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.

	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

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.

- 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.

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.

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

- 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

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

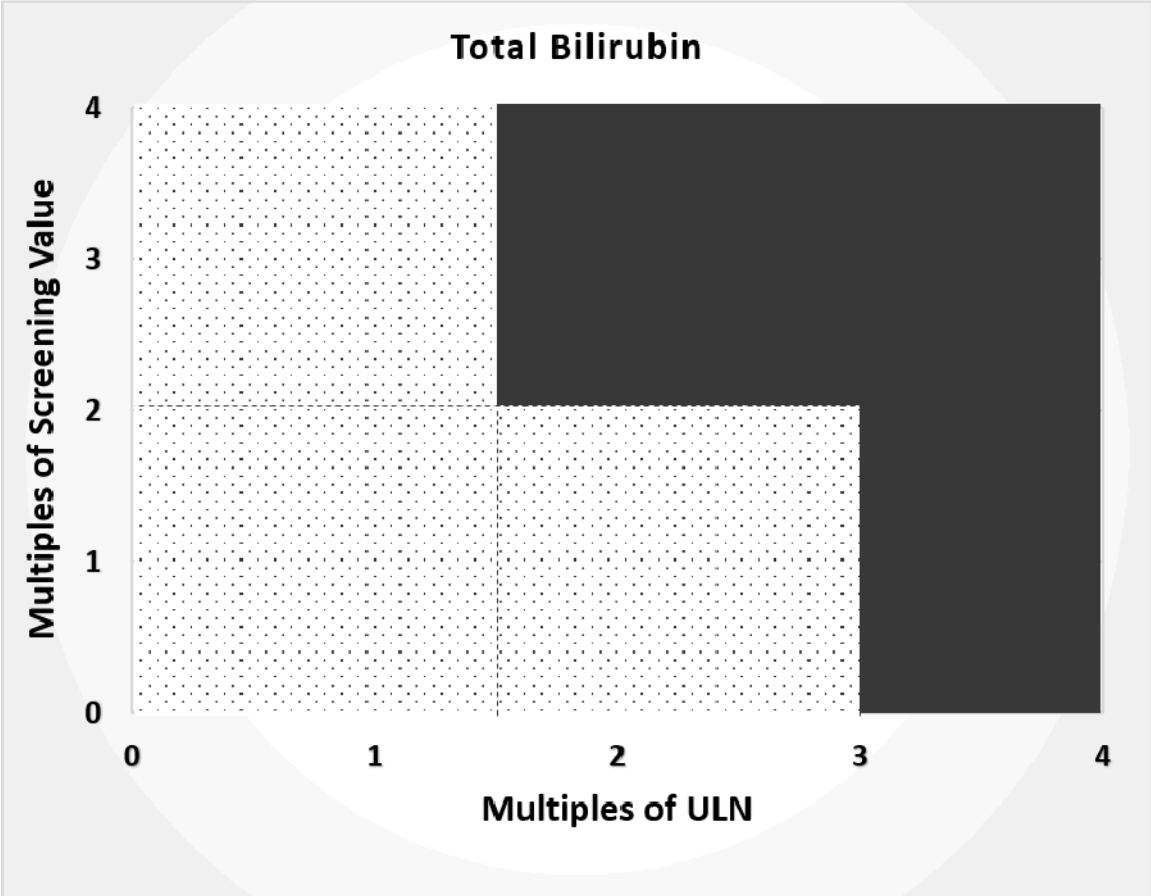
- Samples of whole blood of will be collected for measurement of plasma concentrations of GSK2330672 and/or UDCA as follows:

- 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.

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

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.

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

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.

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.

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.

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).

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

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

[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).

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

- 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.

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

- 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.

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)

12.8. Appendix 8: Country-specific requirements

None