnormal baseline liver chemistry that frequency of liver chemistry monitoring is increased or study treatment is stopped at the most appropriate time to maintain participant safety. For most participants, this is a "fold increase from baseline" in ALT or

Section # and Name	Description of Change	Brief Rationale
	an action column, and simplification of the table format • Revision of thresholds for increased monitoring of liver chemistry and for stopping study treatment to be defined principally in terms of "fold change from baseline values" while retaining some definitions in "fold of change from ULN values" in extreme cases. Revision of section text to refer to liver chemistry criteria for increased monitoring and stopping of study treatment	total bilirubin values. For those with the largest baseline abnormalities, an absolute stopping threshold defined in multiples of ULN is retained. • To clarify that repeat testing applies to both increased monitoring and stopping criteria, and that "stopping" refers to stopping of study treatment • To improve clarity by aligning requirements for stopping criteria to Appendix 4
8.1.2 QTc Stopping Criteria	• Amendment of threshold for stopping study treatment to QTc ≥530 msec • Removal of criteria for bundle branch block	The trial population will more closely reflect the intended treatment population. Since the exclusion criteria was changed, the stopping criteria had to be changed accordingly to ensure that study treatment is stopped appropriately in the event of QTc prolongation. As previously, an increase in QTc of >60 msec will also trigger study treatment discontinuation.
9.1.1 Electronic Data Collection	Change of "eDevice" to "TrialMax Slate"	To clarify that the electronic device that is used in the clinic is called a "TrialMax Slate"
9.1.2.1 Patient Reported Symptom Questionnaires	Update of the interference of itch with sleep NRS to indicate that a score of CCI represents CCI [redacted]	To correct an error and to align with the eDiary
9.2.1 Time Period and Frequency for	Clarification that SAEs should be reported to the Sponsor immediately and reporting must	Administrative update of Sponsor-required protocol text

Section # and Name	Description of Change	Brief Rationale
Collecting AE and SAE Information	not exceed 24 hours from the time that the site is notified	
9.4.4 Clinical Safety Laboratory Assessments	Deletion of final bullet requiring collection in the eCRF of non-protocol specified local laboratory values that are considered clinically significant or that result in a change in the participant's management. (Note AEs/SAEs associated with laboratory findings continue to be reported in the eCRF).	Administrative update of Sponsor-required protocol text
10.1 Sample Size Determination	Change from "Table 4" to "Table 6"	To realign the table numbers within the protocol after providing numbers to other tables within the document
10.3.4 Interim Analyses	Removal of the word "Sponsor's"	To clarify that trial leadership will review the results of the analysis
12.2. Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information	• Change from "Table 5" to "Table 7" • Removal of footnote "b" superscript	• To realign the table numbers within the protocol after providing numbers to other tables within the document • No footnote "b" exists in the table.
12.3. Appendix 3: Study Governance Considerations	• Sub-section on **Informed Consent Process:** deletion of paragraph beneath bullets • Added section called "Dissemination of Clinical Study Data"	• Included in error since use of remaining mandatory biomarker samples for optional exploratory research does not apply • Administrative update of Sponsor-required protocol text
12.4 Appendix 4: Liver Safety: Required Actions and	• Insertion of Figures 3 and Figures 4	• To facilitate understanding of how to implement the liver criteria for increased monitoring and for stopping study treatment

Section # and Name	Description of Change	Brief Rationale
Follow-up Assessments	• Insertion of Section header 12.4.1 (Procedures When Liver Stopping Criteria are Met) above pre-existing text (unchanged). • Reordering of bulleted list under 12.4.1	• To improve clarity • To list the actions in the likely order they will be conducted
12.5 Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Under SAE Reporting to GSK via Electronic Data Collection Tool: revision of second bullet to clarify that if the electronic system is unavailable, the paper reporting tool should be used to ensure SAE reporting within 24 hours.	Administrative update of Sponsor-required protocol text
12.6 Appendix 6: Clinical Laboratory Tests	Change Table from Table 6 to Table 8	To realign the table numbers within the protocol after providing numbers to other tables within the document

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1. SYNOPSIS

Protocol Title: A randomized, double-blind, multi-dose, placebo-controlled study to evaluate the efficacy, safety and tolerability of GSK2330672 administration for the treatment of pruritus in patients with primary biliary cholangitis.
*(**GLIMMER: G**SK2330672 tria**L** of **I**BAT inhibition with **M**ultidose **M**easurement for **E**valuation of **R**esponse).*

Short Title: Dose response study of GSK2330672 for the treatment of pruritus in patients with primary biliary cholangitis.

Rationale:

This study is being conducted to evaluate the efficacy, safety, and tolerability of a range of doses of GSK2330672 for the treatment of adults with moderate to severe pruritus associated with primary biliary cholangitis (PBC).

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To investigate the dose response of oral GSK2330672 on itch in PBC patients with moderate to severe pruritus at Baseline.	• Mean change from Baseline at Week 16 in the Mean Worst Daily Itch Score[1].
Key Secondary	
• To characterize the effects of GSK2330672 compared to placebo on impact of symptoms and quality of life in PBC patients with moderate to severe pruritus at Baseline.	• Mean change from Baseline at Week 16 in PBC-40 Scale.
• To evaluate the effects of GSK2330672 compared to placebo on markers of disease among participants at high risk of PBC progression (i.e., those with serum alkaline phosphatase [ALP] concentrations ≥1.67x upper limit of normal [ULN] and/or total bilirubin concentrations >ULN at Day 1).	In participants meeting the criteria for high risk of PBC progression: • Mean change from Baseline at Week 16 in serum ALP concentrations. • Proportion of participants having serum ALP concentrations <1.67x ULN and total bilirubin concentrations ≤ULN at Week 16. • Mean change from Baseline at Week 16 in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total bilirubin and albumin concentrations, and prothrombin time/international normalised ratio (PT/INR).

Objective	Endpoint
Other Secondary	
• To determine the safety and tolerability of GSK2330672 compared to placebo in PBC patients with moderate to severe pruritus at Baseline.	• Adverse events (AEs), clinical laboratory parameters, electrocardiograms (ECGs) and vital signs and the Gastrointestinal Symptoms Rating Scale (GSRS).

• To evaluate to the effects of GSK2330672 compared to placebo on itch response rates in PBC patients with moderate to severe pruritus at Baseline.	• Proportion of participants who are responders at Week 16 based on each of the following separate definitions:
	  • Mean Worst Daily Itch Score[1] of <4.
	  • At least a 30% reduction from Baseline in the Mean Worst Daily Itch Score[1].
	  • At least a 2-point reduction from Baseline in the Mean Worst Daily Itch Score[1].
	• Mean number of responder days during Weeks 5 to 16 based on each of the following separate responder day[2] definitions:
	  • Worst Daily Itch Score of <4.
	  • Worst Daily Itch Score at least 30% lower than the Baseline Mean Worst Daily Itch Score.
	  • Worst Daily Itch Score at least 2-points lower than the Baseline Mean Daily Score.

• To further characterize the effects of GSK2330672 compared to placebo on symptoms and quality of life in PBC patients with moderate to severe pruritus at Baseline.	Change from Baseline at Week 16 in: • Mean Daily Sleep Score[3]. • Mean Daily Fatigue Score[4]. • 5-D Itch scale
• To evaluate the effects of GSK2330672 compared to placebo on total serum bile acid concentrations and on bile acid synthesis in PBC patients with moderate to severe pruritus at Baseline.	• Mean change from Baseline at Week 16 in serum concentrations of total bile acids and serum 7-α-hydroxy-4-cholesten-3-one (C4) as a marker of bile acid synthesis.

Objective	Endpoint
• To investigate the pharmacokinetics (PK) of oral GSK2330672 in PBC patients with moderate to severe pruritus at Baseline.	• Plasma concentrations of GSK2330672 after sparse sampling (PK parameters will be reported if data permit).

1. Mean Worst Daily Itch Score: participant's itch severity is recorded on an electronic diary (eDiary) each morning and evening using a 0-10 numerical rating scale (NRS), the Worst Daily Itch Score is averaged over the 7 days preceding randomization at Visit 3 (Baseline) and over the 7 days preceding Visit 6 (Week 16).
2. A responder day is based on the Worst Daily Itch Score recorded using the 0-10 NRS for that day. When the responder day definition is relative to Baseline, the Worst Daily Itch Score is compared to the Mean Worst Itch Daily Score for Baseline (see 1 above).
3. Mean Daily Sleep Score: participant's sleep quality is recorded on the eDiary each morning using a 0-10 NRS and the Daily Sleep Score is averaged over the 7 days preceding randomization at Visit 3 (Baseline) and over the 7 days preceding Visit 6 (Week 16).
4. Mean Daily Fatigue Score: participants fatigue level is recorded on the eDiary each evening using a 0-10 NRS and the Daily Fatigue Score is averaged over the 7 days preceding randomization at Visit 3 (Baseline) and over the 7 days preceding Visit 6 (Week 16).
   Note:
   For all other endpoints Baseline is defined as the Visit 3 assessment and Week 16 is defined as the Visit 6 assessment.
   In addition to Week 16, which is the primary time point of interest, other intermediate time points will also be assessed.

Overall Design:

This is a phase IIb, multicenter, randomized, double-blind, placebo-controlled, parallel group, five arm dose-finding study in adults with moderate to severe pruritus associated with PBC. The study has an adaptive design which aims to utilize interim data to further inform and potentially optimize the doses under investigation.

Following the Screening Visit, there will be four study periods:

- Initial Study Period: Single-blind placebo treatment for 4 weeks during which participant's symptoms will be recorded in the electronic diary (eDiary) to establish baseline symptoms and assess eligibility for randomization and compliance with study procedures.
- Main Study Period: Eligible participants will be randomized to receive 12 weeks double-blind treatment with either placebo or one of 4 doses of GSK2330672 administered either once daily or twice daily. Randomization will be stratified based on participant's risk of PBC disease progression based on serum alkaline phosphatase (ALP) and total bilirubin concentrations at Day 1. Participants will attend study visits every 4 weeks.
- Final Study Period: Single-blind placebo treatment for 4 weeks to assess symptoms and safety post-completion of double-blind treatment.
- Follow-up Period: to assess symptoms and use of anti-pruritus medications by telephone visit.

Eligible participants may continue to receive some therapies for the treatment of PBC provided these are maintained at stable doses and there is no plan to discontinue them during the study. Concomitant use of cholestyramine, colesevalem, colestimide or colestipol is not permitted until after completion of the Main Study Period. Obeticholic acid use is not permitted at any time during the study.

In addition, an exploratory Actigraphy Sub-study will be conducted in a sub-set of participants who give consent.

Number of Participants:

Approximately 150 adult participants with PBC and moderate to severe pruritus will be screened to achieve approximately 118 randomized and approximately 100 evaluable participants overall. Should emerging data diverge significantly from protocol assumptions, the total sample size will be adjusted to include up to 160 randomized participants, and approximately 200 screened participants.

If during the study screen failure rates are higher than anticipated, the number of screened participants may be increased.

Treatment Groups and Duration:

- Following the Screening Visit (Visit 1) eligible participants will enter the Initial Study Period within 45 days.
- Initial Study Period: Single-blind placebo treatment for 4 weeks. Participants will commence single-blind study treatment at Visit 2 (Day 1).
- Main Study Period: Eligible participants will be randomized to receive 12 weeks double-blind treatment with either placebo or one of 4 dose regimens of GSK2330672 (20 mg, 90 mg or 180 mg taken once daily or 90 mg twice daily).
- Final Study Period: Single-blind placebo treatment for 4 weeks.
- Follow-up Period: 4 weeks.

A participant's total duration of study participation will be approximately 24 weeks from Visit 2 (Day 1) of the Initial Period to completion of the Follow-up Telephone Visit.

All study treatment will be administered orally twice daily, using placebo tablets as necessary to blind dose and regimen. During the Initial, Main and Final Study Periods it is important that participants remain blind to changes in study treatment e.g. from single-blind placebo to randomized double-blind treatment and subsequently to single-blind placebo. Investigator and study site staff communication with participants should ensure maintenance of each participant's blinding to treatment throughout the study.

Based on interim data, the study may be adapted to remove or add dose regimens of GSK2330672 up to a maximum total daily dose of 360 mg.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Schedule of Activities

	Screening	**Initial Study Period**	**Main Study Period**				**Final Study Period**	**Follow-up Period (FU)**	**Early End of Treatment or Study Withdrawal Assessments[1]**
Visit Name	**Visit 1 (Screening)**	**Visit 2 (Day 1)**	**Visit 3[11] (Baseline/ Week 4)**	**Visit 4 (Week 8)**	**Visit 5 (Week 12)**	**Visit 6 (Week 16)**	**Visit 7 (Week 20)**	**Visit 8 (End of FU Phone Visit/ Week 24)**	
Day number (window)	Day -45 to -1	Day 1	Day 28 (Day 28 to 35)	Day 56 (Day 56 to 63)	Day 84 (Day 84 to 91)	Day 112 (Day 112 to 119)	Day 140 (Day 140 to 147)	Day 168 (Day 168 to 175)	
Procedure									
Screening procedures	X[2]								
Brief physical exam inc. weight		X	X	X	X	X	X		X
Concomitant medications	X[2]	X	X	X	X	X	X		X
12-lead ECG	X[2]	X	X	X	X	X	X		X
Vital signs (HR and BP)	X[2]	X	X	X	X	X	X		X
Pregnancy test (urine dipstick) in WOCBP	X[2]	X[3]	X	X	X	X	X		X
Clinical laboratory tests[4]	X[2]	X	X	X	X	X	X		X
AE Assessment		X	X	X	X	X	X		X
Study treatment dispensing		X	X	X	X	X			
Study treatment administration		<----------Participants administer morning and evening each day---------->							
Study treatment compliance			X	X	X	X	X		
Final eligibility and Randomization			X[12]						

	Screening	**Initial Study Period**	**Main Study Period**				**Final Study Period**	**Follow-up Period (FU)**	**Early End of Treatment or Study Withdrawal Assessments[1]**
Visit Name	**Visit 1 (Screening)**	**Visit 2 (Day 1)**	**Visit 3[11] (Baseline/ Week 4)**	**Visit 4 (Week 8)**	**Visit 5 (Week 12)**	**Visit 6 (Week 16)**	**Visit 7 (Week 20)**	**Visit 8 (End of FU Phone Visit/ Week 24)**	
Day number (window)	Day -45 to -1	Day 1	Day 28 (Day 28 to 35)	Day 56 (Day 56 to 63)	Day 84 (Day 84 to 91)	Day 112 (Day 112 to 119)	Day 140 (Day 140 to 147)	Day 168 (Day 168 to 175)	
PD/Biomarker blood samples[4]			X	X	X	X	X		X
FOBT[5]			X			X			
Genetics sample[6]			X						
PK samples[7]			X	X	X				
Symptom eDiary		<----------Morning and evening each day---------->							
GSRS and GI symptoms on eDiary		<----------Once weekly---------->							
PBC-40 Scale	X[2]	X	X	X	X	X	X		X
5D-Itch Scale		X	X			X	X		X
EuroQOL 5D-5L		X	X			X			X
PGI-S		X	X	X	X	X	X		X
PGI-C			X	X	X	X	X		X
BDI-II	X[2]		X			X			X
Actigraphy[8]		X		X	X				
Participant Treatment Experience Assessment						X			X[9]
Telephone review[10]								X	

Footnotes:

1. Early End of Treatment Assessments to be completed for participants who prematurely discontinue study treatment following randomization (see Section 8.1). Study Withdrawal Assessments to be completed for participants who withdraw consent for any further participation in the study following randomization (see Section 8.2). Note: If a participant discontinues study treatment at the same time they withdraw from the study, only the End of Treatment Assessments are required.
2. See Table 2 for detailed description of Screening Procedures.
3. Urine dipstick pregnancy test will be standard unless serum testing is required by local regulation or IRB/IEC. Urine dipstick test at Visit 2 not required if the screening test was

performed <1 week of Visit 2.
4. For clinical laboratory tests see Section 9.4.4 and biomarkers see Section 9.8. All laboratory and biomarker assessments will be fasting (water, study treatment and other medications are permitted) except for Screening Visit.
5. FOBT (card test on 2 different stool/fecal samples) will be performed by participant at home prior to the visit.
6. Genetics sample in randomized participants only, to be collected preferably at Visit 3, but may be collected at Visit 4.
7. PK sample at Visit 3 for participants on UDCA only. At other visits, two plasma samples will be collected on each PK occasion in all participants (see Section 9.5). If PK sample collection is not collected at Visit 5 it may alternatively be collected at Visit 6. Note: PK sample collection is not required for participants who have prematurely discontinued study treatment and have not taken study treatment on the 3 or more days prior to the Visit.
8. Participants who give consent for the Actigraphy Sub-study will be given actigraphy monitors at Visit 2, Visit 4 and Visit 5 with activity measurements performed over at least 5 nights during Weeks 2 or 3, 9 or 10, and 13 or 14 respectively (see Section 9.1.3).
9. Participant Treatment Experience Assessment only required for Early End of Treatment Assessments.
10. End of Follow Up Telephone Visit to review participant's itch and anti-pruritus medications.
11. In the event of a **confirmed** baseline (run-in) failure at Visit 3, blood, urine, ECG, and TrialMax Slate assessments are not required, and no further study treatment will be dispensed. If the FOBT has been collected and returned by the participant, it should be sent to the laboratory for evaluation. Refer to Section 6.5.2 for more information.
12. Randomization criteria must be met at this visit for a participant to be randomized. Refer to Section 6.3.

Abbreviations:
AE= Adverse Event; BDI-II= Beck Depression Inventory-II; BP= Blood Pressure; ECG= Electrocardiogram; EQ-5D= EuroQOL 5D-5L; FOBT= Fecal Occult Blood Test; GI= gastrointestinal; GSRS= Gastrointestinal Symptoms Rating Scale; HR= Heart Rate; IEC= Independent Ethics Committee; IRB= Institutional Review Board; PD= Pharmacodynamic; PGI-S= Patient Global Impression of Severity; PGI-C= Patient Global Impression of Change; PK= Pharmacokinetics; UDCA= Ursodeoxycholic acid; WOCBP= Women of Child Bearing Potential

- For assessments scheduled at the same visit, where possible they should be performed in the following order: fasting blood tests and pharmacokinetic (PK) sample (1-3 hour post-dose), patient reported outcomes (PROs) [i.e., PGI-S, PGI-C, PBC-40, 5D-Itch, EQ-5D, BDI-II, Participant Treatment Experience Assessment], ECGs, vital signs, physical exam, other assessments, PK sample (5-8 hours post-dose). See Section 9 for further details.
- All reasonable attempts should be made to ensure compliance with the visit schedule, however participants will not be considered out of compliance if visit windows extend because of extraordinary events that make it impossible for participants to complete a visit within the required window. Determination of the maximum visit window deviation is at the discretion of the Medical Monitor.
- The timing and number of planned study assessments specifically PK or pharmacodynamic (PD)/biomarkers assessments 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.

- Any changes in the timing or addition of time points for any planned study assessments specified above must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The Institutional Review Boards (IRB)/ Independent Ethics Committees (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF).

Table 2 Screening Procedures

	Screening Visit 1	**Notes**
Window	**Day -45 to -1**	
Procedure		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Demography	X	
Full physical examination including height and weight	X	
Medical history (includes substance usage, family history of liver disease, cancer and cardiovascular disease)	X	Substances: alcohol and tobacco
Past and current medical conditions, including PBC and pruritus history, and associated medications	X	Includes use and response to UDCA, cholestyramine, colesevalem and other anti-pruritus medications
PBC-40 Scale	X	
BDI-II	X	
12-lead ECG	X	
Vital signs	X	
Laboratory assessments (non-fasting), including liver chemistries	X	
Urine dipstick pregnancy test (WOCBP only)[1]	X	
Hepatitis B and C screening	X	

Footnotes:
1. Urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.

Abbreviations
BDI-II= Beck Depression Inventory-II
ECG= electrocardiogram
PBC= Primary Biliary Cholangitis
WOCBP = Women Of Child Bearing Potential
UDCA = Ursodeoxycholic acid

3. INTRODUCTION

GSK2330672 is a selective inhibitor of the human ileal bile acid transporter (IBAT) that is being developed as a novel, oral treatment for pruritus associated with primary biliary cholangitis (PBC).

3.1. Study Rationale

This study is being conducted to evaluate the efficacy, safety and tolerability of a range of doses of GSK2330672 for the treatment of adults with moderate to severe pruritus associated with PBC. A secondary objective is to evaluate the potential of GSK2330672 to improve markers of disease progression in PBC patients at increased risk of developing advanced disease.

3.2. Background

Primary biliary cholangitis is a rare, chronic condition caused by the inflammatory destruction of the intrahepatic bile ducts giving rise to impaired bile acid flow and retention in the liver, leading to hepatic scarring, fibrosis and ultimately cirrhosis and liver failure. A major symptom associated with PBC is pruritus, which is an intense itching that can occur anywhere on the body, often resulting in disturbed sleep and having a significant impact on a patient's quality of life. Currently there are few therapies that provide effective relief of pruritus.

Located in the distal ileum of the gastrointestinal tract, IBAT is responsible for the active reuptake of bile acids from the gut lumen that are then returned to the liver via the portal vein, resulting in efficient enterohepatic conservation of bile acids, and negative feedback regulation of hepatic bile acid synthesis.

For patients with PBC, inhibition of IBAT by GSK2330672 is anticipated to increase excretion of bile acids and reduce bile acid concentrations in the liver and systemic circulation, resulting in reduced pruritus and associated symptoms. The associated alterations in hepatic bile acids have the potential to reduce liver damage and slow PBC disease progression.

A previous study in 22 PBC patients with pruritus (GSK study BAT117213) demonstrated an improvement in patient-reported itch symptoms during 14 days treatment with GSK2330672 90mg twice daily compared to placebo. Where improvements in itch were observed, they were evident by 7 days of treatment and continued through the treatment period. Most itch scores began to worsen following end of treatment with the majority not returning to baseline within 2 weeks. The present study is designed to further assess the drug's therapeutic potential in terms of efficacy, durability of effect, dose-response relationship, safety and tolerability.

A detailed description of the chemistry, pharmacology, efficacy, and safety of GSK2330672 is provided in the Investigator's Brochure (IB).

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of GSK2330672 may be found in the IB and Participant Information Leaflet.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product [GSK2330672]		
• Gastrointestinal effects including diarrhea.	• Animal studies including altered bowel motions (see IB Section 4.5). • AEs in humans including loose stools (see IB Section 5.3).	• Exclusion of participants with current diarrhea (see Section 6.2).
• Potential gallstones due to interruption of enterohepatic recirculation of bile acids.	• Report of gallstone-related AE in human studies (see IB Section 5.3).	• Exclusion of participants with current symptomatic cholelithiasis or inflammatory gall bladder disease (see Section 6.2).
• Hypertriglyceridemia due to interruption of enterohepatic recirculation of bile acids.	• Slight increases in triglycerides seen in humans (See IB Section 5.3).	• Monitoring of lipid profiles (see Section 9.4.4).
• Increase in alanine aminotransferase (ALT).	• Minor reversible ALT elevations reported in healthy volunteers and patients with type 2 diabetes (see IB Section 5.3).	• Stopping rules for liver chemistry (see Section 8.1.1). • Monitoring of liver chemistry (see Section 9.4.4).
Study Procedures		
• Potential risk the participant does not follow the correct study treatment administration due to the number of bottles dispensed.	• To maintain the blind across study treatment groups and study periods, participants will be dispensed several bottles of study treatment and are	• Bottles are clearly labelled for morning and evening dosing, and the number of tablets to take (see Section 7.1.1). A dosing card with instructions will also

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	required to take tablets from each bottle (see Section 7.1.1). If the participant misunderstands the instructions or confuses the bottles, study treatment may be administered incorrectly.	be given to the participant. • Investigator and site staff training, and a pharmacy manual will be provided.

3.3.2. Benefit Assessment

Potential benefits of study participation include:

- Possible improvement in symptoms of pruritus associated with PBC during study treatment.
- 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.

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with GSK2330672 are justified by the anticipated benefits that may be afforded to participants with pruritus associated with PBC.

4. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
• To investigate the dose response of oral GSK2330672 on itch in PBC patients with moderate to severe pruritus at Baseline.	• Mean change from Baseline at Week 16 in the Mean Worst Daily Itch Score[1].
Key Secondary	
• To characterize the effects of GSK2330672 compared to placebo on impact of symptoms and quality of life in PBC patients with moderate to severe pruritus at Baseline.	• Mean change from Baseline at Week 16 in PBC-40 Scale.
• To evaluate the effects of GSK2330672 compared to placebo on markers of disease among participants at high risk of PBC progression (i.e., those with serum ALP concentrations ≥1.67xULN and/or total bilirubin concentrations >ULN at Day 1).	In participants meeting the criteria for high risk of PBC progression: • Mean change from Baseline at Week 16 in serum ALP concentrations. • Proportion of participants having serum ALP concentrations <1.67x ULN and total bilirubin concentrations ≤ULN at Week 16. • Mean change from Baseline at Week 16 in serum ALT, AST, GGT, total bilirubin and albumin concentrations and PT/INR.

Objective	Endpoint
Other Secondary	
• To determine the safety and tolerability of GSK2330672 compared to placebo in PBC patients with moderate to severe pruritus at Baseline.	• AEs, clinical laboratory parameters, ECGs, vital signs and the GSRS.

• To evaluate the effects of GSK2330672 compared to placebo on itch response rates in PBC patients with moderate to severe pruritus at Baseline.	• Proportion of participants who are responders at Week 16 based on each of the following separate definitions:
	  • Mean Worst Daily Itch Score[1] of <4.
	  • At least a 30% reduction from Baseline in the Mean Worst Daily Itch Score[1].
	  • At least a 2-point reduction from Baseline in the Mean Worst Daily Itch Score[1].
	• Mean number of responder days during Weeks 5 to 16 based on each of the following separate responder day[2] definitions:
	  • Worst Daily Itch Score of <4.
	  • Worst Daily Itch Score at least 30% lower than the Baseline Mean Worst Daily Itch Score.
	  • Worst Daily Itch Score at least 2-points lower than the Baseline Mean Daily Score.

• To further characterize the effects of GSK2330672 compared to placebo on symptoms and quality of life in PBC patients with moderate to severe pruritus at Baseline.	Change from Baseline at Week 16 in: • Mean Daily Sleep Score[3]. • Mean Daily Fatigue Score[4]. • 5-D Itch Scale.
• To evaluate the effects of GSK2330672 compared to placebo on total serum bile acid concentrations and on bile acid synthesis in PBC patients with moderate to severe pruritus at Baseline.	• Mean change from Baseline at Week 16 in serum concentrations of total bile acids and serum C4 as a marker of bile acid synthesis.

Objective	Endpoint
• To investigate the PK of oral GSK2330672 in PBC patients with moderate to severe pruritus at Baseline.	• Plasma concentrations of GSK2330672 after sparse sampling (PK parameters will be reported if data permit).
Exploratory	
• To evaluate participant's treatment experience and health status with GSK2330672 compared to placebo in PBC patients with moderate to severe pruritus at Baseline.	• Treatment benefits and disadvantages as elicited in a Participant Treatment Experience Assessment at Week 16. • Time to worsening of itch during Weeks 17-20 in participants with an improved Worst Daily Itch Score at Week 16 relative to Baseline. • Change from Baseline at Week 16 in EQ-5D-5L health dimensions and utility index. • Change from Baseline at Week 16 in Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C).
• To evaluate the effect of GSK2330672 compared to placebo on exploratory biomarkers of PBC and bile acid physiology in PBC patients with moderate to severe pruritus at Baseline.	• Change from Baseline at Week 16 in serum autotaxin, fibroblast growth factor-19 (FGF-19), enhanced liver fibrosis (ELF) test and individual serum bile acid species.
• To evaluate the effect of GSK2330672 compared to placebo on serum lipids and absorption of fat-soluble vitamins in PBC patients with moderate to severe pruritus at Baseline.	• Change from Baseline at Week 16 in fasting lipid profile, including direct low density lipoprotein (LDL) cholesterol. • Change from Baseline at Week 16 in Vitamins A, D, E and K.
• To evaluate the effect of GSK2330672 compared to placebo on depressive symptoms associated with PBC in PBC patients with moderate to severe pruritus at Baseline.	• Change from Baseline at Week 16 in the Beck Depression Inventory-II (BDI-II).
• To explore the effect of GSK2330672 on ursodeoxycholic acid (UDCA) concentrations in PBC patients with moderate to severe pruritus at Baseline.	• Plasma concentrations of UDCA after sparse sampling (in participants on UDCA).

Objective	Endpoint
• To evaluate the pharmacogenomics of PBC and response to GSK2330672 in PBC patients with moderate to severe pruritus at Baseline.	• Pharmacogenomics for genes related to PBC, pruritus and IBAT response (in consenting participants).
• To evaluate the potential of actigraphy to quantify scratching activity and sleep quality due to pruritus associated with PBC and to assess the effect of GSK2330672 on these parameters in PBC patients with moderate to severe pruritus at Baseline.	• Mean scratching event duration, and frequency (events/night) of specific scratching movements measured by wrist actigraphy and derived parameters (in participants in the Actigraphy Sub-study).

1. Mean Worst Daily Itch Score: participant's itch severity is recorded on an electronic diary (eDiary) each morning and evening using a 0-10 numerical rating scale (NRS), the Worst Daily Itch Score is averaged over the 7 days preceding randomization at Visit 3 (Baseline) and over the 7 days preceding Visit 6 (Week 16).
2. A responder day is based on the Worst Daily Itch Score recorded using the 0-10 NRS for that day. When the responder day definition is relative to Baseline, the Worst Daily Itch Score is compared to the Mean Worst Itch Daily Score for Baseline (see 1 above).
3. Mean Daily Sleep Score: participant's sleep quality is recorded on the eDiary each morning using a 0-10 NRS and the Daily Sleep Score is averaged over the 7 days preceding randomization at Visit 3 (Baseline) and over the 7 days preceding Visit 6 (Week 16).
4. Mean Daily Fatigue Score: participants fatigue level is recorded on the eDiary each evening using a 0-10 NRS and the Daily Fatigue Score is averaged over the 7 days preceding randomization at Visit 3 (Baseline) and over the 7 days preceding Visit 6 (Week 16).

   Note:

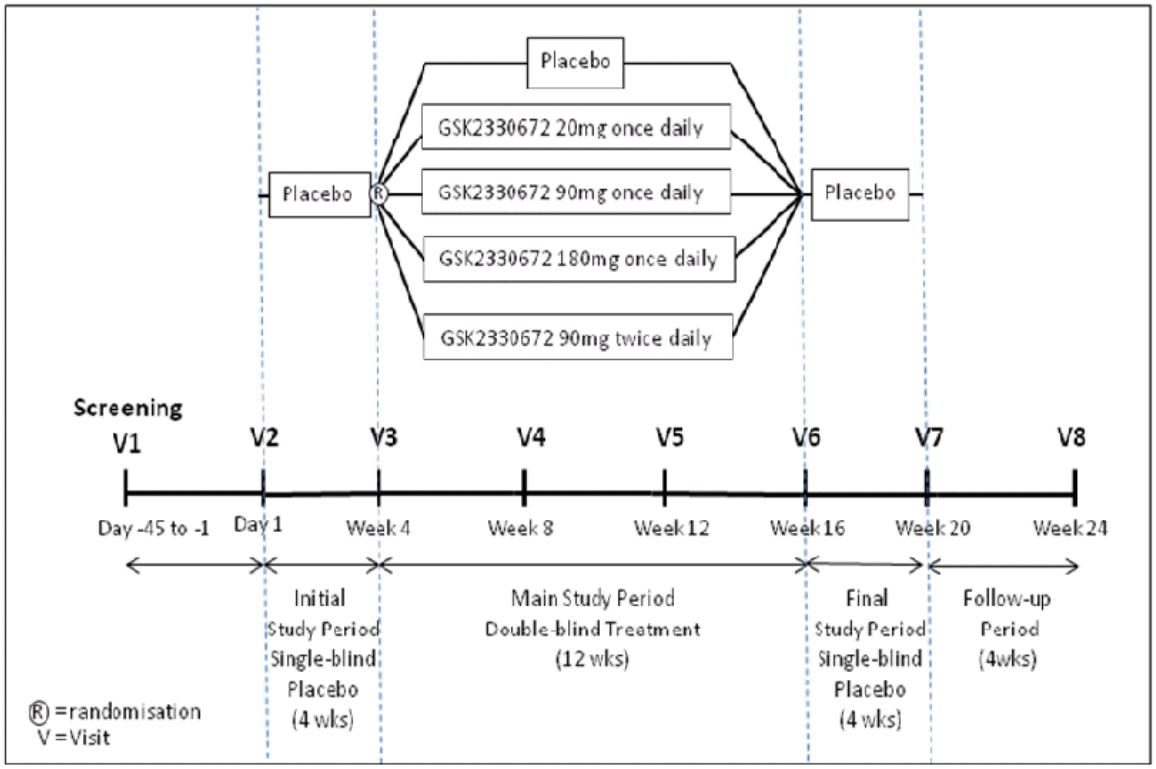
   For all other endpoints Baseline is defined as the Visit 3 assessment and Week 16 is defined as the Visit 6 assessment.

   In addition to Week 16, which is the primary time point of interest, other intermediate time points will also be assessed.

5. STUDY DESIGN

5.1. Overall Design

Figure 1 Study Schematic



This is a phase IIb, multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-finding study in adults with moderate to severe pruritus associated with PBC. The study has an adaptive design which aims to utilize interim data to further inform and potentially optimize the doses under investigation (see Section 10.3.4).

Following the Screening Visit, there will be four study periods:

- Initial Study Period: Single-blind placebo treatment for 4 weeks during which participants' symptoms will be recorded in the eDiary to establish baseline symptoms and assess eligibility for randomization and compliance with study procedures.
- Main Study Period: Eligible participants will be randomized to receive 12 weeks double-blind treatment with either placebo or one of 4 dose regimens of GSK2330672 (20 mg, 90 mg or 180 mg taken once daily or 90 mg twice daily). Randomization will be stratified based on participant's risk of PBC disease progression based on serum ALP and total bilirubin concentrations at Day 1 (see Section 7.3.1).
- Final Study Period: Single-blind placebo treatment for 4 weeks to assess symptoms and safety post-completion of double-blind treatment.

- Follow-up Period: to assess symptoms and use of anti-pruritus medications by telephone visit.

Eligible participants may continue to receive some therapies for the treatment PBC provided these are maintained at stable doses and there is no plan to discontinue them during the study. Concomitant use of cholestyramine, colesevelam, colestipol or colestimide is not permitted until after completion of the Main Study Period. Obeticholic acid use is not permitted at any time during the study.

All study treatment will be administered orally twice a day, using placebo tablets as necessary to blind dose and regimen. Participants will commence single-blinded study treatment at Visit 2 [Day1]. During the Initial, Main and Final Study Periods it is important that participants remain blind to changes in study treatment from single-blind placebo to randomized double-blind treatment and subsequently to single-blind placebo. Investigator and study site staff communication with participants should ensure maintenance of each participant's blinding to treatment throughout the study.

A participant's total duration in the study will be approximately 24 weeks from Day 1 to completion of the Follow-up Telephone Visit.

The study also includes an exploratory Actigraphy Sub-study which will be conducted at a limited number of study sites and in a sub-set of participants who give their consent.

5.2. Number of Participants

Approximately 150 adult participants with PBC and moderate to severe pruritus will be screened to achieve 118 randomized and 100 evaluable participants overall. Should emerging data diverge significantly from protocol assumptions, the total sample size will adjusted to include up to 160 randomized participants, and to approximately 200 screened participants (see Section 10.3.4).

If during the study the screen failure rate is higher than anticipated, the number of screened participants may be increased.

Participants are considered evaluable if they have taken at least one dose of double-blind study treatment and have both a Baseline and a Week 16 assessment for itch (see Section 10.1).

If participants discontinue single-blind study treatment during the Initial Study Period or do not meet the additional criteria for randomization (see Section 6.3), they will not be randomized or continue in the study and may be replaced.

Participants who prematurely discontinue double-blind study treatment after randomization will stay in the study and complete the remaining scheduled visits, if possible. Any participant who withdraws from the study after randomization will not be replaced.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all periods of the study including the Follow-up Telephone Visit. A participant is considered to have completed study treatment if he/she has taken study treatment through to the end of the Final Study Period (Visit 7).

The end of the study is defined as the date of the last Follow-up telephone contact of the last participant in the study.

5.4. Scientific Rationale for Study Design

The study is designed to evaluate the efficacy and safety of different doses of GSK2330672 and includes placebo to support the evaluation of treatment response. During the Main Study Period study treatment will be provided using randomized, double-blind methodology. Previous studies have demonstrated that patient-reported itch may show some improvement on placebo treatment, so placebo control is used in this study to help distinguish the effect of GSK2330672 relative to no treatment.

The use of single-blind placebo in the Initial Study Period will establish each participant's baseline level of itch, against which their response to GSK2330672 will be assessed. Participants whose itch score at the end of single-blind placebo (i.e. baseline) is too low to reliably detect an improvement on blinded study treatment, or who do not complete sufficient daily eDiary entries, will be withdrawn from the study at the end of the Initial Study Period.

The Final Study Period uses single-blind placebo to support the evaluation of the recurrence of symptoms upon cessation of blinded study treatment.

Assignment of randomized study treatment will be stratified according to the participant's risk of PBC progression at baseline, with the treatment allocation ratios varying across the two strata (see Section 7.3.1). This is intended to increase the ability of the study to detect any difference in change in markers of PBC progression between placebo and GSK2330672 in participants whose liver chemistry indicates an increased risk of disease progression.

The study duration has been chosen to ensure adequate time to assess the effect of GSK2330672, whilst minimizing the period of restrictions on use of concomitant medications and the associated inconvenience to participants with troublesome symptoms.

During the study, participants may continue to receive selected agents for the treatment of PBC (e.g. ursodeoxycholic acid [UDCA]), provided the dosage prior to and during the study, is stable. Prohibited agents include those that bind bile acids (cholestyramine, colesevelam, colestipol or colestimide) or that may exacerbate symptoms of pruritus (obeticholic acid), since their use during the study may compromise the efficacy and safety evaluation of GSK2330672 (see also Section 6.2). However, during the Final Study Period whilst receiving single-blind placebo, and during the Follow Up Period, if

participants report their itch has recurred or persists they may receive previous or new anti-pruritus therapies as clinically indicated (see Section 7.7).

The use of an adaptive design, with the evaluation of interim efficacy and safety data, will facilitate characterisation of the dose-response relationship of GSK2330672 (see Section 10.3.4).

5.5. Dose Justification

To date PBC patients have received GSK2330672 at a dose of 45 mg twice daily increased to 90 mg twice daily after 3 days and continued for 14 days in total. The dose range for the current study is based on responses observed in these PBC patients and in the biomarkers total serum bile acids and 7-α-hydroxy-4-cholesten-3-one (C4) measured in Type II diabetic (T2DM) patients. The IB provides further details on the findings in these studies.

The doses selected for the current study provide an initial range in order to characterize the effects of GSK2330672 on pruritus in PBC patients. Since the ED50 was observed to be in the range of 30 to 60 mg for both biomarkers in T2DM, a lower, potentially minimally effective dose of 20 mg was selected to explore the GSK2330672 dose associated with a minimum effect on itch. A 90 mg twice daily dose is included given its observed efficacy from the study in PBC patients. A 180 mg once daily dose is also included to determine if once daily dosing would have a similar impact on itch as twice daily dosing.

The study treatment arms planned for this study are:

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

Following the interim analysis, the GSK2330672 arms may be adapted up to a maximum total daily dose of 360mg (see Section 10.3.4). This dose has adequate nonclinical toxicology cover for local gastrointestinal tract exposure (based on administered oral dose, i.e., 7.2 mg/kg/day assuming 50 kg body weight): 139-fold No Observed Adverse Effect Level (NOAEL) in the rat and 69-fold NOAEL in the dog for local gastrointestinal tract exposure (mg/kg/day dose). Further information on nonclinical toxicology studies can be found in the IB.

6. STUDY POPULATION

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

To qualify for screening and enrollment, the prospective participant must present with pruritus associated with PBC. Prior to requesting informed consent, the investigator will review (where practical) a prospective participant's case notes or medical history, to evaluate his/her experience of itch and medications, to assess consistency with the inclusion/exclusion criteria.

Following the investigator's pre-screening assessment, potential participants will be asked to give their written informed consent prior to any study specific procedures being performed, and their eligibility assessed (see Section 6.1 and Section 6.2).

Screening procedures to be performed following completion of the informed consent process are listed in Table 2.

6.1. Inclusion Criteria

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

Age

1. Participant must be 18 to 80 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who have proven PBC, as demonstrated by having at least 2 of the following:

- History of sustained increased ALP levels >upper limit of normal (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 institution of UDCA therapy as described in inclusion number 4).
- Documented positive anti-mitochondrial antibody (AMA) titer (>1:40 titer on immunofluorescence or M2 positive by ELISA) or PBC-specific antinuclear antibodies (antinuclear dot and/or nuclear rim positive).
- Liver biopsy (at any time in the past) consistent with PBC.

3. Participants must rate their itch severity as being ≥4 on a 0 to 10-point scale for the majority of time (at least half the days, as recalled by the participant) during the 8 weeks prior to the Screening Visit. Periods of low itch or no itch are acceptable as long as the worst daily itch score is ≥4 on the majority of days.
4. Participants who are currently taking UDCA should be on stable doses of UDCA for >8 weeks at time of screening. Participants not taking UDCA due to

intolerance may be enrolled 8 weeks after their last dose of UDCA.
Note: no changes or discontinuation is permitted until completion of the Main Study Period.

Sex

5. Male and/or female**:**

a. Female participants:

A female participant is eligible to participate if she is not pregnant (see Appendix 2), not breastfeeding, and at least one of the following conditions applies:

i. Not a woman of childbearing potential (WOCBP) as defined in Appendix 2

OR

ii. A WOCBP who agrees to follow the contraceptive guidance in Appendix 2 during the treatment period and until at least 4 weeks after the last dose of study treatment.

Informed Consent

6. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

6.2. Exclusion Criteria

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

Medical Conditions

1. Screening total bilirubin >2x ULN. Total bilirubin >2x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%.
2. Screening ALT or aspartate aminotransferase (AST) >6x ULN.
3. Screening estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m² based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
4. History or presence of hepatic decompensation (e.g., variceal bleeds, encephalopathy or ascites).
5. Presence of actively replicating viral hepatitis B or C (HBV, HCV) infection and/or confirmed hepatocellular carcinoma or biliary cancer.

Note: Other hepatic conditions (e.g., primary sclerosing cholangitis (PSC), alcoholic liver disease, autoimmune hepatitis, non-alcoholic steatohepatitis [NASH] are permitted **if PBC is the dominant liver injury** in the investigator's opinion.

6. Current diarrhea.

7. Current symptomatic cholelithiasis or inflammatory gall bladder disease. Participants with history of cholecystectomy ≥3 months before screening may be eligible for enrollment.
8. Any current medical condition (e.g. psychiatric disorder, senility or dementia), which may affect the participant's ability to comply with the protocol specified procedures.

Prior/Concomitant Therapy

9. Initiation or increase in dose of colchicine, methotrexate, azathioprine, or systemic corticosteroids in the 2 months 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. *[Rationale: Limited evidence indicates these drugs may alter disease progression in some PBC patients.]*

10. Initiation or increase in dose of bezafibrate or fenofibrate at any time during the 3 months prior to screening. Participants may join the study on stable doses of these medications, but no change or discontinuation is permitted until completion of the Main Study Period. *[Rationale: limited evidence suggests fibrates may improve ALP and pruritus.]*
11. Initiation or increase in dose of any of the following in the 8 weeks prior to screening: rifampicin, naltrexone, naloxone, nalfurafine, or sertraline. Participants may join the study on stable or decreased doses of these medications, but no change in dose is permitted until completion of the Main Study Period. *[Rationale: There is limited evidence these drugs improve pruritus due to PBC.]*
12. Bile acid binding resin use: a participant must discontinue use of cholestyramine, colesevelam, colestipol or colestimide prior to the start of the Initial Study Period (no later than Day -2). Note: these drugs may be administered after completion of the Main Study Period, if clinically indicated. *[Rationale: these resins may bind GSK2330672 and interfere with its effects.]*
13. Obeticholic acid use: a participant must discontinue use of obeticholic acid at least 8 weeks prior to the start of the Initial Study Period and may not restart until after the end of the study. *[Rationale: obeticholic acid use can cause changes in ALP and pruritus which may confound evaluation of the effects of GSK2330672.]*
14. Administration of any other IBAT inhibitor in the 3 months prior to screening *[Rationale: Effects of another IBAT inhibitor may influence pruritus.]*

Prior/Concurrent Clinical Study Experience

15. Current enrollment or participation within the 8 weeks before start of the Initial Study Period, in any other clinical study involving an investigational study treatment.

Diagnostic assessments

16. 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. 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

17. History of sensitivity 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.
18. History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 measure (25 mL) of spirits.

6.3. Criteria for Randomization

Following completion of the Initial Study Period, participants will be required to meet the following criteria for randomization at Visit 3 [Week 4]:

- Participants with a Worst Daily Itch Score on the 0-10 numerical rating scale (NRS) which is ≥3 on at least 5 of the previous 7 days.
- Participant has entered data into the eDiary on at least 10 of the 14 required occasions in the previous 7 days.

Otherwise, the participant will stop participation in the study without additional follow-up after Visit 3 and will be considered a baseline (run-in) failure. The Study Reference Manual will contain details on how to access this eligibility information. Refer to Section 6.5.2 of the protocol for further information.

6.4. Lifestyle Restrictions

6.4.1. Meals and Dietary Restrictions

Following screening, participants will be required to attend all study visits having fasted for at least 6 hours (water, study treatments and other medications are permitted).

6.4.2. Caffeine, Alcohol, and Tobacco

There are no restrictions.

6.4.3. Activity

There are no restrictions.

6.5. Screen and Baseline Failures

6.5.1. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the Initial Study Period of 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, and any serious AEs (SAEs). Additionally, the PBC-40 Scale, current and previous treatments for pruritus associated with PBC, observed efficacy and side effects of those treatments and reasons for discontinuation will also be collected.

Some individuals who do not meet the criteria for participation in Initial Study Period may be rescreened. The only criteria for which this is acceptable are those related to the use of PBC or anti-pruritus medications (e.g., requirements on dose stability, minimum time since stopping therapy), where a delay in rescreening would allow the participant to become eligible. Participants should continue to meet all other eligibility criteria at the time of rescreening. Participants may only be rescreened once.

Additionally, participants who could become eligible as a result of a protocol amendment may be rescreened. Rescreening is only permitted where the participant would have met all the eligibility requirements of the amended protocol at the time of the first (original) screening visit. The rescreened participants must meet all the eligibility requirements at the time of the rescreening (subsequent screening) visit to become eligible. Rescreening is only permitted once for each relevant amendment.

All rescreened participants will be reconsented and assigned a new participant number.

6.5.2. Baseline (Run-In) Failures

Participants who do not complete the Initial Study Period or who do not meet the criteria for randomization at the end of the Initial Study Period (see Section 6.1) are considered baseline (run-in) failures and may not be rescreened without prior discussion with the Medical Monitor.

In the event of a **confirmed** baseline failure at Visit 3, the blood, urine, ECG, and TrialMax Slate assessments for Visit 3 are not required, and no further study treatment will be dispensed. If the FOBT has been collected and returned by the participant, it should be sent to the laboratory for evaluation.

The Visit 3 activities in the event of a baseline failure are listed in Table 1.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Study Treatment Name:	GSK2330672	Placebo
Dosage formulation:	White film-coated tablet	White film-coated tablet
Unit dose strength(s):	10 and 45 mg tablets	Tablets to match
Route of Administration	Oral	Oral
Packaging and Labeling	Study Treatment will be provided in 45 cc high density polyethylene bottles (HDPE) bottles. Each bottle will be labelled as required per country requirements.	Matching bottles
Storage conditions	Store up to 30°C (86°F)	Store up to 30°C (86°F)
Manufacturer	Wuxi Apptec	Wuxi Apptec

7.1.1. Study Treatment Administration

Study treatment will comprise:

- Initial Study Period: Single-blind placebo.
- Main Study Period: Double-blind randomized treatment of either placebo or one of 4 different dose regimens of GSK2330672.
- Final Study Period: Single-blind placebo.

Each study treatment will be provided to participants according to Table 3.

Table 3 Study Treatments

			GSK2330672			
		Placebo	**20 mg Once Daily**	**90 mg Once Daily**	**180 mg Once Daily**	**90 mg Twice Daily**
Bottles dispensed	Morning Dosing	2 bottles placebo	1 bottle 10 mg 1 bottle placebo	1 bottle 45 mg 1 bottle placebo	1 bottle 45 mg 1 bottle 45 mg	1 bottle 45 mg 1 bottle placebo
	Evening Dosing	1 bottle placebo	1 bottle placebo	1 bottle placebo	1 bottle placebo	1 bottle 45mg
Dosing Instructions on each bottle		Take 2 tablets in the morning [evening]	Take 2 tablets in the morning [evening]	Take 2 tablets in the morning [evening]	Take 2 tablets in the morning [evening]	Take 2 tablets in the morning [evening]

Each bottle will contain 70 tablets, sufficient for 35 days treatment. Participants should take their study treatment twice a day approximately 12 hours apart.

Following an interim analysis the study design may be adapted to add or remove dose regimens of GSK2330672 up to a maximum total daily dose of 360 mg. Blinding of study treatment across all study periods will be maintained. Consequently, depending on the dose/regimen selected, participants enrolled into the study after the interim may be dispensed either up to 3 bottles of study treatment for morning dosing or up to 2 bottles of study treatment for evening dosing. The maximum of number bottles that will be given to an individual participant at each dispensing will be 4. Participants will be instructed to take 2 tablets from each bottle. Further details are provided in the Study Reference Manual (SRM).

At the start of the Initial Study Period (Visit 2 [Day1]) participants meeting all inclusion criteria and no exclusion criteria will be dispensed study treatment and instructed on how to take their medication. Study treatment administration will start with the evening dose on the day of the study visit, but may be deferred to next morning if the participant prefers. Participants will continue taking study treatment twice a day as instructed and will return for their next study visit having fasted for at least 6 hours (water permitted) and having taken their morning dose of study treatment.

At the start of the Main Study Period (Visit 3 [Week 4]) participants randomized to double-blind study treatment will commence taking treatment that evening. They should return for each study visit having taken their morning dose fasted as above.

At the start of the Final Study Period (Visit 6 [Week 16]) participants will commence study treatment that evening, returning for their final clinic visit (Visit 7 [Week 20]) having taken their morning dose fasted as above.

At each study visit new bottles of study treatment will be dispensed in accordance with the SoA (see Section 2).

7.2. Dose Modification

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

7.3. Method of Treatment Assignment

During all study periods participants will be allocated study treatment using an Interactive Voice/Web Response System (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.

At the start of the Main Study Period all participants will be centrally randomized to double-blind study treatment using IVRS/IWRS, and randomization will be implemented based on a sequestered fixed randomization schedule, and will be blocked at the overall study level. The randomization schedule will be computer generated by GlaxoSmithKline (GSK) using the randomization system Randall. Participants will be stratified as outlined in Section 7.3.1. Blinded study site personnel will receive a randomization notification indicating the unique participant identifier (randomization number) and the date and time of randomization. Each randomization number will be a unique identifier. Once a randomization number has been assigned, the number will not be reused even if the participant is not administered any study treatment. Returned study treatment should not be re-dispensed to the participants.

Details of the treatment assignment process are contained in the SRM.

7.3.1. Treatment Assignment in the Study Periods

Initial Study Period

At Visit 2 [Day1] participants who meet all inclusion and no exclusion criteria will be allocated single blind placebo.

Main Study Period

At the Visit 3 [Week 4] participants meeting the randomization criteria will be allocated to double-blind study treatment in accordance with the randomization schedule. Randomization will be stratified according to region (Europe, North America, Japan) and the participant's risk of PBC progression at baseline based on serum ALP and total bilirubin concentrations obtained at Visit 2 [Day 1] as follows:

- ALP <1.67x ULN and total bilirubin ≤ULN (estimated 60% of participants), or
- ALP ≥1.67x ULN and/or total bilirubin >ULN (estimated 40% of participants).

Treatment allocation ratios will vary across these two strata (see Section 10.1). This is to increase the ability of the study to detect any difference in change in markers of PBC progression between placebo and active treatment in participants whose liver chemistry indicates increased risk of disease progression.

Final Study Period

At Visit 6 [Week 16] participants will be allocated single blind placebo.

7.4. Blinding

During the Initial, Main and Final Study Periods it is important that participants remain blinded to changes in study treatment from single-blind placebo to randomized double-blind treatment and subsequently to single-blind placebo. Investigator and study site staff communication with participants during the informed consent procedure and all subsequent study procedures/visits should ensure maintenance of each participant's blinding to treatment.

The IVRS/IWRS will be programmed with blind-breaking instructions. The double-blind may be broken if, in the opinion of the investigator, it is in the participant's best interest for the investigator or treating physician, to know the study treatment assignment. GSK must be notified before the double-blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition. In this case, GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

If the participant's treatment code is unblinded by the investigator or treating physician, the participant must discontinue study treatment, but remain in the study and complete all remaining study visits (see Section 8.1). The primary reason for the discontinuation of study treatment (i.e. the event or condition that led to the unblinding) will be recorded in the eCRF.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment 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 treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the SRM.

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

Blinded study treatment will be dispensed to participants at each study visit with sufficient tablets until the next visit based on the visit windows (see SoA [Section 2]). At each visit the participants will be required to return all unused study treatment.

When participants self-administer study treatment at home, they will be required to document missed doses of study treatment in their eDiary. Compliance with study treatment will be assessed through review of the eDiary and returned tablets, and by querying the participant during the study visits. Compliance will be documented in the source documents and eCRF. A record of the number of study treatment tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates will also be recorded in the eCRF.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, topical agents including topical corticosteroids, vitamins, and/or herbal supplements) that the participant has taken in the 3 months prior to Screening, or is receiving at the time of enrollment 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 and frequency

Note: Anti-pruritus medications (including any topical medications and rescue therapy) or other interventions during the Final Study Period and reported in the Follow-up Telephone Contact will be recorded in the eCRF.

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

7.7.1. Prohibited Medications

Other IBAT inhibitors: Use of any other IBAT inhibitor is not permitted at any time during the study.

Obeticholic acid: Use is not permitted at any time during the study and obeticholic acid should be discontinued at least 8 weeks before the start of the Initial Study Period.

Cholestyramine, colesevelam, colestipol or colestimide: Use of any of these agents is not permitted during the Initial or Main Study Periods and will be discontinued no later than one full day (i.e., no later than Day -2) before the start of the Initial Study Period (Visit 2). During the Final Study Period and the Follow Up Period, use of these agents may be permitted (see Section 7.7.3).

7.7.2. Permitted Medications

Other than the prohibited medications (see Section 7.7.1), participants may take medications for concomitant conditions or inter-current illness as necessary. **All use of any concomitant medications, including topical agents, must be recorded within the eCRF.**

Permitted agents for the treatment of PBC and its associated symptoms are as follows:

UDCA: Participants may be enrolled in the study on UDCA provided the dose has been stable during the 8 weeks prior to screening. No change or discontinuation is permitted until completion of the Main Study Period. Note participants not taking UDCA due to intolerance may be enrolled if their last dose was at least 8 weeks prior to screening (see Section 6.1). During the Final Study Period and the Follow Up Period UDCA may be permitted (see Section 7.7.3).

Participants taking UDCA will be required to not administer their morning dose of UDCA (if applicable) before each of the PK sampling visits and to record the time of their last UDCA dose (see Section 9.5).

Colchicine, methotrexate, azathioprine, or systemic corticosteroids: Use of these agents is permitted during the study as long as the dose has remained stable (i.e., unchanged) during the 2 months prior to the screening visit and the dose does not change throughout the study. 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 the Final Study Period and the Follow Up Period UDCA may be permitted (see Section 7.7.3).

Rifampicin, naltrexone, naloxone, nalfurafine, or sertraline: Participants may be enrolled into the study on stable or decreased doses of any of these agents. However, no dose increase is permitted until completion of the Main Study Period. Note: A participant is not eligible for the study if he/she started or had a dose increase in any of these agents during the 8 weeks prior to screening (see Section 6.2). During the Final Study Period and the Follow Up Period, use of these agents may be permitted (see Section 7.7.3).

Bezafibrate or fenofibrate: Participants may be enrolled in the study on stable doses of these medications, but no change or discontinuation is permitted until completion of the Main Study Period. Note: A participant is not eligible for the study if he/she started or had a dose increase in either of these agents during the 3 months prior to screening (see Section 6.2). During the Final Study Period and the Follow Up Period, use of these agents may be permitted (see Section 7.7.3).

Antihistamines: Participants may be enrolled on antihistamines if taken regularly and at a stable dose.

Anti-diarrheals: Participants experiencing diarrhea may take anti-diarrheal treatments obtained over-the-counter or prescribed by the investigator or another practitioner. Use of these treatments and their effect will be recorded at each review of concomitant medications.

7.7.3. Rescue Therapy

During the Final Study Period and Follow Up Period only, if participants' itching recurs or persists and they request additional therapy, they may resume their previous anti-pruritus medication if clinically indicated. If the participant's itching warrants new or increased doses of anti-pruritus therapy, this can be administered if clinically indicated. Other non-pharmacologic interventions may also be used (e.g., nasobiliary drainage) if clinically indicated. Use of any rescue therapy should be recorded within the eCRF.

7.8. Treatment after the End of the Study

The Sponsor will not provide treatment after the end of the study; participants should be managed according to their treating physician.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants may prematurely discontinue study treatment due to AEs or poor tolerance or for any other reason including withdrawal of consent. In all cases the participant should be encouraged to discuss any potential study treatment discontinuation with the investigator prior to stopping treatment.

Premature discontinuation of study treatment due to lack of efficacy is discouraged; where possible participants should be encouraged to remain on study treatment until the end of Final Study Period.

Participants who discontinue study treatment following randomization and before the scheduled end of the Final Study Period will complete Early End of Treatment Assessments (see SoA [Section 2]) before their last dose of study treatment, if possible. Participants will not be withdrawn from the study but should complete the remaining scheduled visits and assessments, including the eDiary, up to and including the end of the Final Study Period (Visit 7 [Week 20]) and undergo the End of Follow-up Telephone Visit (Visit 8 [Week 24]).

8.1.1. Liver Chemistry Increased Monitoring and Stopping Criteria

Liver chemistry increased monitoring and stopping criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

The study population will be recruited based on the presence of pre-existing hepatobiliary disease. Study specific withdrawal criteria have been instituted in consultation with internal GSK advisors and external experts.

Based upon screening lab results for serum ALT and total bilirubin, participants will be required to **return to the clinic or local specialist/collaborator within one week or sooner for repeat testing** (including AST, ALT, total bilirubin, ALP and PT/INR) **as indicated below** if any of the following liver chemistry criteria for increased monitoring or for stopping study treatment are met:

Table 4 Liver Chemistry Criteria for Increased Monitoring

Post-Screening Lab Result	Actions
ALT > 2x participant's screening ALT AND >3x ULN	Repeat liver chemistry testing **within 1 week** (AST, ALT, total bilirubin, ALP, and PT/INR). **Inform Medical Monitor.** Continue to monitor the above liver chemistries **at least weekly** until values stabilize or fall below the criteria for increased monitoring**.**

Study treatment will be stopped for a participant if **any** of the following liver chemistry stopping criteria are met:

Table 5 Liver Chemistry Criteria for Stopping Study Treatment

Post-Screening Lab Result	Actions
Total bilirubin > 2x participant's screening AND >1.5x ULN	**Stop study treatment immediately.** **Discuss with Medical Monitor within 24 hours**. Repeat liver chemistry testing (including AST, ALT, total bilirubin, ALP, and PT/INR) **within 24-72 hours** where possible **but within 1 week,** and thereafter **at least weekly** until values stabilize or fall below the criteria for increased monitoring. Refer to **Protocol Appendix 4** for further follow-up and monitoring requirements.
Total bilirubin >3x ULN	
ALT > 3x participant's screening ALT result AND > 5x ULN	
ALT >8x ULN of ALT	

In addition, study treatment will be stopped for a participant 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 symptoms which may typically be associated with drug-induced liver injury (including fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%]).

NOTE: Refer to Section 12.4.1 for details of the required assessments if a participant meets the above stopping criteria. Section 12.4 also provides diagrams to facilitate implementation of the criteria for increased monitoring and for stopping study treatment.

8.1.2. 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 electrocardiogram (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 treatment:

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

8.1.3. Renal Stopping Criteria

A serum creatinine stopping criterion has been included to support participant safety.

A participant's study treatment will be interrupted if there is an increase from Baseline (Visit 3) in serum creatinine of >0.3 mg/dL (26.52 μmol/L). The investigator should consult with the Medical Monitor to determine the appropriate evaluation and guidance on whether study treatment may be re-started.

8.1.4. Other Stopping Criteria

Female participants who become pregnant during the study should discontinue study treatment immediately (see Section 9.2.6).

8.1.5. Temporary Discontinuation

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

Participants who forget to take a dose of study treatment should take their next dose according to the dosing schedule.

8.1.6. Rechallenge

8.1.6.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

8.2. Withdrawal from the Study

- Participants should be encouraged to remain on study treatment and stay in the study completing study assessments (see Section 8.1). Where possible, the investigator should consider consultation with the Medical Monitor prior to withdrawing a participant from the study.
- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.
- 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 withdrawing from the study after randomization should undergo Study Withdrawal Assessments, if possible, and be asked if they may be contacted for an End of Follow-up Telephone Visit (see the SoA [Section 2]).

8.3. 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 with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (see Section 2).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Table 1), 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 (Table 1).
- 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 450 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Efficacy Assessments

9.1.1. Electronic Data Collection

An eDiary will be used to collect participant's daily symptoms and the weekly assessment of participant's gastrointestinal symptoms (GI) and the Gastrointestinal Symptom Rating Scale (GSRS) (see Section 9.1.2). Additionally, the eDiary will prompt participants to record aspects of their study treatment such as whether they have missed doses.

At the start of the Initial Study Period (Visit 2 [Day 1]) each participant will be provided with the eDiary and will be trained on its correct use, including how to complete the GSRS. During the study investigators and study site staff will have on-line access to their individual participant's eDiary data in order to monitor compliance with the completion requirements and compliance with study treatment.

At study visits participants will complete all Patient Reported Outcomes (PROs) measures using an electronic device called a TrialMax Slate; all participants will be trained on the use of the TrialMax Slate and on completion of the PROs.

The SRM provides further details on the use of the eDiary and TrialMax Slate, and on the completion of the PROs. Participants will be provided with a simple user manual to support correct use of the eDiary at home.

9.1.2. Patient Reported Outcomes (PROs)

All PRO measures will be completed by the participant before any other study procedures are performed, the only exception to this will be the collection of fasting laboratory tests (Note: Participants may consume a light snack before completing the PROs). The intent is to minimise the interaction with the investigator and study staff prior to completion of the PROs.

9.1.2.1. Patient Reported Symptom Questionnaire

Using the eDiary participants will record details of their symptoms of itch, and its impact on their sleep and level of fatigue. The eDiary will be completed twice each day, in the morning and evening approximately at the time of study treatment dosing.

- Participants will score the severity of their itching using a NRS from 0 to 10 where CCI represents CCI and CCI. The NRS recorded in the morning will characterize the itch experienced during the night-time, whilst the NRS recorded in the evening will characterize the itch experienced during the day-time hours. The Worst Daily Itch Score is the most severe (highest) NRS recorded on a given day.
- Each morning participants will also score the interference of itch on their sleep using a NRS from 0 to 10 where CCI represents CCI and CCI represents CCI CCI.
- Each evening participants will also score their level of fatigue using a NRS from 0 to 10 where CCI represents CCI and CCI represents CCI.

Other aspects of symptoms associated with PBC and study treatment will also be collected, including weekly assessment of participant's GI symptoms.

9.1.2.2. 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 was devised and validated with a 4 week recall period, which in this study will be modified to a recall period of 'the past 7 days'.

The PBC-40 scale will be administered with a 7 day recall period at Visits 2 through 7 [Day1 through Week 20] in the study, and if applicable at early study treatment discontinuation and at study withdrawal.

In addition, the PBC-40 will be performed at Screening (Visit 1) in all enrolled participants in order to investigate the quality of life and previous treatment experience in the population being considered for inclusion in the study and to assess whether the study exclusion criteria preferentially include a sub-group distinct from the general patient population.

9.1.2.3. 5-D Itch Scale

The 5-D itch scale has been developed as a brief, single page, instrument for the multidimensional quantification of itch that is sensitive to change over time. It has data to support its validity in a population of patients with pruritus and covers five dimensions of itch experienced by participants: duration, degree, direction, disability and distribution [Elman, 2010]. The distribution dimension is assessed by reference to a checklist of potential locations and can be summarized by counting the number of locations identified as itching.

The 5-D Itch scale will be administered at Visits 2, 3, 6 and 7 [Day 1 and Weeks 4, 16 and 20] in the study, and if applicable at early study treatment discontinuation and at study withdrawal.

9.1.2.4. Gastrointestinal Symptom Rating Scale (GSRS)

The GSRS is a validated scale that will be used to assess gastrointestinal symptoms experienced by participants over the preceding 5 to 7 days [Svedlund, 1988].

Participants will be asked to complete the GSRS every week starting at Visit 2 through to Visit 7 [Day 1 through Week 20] in the study.

9.1.2.5. Other PRO Measures

EuroQOL 5D-5L (EQ5D-5L) will be used to assess patient health utility. Within the literature, there are few reported measures of health utility in the PBC patient population including those with pruritus. The measurements will be used to better understand change in participant's symptoms, preference for treatment, and overall health utility for use in health economic evaluations. The EQ5D-5L will be completed at Visits 2, 3, and 6 [Day 1 and Weeks 4 and 16] in the study, and if applicable at early study treatment discontinuation and at study withdrawal.

Patient's Global Impression of Severity (PGI-S) will be used to understand how participant's daily itch score using the 0-10 NRS relates to overall participant-reported itch severity. The PGI-S uses a 5-level response scale and will be collected at Visit 2 through to Visit 7 [Day 1 through Week 20] in the study, and if applicable at early study treatment discontinuation and at study withdrawal.

Patient's Global Impression of Change (PGI-C) will be used to understand how participant's daily itch score using the 0-10 NRS relates to overall participant-reported change in itch severity. 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 Visit 3 through to Visit 7 [Week 4 through Week 20] in the study, and if applicable at early study treatment discontinuation and at study withdrawal.

Beck Depression Inventory-II (BDI-II) is a 21-item questionnaire that will be used to assess the effect of GSK2330672 on depression associated with pruritus in PBC participants. The questionnaire will be completed at Screening, Visits 3 and 6

[Screening, Weeks 4 and 16] in the study, and if applicable at early study treatment discontinuation and at study withdrawal.

Participant Treatment Experience Assessment is a questionnaire that will evaluate participants' experience of itch and their satisfaction (benefits and disadvantages) with treatment, which will be performed at the end of the Final Study Period (Visit 6 [Week 16]), or at early study treatment discontinuation.

9.1.3. Actigraphy Sub-Study

An Actigraphy Sub-study will be conducted and is optional for investigator sites and participants. Participants who give their informed consent will wear an activity monitor device (similar to a wristwatch) on each wrist during the period of measurement, which will be used to assess the frequency and duration of scratching events.

Participating sites may offer the Sub-study to any participant considering the main study, providing in the investigator's option, he/she is capable of understanding and performing the sub-study procedures. Willingness to participate in the Sub-study will not influence a participant's acceptance into the main study. Participants who do not complete all the requested periods of measurement may continue in the main study. Failure to complete the Sub-study measurements will not constitute a protocol deviation.

Participants will be trained on how and when to use the actigraphy monitors, which will be given to them at Visit 2, Visit 4 and Visit 5, with activity measurements performed on three occasions, over at least 5 nights during a 7-day period. In order to allow flexibility for participants each of the 7-day measurement periods can occur during either Week 2 or Week 3 (for the first measurement), Week 9 or Week 10 (for the second measurement), and Week 13 or Week 14 (for the third measurement), respectively. During the measurement period participants may keep the monitors on all the time, or may remove them in the morning and put them back on before going to bed. Participants will return the monitors to site staff at their next study visit when data will be downloaded and stored for analysis.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 5.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 8).

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

- All SAEs will be collected from time informed consent is signed until the end of the Final Study Period (Visit 7) at the time points specified in the SoA (Section 2).

- All AEs will be collected from the start of study treatment in the Initial Study Period (Visit 2) until the end of the Final Study Period (Visit 7) at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately, and under no circumstances should this exceed 24 hours, as indicated in Appendix 5. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. 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 treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 5.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

9.2.3. 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 Appendix 5), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 5.

9.2.4. Regulatory Reporting Requirements for SAEs

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

investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAE) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular (CV) events detailed in Appendix 5 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV 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 CV 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.

9.2.6. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of the Follow-up Period.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 2.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment immediately but will remain in the study and continue to undergo study assessments (see Section 8.1).

9.3. Treatment of Overdose

For this study, any dose of GSK2330672 greater than 360 mg within a 20-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose as there is no specific antidote for GSK2330672. In the event of a suspected overdose, it is recommended that

the appropriate supportive clinical care should be instituted, as dictated by the participant's clinical status.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until any associated symptoms have resolved, and for at least 5 days.
3. Obtain a plasma sample for PK analysis within 24 - 72 hours from the date of the last dose of study treatment, 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.

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.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (see Section 2).

All safety assessments should be performed by the investigator or a suitably qualified designee.

9.4.1. Physical Examinations

- A complete physical examination (Screening Visit only) will include, at a minimum, assessments of the skin, CV, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured (wearing indoor clothing without shoes) and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, CV system, and abdomen (liver and spleen). Weight will also be measured (wearing indoor clothing without shoes) and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Vital signs (pulse rate and blood pressure) will be assessed as outlined in the SoA (Table 1).
- Blood pressure and pulse measurements will be assessed in the sitting position 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 (should not be performed immediately after blood collection for laboratory tests or PK) will consist of three readings of blood pressure and pulse. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the eCRF.

9.4.3. Electrocardiograms

- A single 12-lead ECG will be obtained as outlined in the SoA (Table 1) using preferably an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. If an automated reading is not available the ECG should be manually over-read by the investigator or an adequately trained physician. Refer to Section 8.1.2 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 and any clinically significant abnormalities reported in the eCRF.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 6 for the list of clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or Medical Monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 6, must be conducted in accordance with the laboratory manual and the SoA (Table 1).

9.5. Pharmacokinetics

- Samples of whole blood of will be collected for measurement of plasma concentrations of GSK2330672 and/or UDCA as follows:

- Visit 3 [Week 4] in participants on UDCA only: A 2 mL sample for analysis of UDCA will be collected between 1 and 3 hours following the morning dose of study treatment.
- Visits 4 and 5 [Weeks 8 and 12 respectively] in all participants on study treatment: The first sample (3 mL) will be collected between 1 and 3 hours following the morning dose of study treatment. The second sample (2 mL) will be collected between 5 and 8 hours after the morning dose of study treatment. The first sample will be used for analysis of both GSK2330672 and UDCA, and the second sample for analysis of GSK2330672.
- If samples are not collected at Visit 5 [Week 12] they may alternatively be collected at Visit 6 [Week 16].
- The actual date and time (24-hour clock time) of each sample collection will be recorded.
- Participants will record the time of their morning dose of study treatment taken at home on a paper diary, as well as the date and time of their last dose of UDCA (if applicable). Participants should bring this information with them to the study visit for entry into the eCRF.
- Participants taking UDCA will be required to not administer a morning dose of UDCA (if applicable), before each of the PK sampling visits and to record the time of their last UDCA dose.
- If more convenient, participants may take their morning dose of study treatment at the clinic visit, provided they comply with other protocol requirements such as fasting, eDiary completion and the sampling time does not interfere with PRO completion (see Section 2).
- Note: PK sample collection is not required for participants who have prematurely discontinued study treatment and have not taken study treatment on 3 or more days prior to the Visit.

- During the study, the timing of PK samples may be altered and/or PK samples may be obtained at additional time points.
- Sample collection, processing, storage and shipping procedures are provided in the Laboratory Manual.
- Plasma analysis for GSK2330672 and UDCA will be performed under the control of Bioanalytical Science and Toxicokinetics, DMPK, GlaxoSmithKline. Concentrations of GSK2330672 and UDCA will be determined in plasma samples using currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.
- Samples collected for analyses of GSK2330672 and/or UDCA plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Once the plasma has been analyzed for GSK2330672 and/or UDCA any remaining plasma may be analyzed for other GSK2330672-related or UDCA-related metabolites and the results reported under a separate protocol.

- Drug concentration information that may unblind the study will not be reported to investigative sites or blinded study personnel until the end of the study and the study has been unblinded.

9.6. Pharmacodynamics

See Section 9.8.

9.7. Genetics

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

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

See Appendix 7 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the Laboratory Manual.

9.8. Biomarkers

The effects of GSK2330672 on markers of PBC disease progression, as well as biomarkers of PBC, bile acid physiology and lipids will be evaluated.

Markers of PBC disease progression: The effects of GSK2330672 on markers of PBC will be evaluated among participants at high risk of PBC progression (i.e., serum ALP ≥1.67x ULN and/or total serum bilirubin >ULN) and in all study participants. PBC markers to be assessed include serum ALP, ALT, AST, gamma-glutamyl transferase (GGT), total bilirubin and albumin concentrations, and prothrombin time/international normalised ratio (PT/INR).

Biomarkers of PBC and bile acid physiology: The effects of IBAT inhibition by GSK2330672 on circulating bile acids and bile acid synthesis will be evaluated in all study participants. Biomarkers include total serum bile acid and serum C4 as a marker of bile acid synthesis. Additional exploratory biomarkers include serum autotaxin, fibroblast growth factor-19 (FGF-19), and enhanced liver fibrosis (ELF) test, and serum bile acid species. Samples may be tested for other biomarkers as new data emerge.

Lipids: The effect of GSK2330672 on fasting lipids, including direct low density lipoprotein (LDL) cholesterol will also be assessed.

- Fasting blood samples for biomarkers and will be collected as outlined in the SoA (Table 1).
- Full details of sample collection and processing are provided in the Laboratory Manual.

- In addition, with the participant's consent, serum samples will be stored and analysis may be performed on biomarker variants thought to play a role in PBC disease and circulating bile acids, to evaluate their association with observed clinical responses to GSK2330672.
- Due to the potential for unblinding, results of biomarkers of PBC and bile acid physiology will not be provided to investigators or blinded study staff until the study has completed and has been unblinded.

9.9. Medical Resource Utilization and Health Economics

The effect of study treatment on healthcare resource utilization parameters such as emergency room visits, details of hospitalisations including intensive care unit stay, will be evaluated.

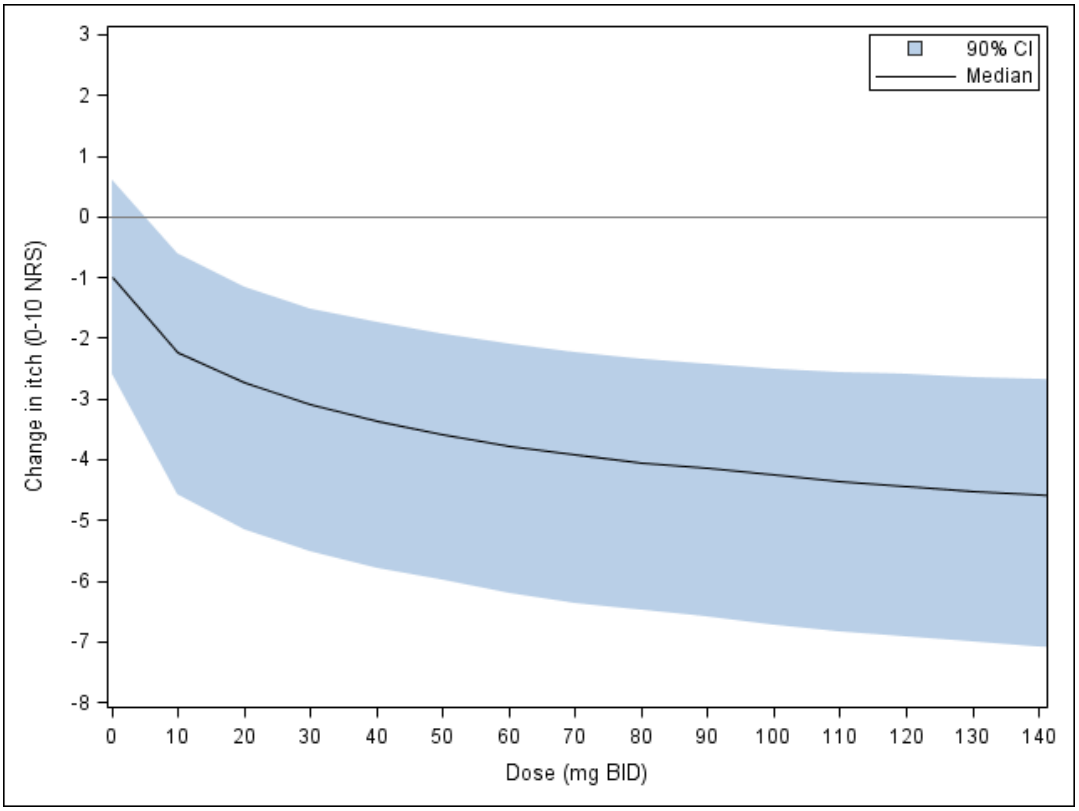
10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

Approximately 118 participants will be randomized to ensure that approximately 100 eligible participants have an evaluable Week 16 assessment of itch.

Sample size calculations were made using simulation to assess the precision of the estimated difference in response between each dose of GSK2330672 and placebo from the Emax dose-response model (see Figure 2).

Figure 2 Simulated Emax Dose-Response Curve



A sample size of approximately 100 eligible participants allows sufficient precision to provide a minimally detectable effect of at least 2 points on the Mean Worst Daily Itch Score (assuming a between-participant SD of 2 points).

Participants will be stratified based on region (Europe, North America, Japan to manage drug supply) and participant risk of PBC progression according to serum ALP and total bilirubin concentrations at Visit 2 [Day 1] (see Table 6).

To optimise the dose response assessment, participants with ALP <1.67x ULN and total bilirubin ≤ULN will be randomized in a 1:1:1:1:1 ratio (Placebo: 20 mg once daily: 90 mg once daily: 180 mg once daily: 90 mg twice daily). Participants with ALP ≥1.67x ULN and/or total bilirubin >ULN will be randomized in a ratio of 3:1:1:2:1, respectively to increase the precision for the comparison of higher doses of GSK2330672 to placebo in participants at higher risk of disease progression.

Table 6 Distribution of Participants to Treatment Arms

Strata		Placebo	GSK2330672			
			Once Daily			Twice Daily
			20 mg	90 mg	180 mg	90 mg
ALP <1.67x ULN and total bilirubin ≤ULN	Ratio:	1	1	1	1	1
	Participants	14	14	14	14	14
ALP ≥1.67x ULN and/or total bilirubin >ULN	Ratio:	3	1	1	2	1
	Participants:	18	6	6	12	6
ALP = Alkaline phosphatase; ULN = Upper Limit of Normal. Participant numbers are approximate based on expected recruitment to rates to each strata.						

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Randomized	All participants who were randomized to receive study treatment, regardless of whether they took study treatment, will be used in the summaries of participant disposition
ITT (Intent to Treat) Population	This population will comprise all randomized participants who receive at least one dose of study treatment, have a baseline and at least one on-treatment assessment. Participants in the ITT Population will be classified according to the treatment as randomized. The ITT population will be the primary population for the statistical assessment of efficacy.
Per Protocol Population	The Per Protocol (PP) Population is a subset of the ITT population who adhere to the major protocol requirements. Protocol violator criteria will be defined in the Reporting Analysis Plan (RAP), and participants to be excluded from the PP population will be identified prior to the unblinding of the data at the end of the study. The PP population will be used for analysis of the primary endpoint to assess the sensitivity of the ITT results. The PP population may not be analysed if it comprises ≥80% of the ITT population and is balanced across dose levels.
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.

10.3. Statistical Analyses

10.3.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary objective is to estimate the relationship between doses of GSK2330672 and itch response. The primary analysis will be a model-based dose-response analysis of the change from Baseline to Week 16 in the Mean Worst Daily Itch Score on the 0-10 NRS. The primary null hypothesis (H0) assumes that there is no effect of the test drug at any dose level and therefore no evidence of dose response. The alternate hypothesis (H1) assumes that there is a monotonic Emax dose response with GSK2330672 on participant experience of itch. A four parameter Emax dose-response model, once fitted, will be used to estimate the minimally effective dose and 95% confidence interval of each dose level of GSK2330672 relative to placebo. If problems are encountered fitting a four parameter Emax model, the model selection approach described by Kirby et al (Kirby, 2011) will be taken (fitting a 3-parameter Emax model and a power model and selecting the one that best fits the data (i.e. smallest Akaike's Information Criterion statistic (AIC)). If both of these models poorly fit, then additional models will be investigated sequentially until an appropriate model can be chosen (i.e. linear, quadratic, log-transformed dose). Further details of the Emax model will be defined in the RAP.
Secondary	Analyses of the following secondary endpoints will be analyzed as the change from Baseline to Week 16 using similar methodology as for the primary endpoint (with an appropriate link-function for binary endpoints): • Mean change from Baseline in PBC-40. • Mean change from Baseline in markers of PBC disease progression including ALP, ALT, AST, GGT, total bilirubin, albumin and PT/INR. • Proportion of participants responding to treatment defined as ALP reduction to <1.67x ULN and total bilirubin ≤ULN at the end of treatment (in participants with ALP ≥ 1.67x ULN and /or total bilirubin >ULN at Day 1). • Proportion of participants who are responders using 3 separate definitions (Mean Worst Daily Itch Score <4, ≥30% reduction in Mean Worst Daily Itch Score, ≥2-point reduction in Mean Worst Daily Itch Score). • Mean number of responder days using 3 separate definitions (Worst Daily Itch Score <4, ≥30% reduction in Worst Daily Itch Score, ≥2-point reduction in Worst Daily Itch Score). • Change from Baseline in Mean Daily Sleep Score.

Endpoint	Statistical Analysis Methods
	• Change from Baseline in Mean Daily Fatigue Score. • Change from Baseline in the 5-D Itch questionnaire. • Change from Baseline in total serum bile acids and C4. • Further details of the analysis methodology, any sensitivity analyses and control of the overall Type I error rate will be defined in the RAP.
Exploratory	Will be described in the reporting and analysis plan

10.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	Overall safety evaluations will be descriptive using the Safety Population (as described in Section 10.2). Graphical and tabular displays will be presented to facilitate safety data review. AEs and SAEs will be summarised, sorted by system organ class and preferred term assigned by MedDRA, and presenting as number and percent by treatment group. Additional summaries of AEs leading to discontinuation of study treatment and study treatment related AEs will also be generated.
Secondary	Change from baseline in GSRS score. Change from baseline and percentage change from baseline for laboratory values will be summarised 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. 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 and separately, those meeting the pre-specified withdrawal criteria will be summarized by treatment group. Criteria for potential clinical importance will be specified in the RAP.
Exploratory	Will be described in the reporting and analysis plan

10.3.3. Other Analyses

Pharmacokinetic, PD and biomarker exploratory analyses will be described in the RAP. Any other population analyses (e.g., dose-response) conducted based on emerging data will be described in the CSR or a separate report as appropriate.

10.3.4. Interim Analyses

An interim analysis of efficacy and safety will be performed in order to determine whether the initial doses of GSK2330672 need to be modified. Once a participant is assigned to a treatment arm, their individual treatment assignment will not change as a result of the outcome of the interim analysis and their data will still contribute to the final dose response analysis.

An interim analysis will allow for potential discontinuation for futility, elimination of less informative doses (e.g., those which are ineffective or poorly tolerated), and/or addition of lower or higher doses to more fully describe the dose-response characteristics of GSK2330672.

In order to minimise bias, a firewalled analytical group will perform the interim analyses to maintain the integrity of the study blind within the study team. The unblinded data will be reviewed by limited members of the trial leadership, who will review the results and may then decide to:

1. Continue as planned.
2. Stop for futility: Proposed futility rule to be based on a low posterior predicted probability that at least one dose will achieve a clinically relevant treatment difference to placebo (based on dose-response model).
3. Amend dose levels: Proposed if dose-response and/or tolerability profile dramatically different to pre-study assumptions. Allocation post-interim would be focused on most informative doses chosen from a set of possible dose levels that includes those used pre-interim (e.g., if larger responses are seen on the lower doses then the ED50 may be smaller than was assumed during design and hence lower dose levels could be included and higher levels dropped).
4. Amend sample size: Proposed if an additional dose is added, or if the observed variability is dramatically different to the assumptions from the initial sample size calculations.

The results of the interim analysis could lead to changes to the randomization ratio and/or a change in the total number of participants to be randomized in the study. The decision to adapt the study will be determined by posterior probability decision rules which will be pre-defined and documented prior to unblinding in the RAP.

Based on the overall panned sample size, an interim analysis will be ideally performed after approximately 40 participants have reached their Visit 5 [Week 12]. However, should enrolment fail to occur as anticipated, the timing of the planned interim may be revised. Additional interim analyses may be conducted based on the initial data.

Details of the analyses to support the interim and the decision rules will be documented in a separate Interim Analysis Plan. The final timings of the interim analyses will be documented in the clinical study report.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

List of Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BDI-II	Beck Depression Inventory-II
C4	7-α-hydroxy-4-cholesten-3-one
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine Phosphokinase
CSR	Clinical Study Report
CV	Cardiovascular
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDevice	Electronic Device
eDiary	Electronic Diary
eGFR	Estimated Glomerular Filtration Rate
ELF	Enhanced Liver Fibrosis
FGF-19	Fibroblast Growth Factor-19
FOBT	Fecal Occult Blood Test

GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
GSRS	Gastrointestinal Symptoms Rating Scale
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High-density Lipoprotein
HDPE	High Density Polyethylene Bottles
HPLC	High Performance Liquid Chromatography
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
IBAT	Inhibitor of the Human Ileal Bile Acid Transporter
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent to Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase

LDL	Low-density Lipoprotein
MSDS	Material Safety Data Sheet
NASH	Nonalcoholic Steatohepatitis
NOAEL	No Observed Adverse Effect Level
NRS	Numerical Rating Scale
PBC	Primary Biliary Cholangitis
PD	Pharmacodynamic
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PRO	Patient Reported Outcome
PSC	Primary Sclerosing Cholangitis
PT	Prothrombin Time
RAP	Reporting Analysis Plan
SAE	Serious Adverse Event
SoA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2DM	Type 2 Diabetes Mellitus
UDCA	Ursodeoxycholic Acid
ULN	Upper Limit of Normal
VLDL	Very low-density Lipoprotein
WOCBP	Women of Child Bearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

   Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-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 enrollment.

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 7.

Table 7 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
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 treatment. 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.)*

NOTES:
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test
- Additional pregnancy testing should be performed at monthly intervals during the treatment period and at the end of the Final Study Period, and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

- Pregnancy testing, with a sensitivity of 25 mIU/mL will be performed using the test kit provided by the central laboratory and in accordance with instructions provided in its package insert

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Pregnancies in female partners of male participants do not need to be collected.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 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 treatment immediately but will remain in the study and continue to undergo study procedures (see Section 8.1).

12.3. Appendix 3: Study Governance Considerations

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) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR (Code of Federal Regulations), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations,

ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- 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.

Committees Structure

The study will be conducted under the auspices of a Steering Committee comprised of academic and clinical experts and Sponsor representatives who will oversee the scientific and operational aspects of the study.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of 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.

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- 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 results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic eCRF 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 eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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 eCRF 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 can be found in the Study Reference Manual.

Study and Site Closure

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

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

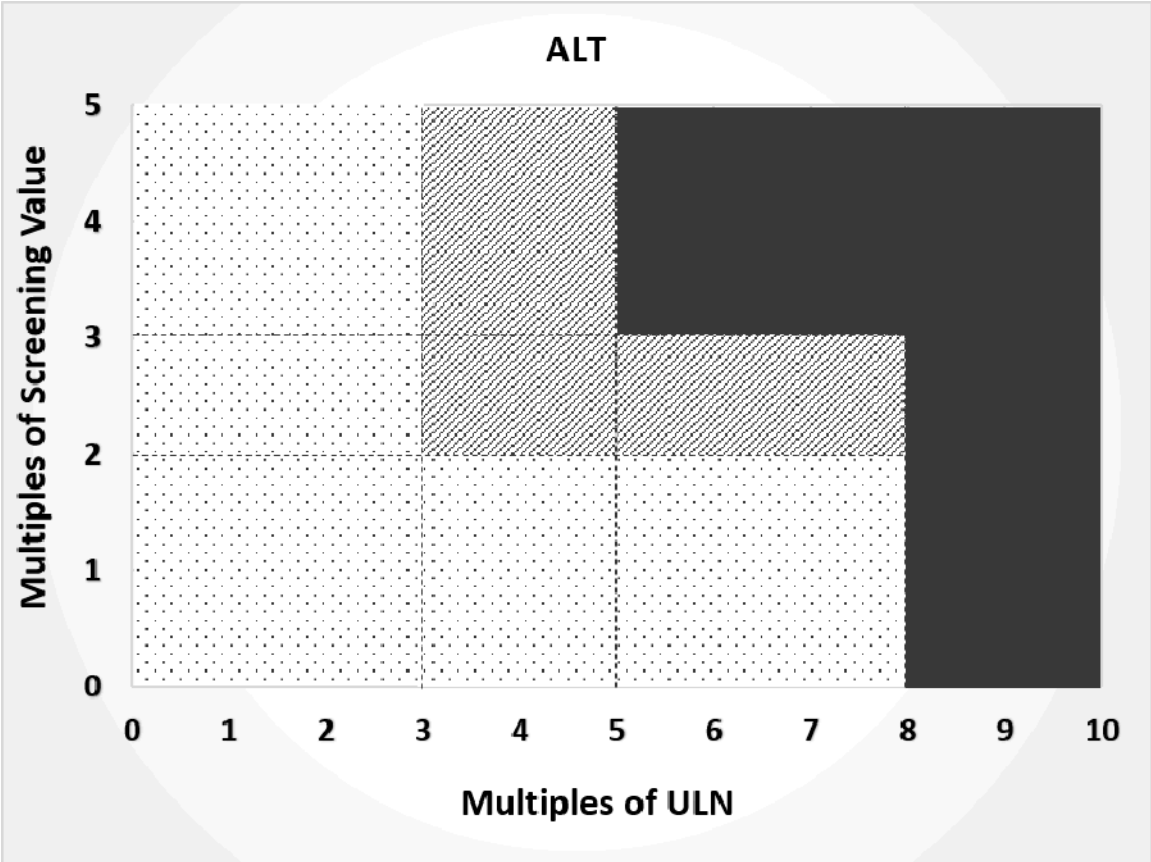
Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

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

12.4. Appendix 4: Liver Safety: Required Actions and Follow-up Assessments

These figures are to assist with application of the liver chemistry increased monitoring and stopping criteria in Section 8.1.1.

Figure 3 Liver Chemistry Criteria for Increased Monitoring and Stopping Study Treatment: ALT

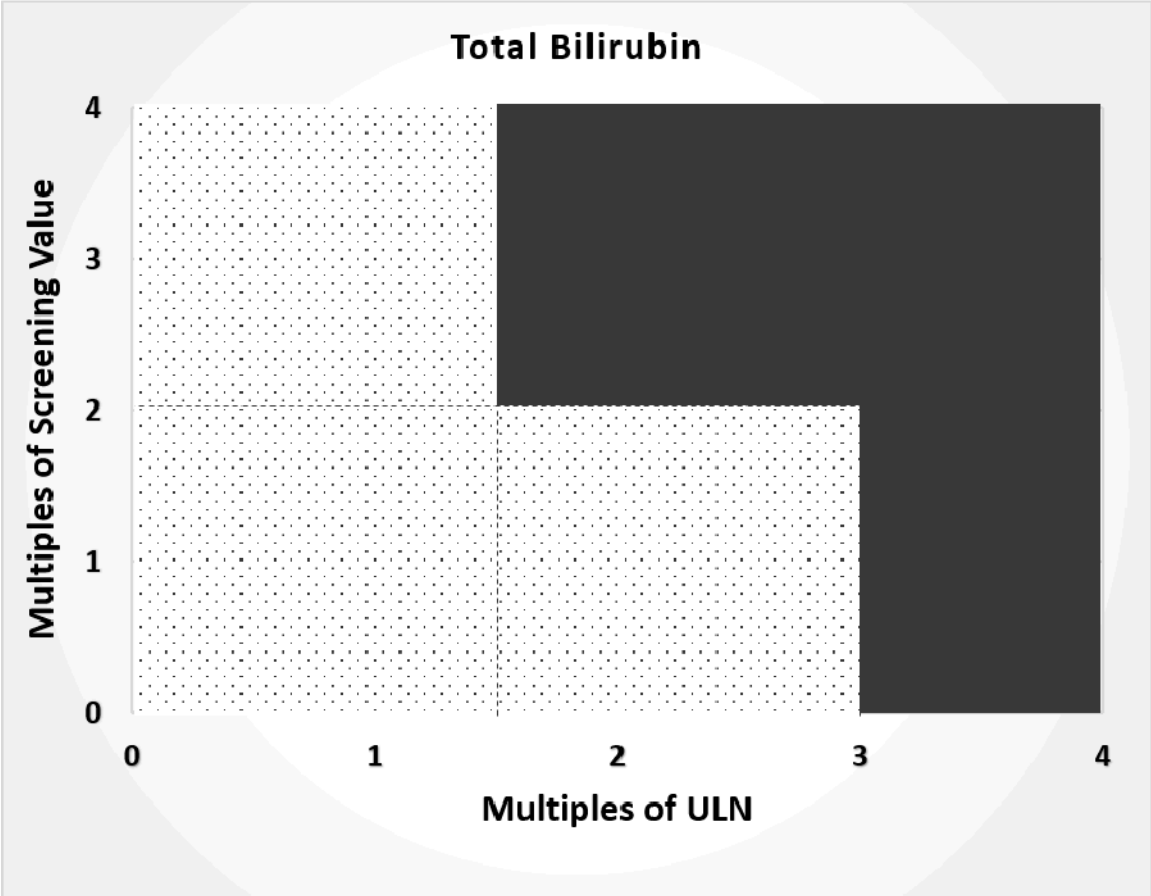


Continue unless investigator concern

Continue with increased monitoring (see protocol section 8.1.1); stop if investigator concern or new symptoms suggestive of liver injury

Discontinue study treatment permanently; follow monitoring requirements in protocol section 8.1.1 and follow-up investigations in protocol appendix 4

Figure 4 Liver Chemistry Criteria for Increased Monitoring and Stopping Study Treatment: Bilirubin



12.4.1. 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 8.1.1.

- Immediately withdraw the participant from study treatment. (Note: The participant should remain in the study completing remaining study visits and assessments [see Section 8.1]).
- 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 within 24 hours of learning of the abnormality to confirm the participant's study treatment cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.
- Complete the liver event CRFs. 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 until the End of Follow-up Telephone Visit; however the participant must not restart study treatment (see Section 8.1.6.1).
- Monitor participants at least weekly until liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin, PT/INR) resolve, stabilize or return to within baseline values.

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

- Viral hepatitis serology including:
  - Hepatitis A 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 treatment 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 (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use 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.

12.5. Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 treatment, whether or not considered related to the study treatment. • 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 treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment 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 fulfill the definition of an AE or SAE.

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

the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that 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.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

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 detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills 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 disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, 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. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Adverse events of special interest include the following:
• Diarrhea reported as an AE
• Elevated ALT meeting stopping criteria

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

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports)

related to the event.

- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

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

taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.

- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF

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

12.6. Appendix 6: Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by the central laboratory. Section 9.8 provides details of biomarkers that will also be assessed.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 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.

Table 8 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	• Platelet Count • RBC Count • Hemoglobin • Hematocrit • % Reticulocytes	RBC Indices: • MCV • MCH	• WBC count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Coagulation	• Prothrombin Time (PT)/International Normalized Ratio (INR)		
Clinical Chemistry[1]	• BUN • Creatinine • eGFR (CKD-EPI) • Potassium • Sodium • Calcium • Glucose (fasting)[2] • Total cholesterol (fasting)[2] • Direct LDL cholesterol (fasting)[2] • Direct HDL cholesterol (fasting)[2]	• Indirect LDL cholesterol (fasting)[2] • Indirect VLDL cholesterol (fasting)[2] • Triglycerides (fasting)[2] • Aspartate Aminotransferase (AST) • Alanine Aminotransferase (ALT) • Alkaline Phosphatase (ALP) • Gamma Glutamyl Transferase (GGT) • Total and direct bilirubin • Total protein • Albumin	
Other	• Vitamins A, D, E, K • Fecal occult blood test (FOBT) (cards to be provided for test)		
Other Screening Tests	• Follicle-stimulating hormone (FSH) (as needed in women of non-childbearing potential only). • Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential).[3] • Serology hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibody (HCV RNA if antibody test positive).		

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 8.1.1 and Appendix 4.
2. Fasting (water, study treatments and other medications are permitted) samples required for all visits except screening.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

12.7. Appendix 7: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK2330672 or PBC and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK2330672, or study treatments of this drug class, and PBC. 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)
- DNA samples will be analyzed for understanding response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines. Additional analyses 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 GSK2330672 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK2330672 (or study treatments of this class) or PBC continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

12.8. Appendix 8: Country-specific requirements

None

12.9. Appendix 9: Protocol Amendment History

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

Amendment 1 15-Nov-2016

Overall Rationale for the Amendment: To clarify requirements for liver safety monitoring and stopping criteria, as well as other administrative changes.

Section # and Name	Description of Change	Brief Rationale
8.1.1 Liver Chemistry Stopping Criteria	Repeat testing should include AST, ALT, total bilirubin, ALP and PT/INR (insertion of tests).	Clarification on which liver tests are required.
12.4 Appendix 4: Liver Safety	Inclusion of PT/INR as part of the liver safety follow-up tests, which are required at least weekly. Following stopping of study treatment participants with liver safety findings should not be withdrawn but as well as liver safety follow-up should remain in the study undergoing study visits and assessments. Participants who stop study treatment for liver safety should not restart study treatment.	Correction for missing test. Correction and alignment with Section 8.1 which states that participants who stop study treatment should remain in the study completing remaining study visits and assessments. Clarification and alignment with Section 8.1.6.1., which states that study treatment restart or rechallenge is not permitted.
2 Schedule of Activities 8.1 Discontinuation of Study Treatment	Update Footnote 1: Early End of Treatment and Study Withdrawal Assessments are only performed post-randomization. If both are required at the same visit only the Early End of Treatment Assessments are performed. Early End of Treatment Assessments are only performed post-randomization.	Clarification that the assessments are required only for randomized participants. As assessments overlap, both are not required for the same visit. However, since the Participant Treatment Experience Assessment is required as part of the Early End of Treatment Assessments, these should be conducted.
8.2 Withdrawal from the Study	Study Withdrawal Assessments are only performed post-randomization.	Clarification that the assessments are required only for randomized participants.

Section # and Name	Description of Change	Brief Rationale
2 Schedule of Activities	Table 1 amended to separate out PGI-C as this is not required at Visit 2.	As a measure of change PGI-C is not appropriate at Visit 2.
2 Schedule of Activities	Sequence of PROs revised to move PGI-S and PGI-C before other PROs.	Correction of order of assessments.
2 Schedule of Activities	Addition of weekly gastrointestinal (GI) symptom collection with the weekly GSRS.	Alignment with eDiary data collection.
9.1.1 Electronic Data Collection	Addition of weekly GI symptom collection with the weekly GSRS.	Alignment with eDiary data collection.
9.1.2.1 Patient Reported Symptom Questionnaire	Addition of weekly GI symptom collection.	Alignment with eDiary data collection.
9.1.2.1 Patient Reported Symptom Questionnaires	Update to the Itch NRS to indicate that a score of CCI represents the CCI [redacted].	Alignment with eDiary.
9.1.2.5 Other PRO Measures	PGI-S is a 5-level response scale. PGI-C comprises a 7-level response scale of change since baseline and a dichotomous (Y/N) question. PGI-C will not be collected at Visit 2.	Correction to accurately describe the measures and alignment with updated SOA.
2 Schedule of Activities	Update Footnote 7 to indicate if Visit 5 PK sample is not collected it may be collected at Visit 6. Addition of note that PK sample collection is not required if participant has prematurely discontinued study treatment and study treatment has not been taken on 3 or more days prior to the Visit.	Alignment with Section 9.5 and to clarify PK sample collection with respect to participants who discontinue treatment.
9.1.1 Electronic Data Collection	Deletion of text relating to collection of study treatment and UDCA dosing times in the eDiary.	Correction. To support PK evaluation participants will record dosing dates/times using a paper based diary (see Section

Section # and Name	Description of Change	Brief Rationale
		9.5).
9.5 Pharmacokinetics	Participants will record the study treatment and UDCA dosing times on a paper diary for visits requiring PK collection and will be entered into the eCRF. Addition of bullet stating PK sample collection is not required if participant has prematurely discontinued study treatment and has been off treatment for greater than 3 days.	Clarification that dosing information will be collected via a paper diary and entered in eCRF. Clarification on PK sample collection in participants who prematurely stop study treatment and remain in the study.
7.7 Concomitant Medication	Medications taken within 3 months of Screening should be recorded in the eCRF.	Clarification.
12.2 Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information	Deletion of footnote b under Table 5.	Footnote was included in error, as GSK2330672 is not expected to be susceptible to interaction with hormonal contraceptives. Women of child-bearing potential therefore may be enrolled in the study using one (not two) highly effective methods of contraception.
12.5 Appendix 5: Adverse Events	Removal of AST meeting stopping criteria as AE of special interest. Cardiovascular events will be collected using specific CV event eCRF. Evidence of Investigator or medically-qualified sub-investigator review and verification of SAE relationship (causality) information is required in eCRF within 72 hours of SAE entry.	Correction as the protocol does not have specified stopping criteria for AST. Update of Sponsor required protocol text for CV event collection. Update of Sponsor required protocol text.
12.6 Appendix 6: Clinical Laboratory Tests	Inclusion of direct HDL cholesterol, indirect LDL cholesterol and indirect VLDL cholesterol in clinical chemistry tests.	Correction to reflect central laboratory's standard lipid panel.

Section # and Name	Description of Change	Brief Rationale
12.3 Appendix 3: Study Governance Considerations	Record retention time of 25 years is from issue of clinical study report/equivalent summary.	Update of Sponsor required protocol text.
12.7 Appendix 7: Genetics	Maximum samples retention will be no longer than 15 years after the last subject last visit or other period as per local requirements.	Update of Sponsor required protocol text.
12.1 Appendix 1: Abbreviations and Trademarks	Addition of abbreviations (ALT, CSR, HDL, INR, PT, VLDL).	Alignment with text.