CLINICAL STUDY PROTOCOL

Title:	TRANSFORM: A 24-week, Randomized, Placebo-controlled, Double-blind, Phase 2b Trial of Setanaxib in Patients with Primary Biliary Cholangitis (PBC) and Elevated Liver Stiffness
NCT number:	NCT05014672
Unique Protocol ID:	GSN000350
Document Date:	27 September 2023

CLINICAL STUDY PROTOCOL

Title:	TRANSFORM: A 24-week, Randomized, Placebo-controlled, Double-blind, Phase 2b Trial of Setanaxib in Patients with Primary Biliary Cholangitis (PBC) and Elevated Liver Stiffness
Short title:	A Phase 2b Trial of Setanaxib in Patients with PBC and Elevated Liver Stiffness
Protocol number:	GSN000350
Study Phase:	Phase 2b
Test product:	Setanaxib
Regulatory agency identifier number(s):	Investigational New Drug number: 132135 EudraCT (EU Drug Regulating Authorities Clinical Trials) number: 2021-001810-13
Sponsor:	Calliditas Therapeutics Suisse SA Chemin des Aulx 14 1228 Plan-les-Ouates Switzerland Calliditas Therapeutics Suisse SA is a subsidiary of Calliditas Therapeutics AB
Contract research organization:	ICON plc Corporate Headquarters South County Business Park Leopardstown, Dublin 18 Ireland Phone (IRL): +353 1 291 2000 Phone (US): +1 215 616 3000 Fax: +353 1 247 6260
Coordinating Investigators:	Division of Digestive Health and Liver Diseases Schiff Center for Liver Diseases University of Miami 1500 NW 12th Avenue, Suite 1101 Miami, FL 33136 US

	NIHR Newcastle Biomedical Research Centre Newcastle upon Tyne NHS Foundation Trust & Newcastle University Newcastle upon Tyne, NE4 5P UK
Protocol version and date:	Version 5.0 (27 September 2023), incorporating Global Amendment 4

This study will be performed in compliance with the principles of Good Clinical Practice.

PROTOCOL SIGNATURE PAGE – SPONSOR

This protocol has been reviewed and approved by the representative(s) listed below. Any modification of the protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

Sponsor representative:

Print Name	Title
Signature	Date

PROTOCOL SIGNATURE PAGE – SPONSOR (CONTINUED)

This protocol has been reviewed and approved by the representative(s) listed below. Any modification of the protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

Sponsor representative:

Print Name	Title
Signature	Date

PROTOCOL SIGNATURE PAGE – COORDINATING INVESTIGATOR

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH GCP), and applicable regional regulatory requirements.

Coordinating Investigator:

Print Name	Title
Institution	
Signature	Date

PROTOCOL SIGNATURE PAGE – COORDINATING INVESTIGATOR (CONTINUED)

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH GCP), and applicable regional regulatory requirements.

Coordinating Investigator:

Print Name	Title
Institution	
Signature	Date

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

I have read this protocol, which has been agreed by the Sponsor and given approval/favorable opinion by the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), and I agree that it contains all necessary details for my staff and I to conduct this study as described. I will provide copies of the protocol and any amendments to all study personnel under my supervision and provide access to all information provided by the Sponsor or their specified designees. I will discuss the material with the study personnel to ensure that they are fully informed about the study.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a patient in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH GCP), and applicable regional regulatory requirements.

I agree to comply with the procedures described for data recording and reporting and to permit monitoring and auditing by the Sponsor (or designee), and inspection by the appropriate regulatory authorities.

I agree to make my patients' study records available to the Sponsor's personnel, their representatives, and relevant regulatory authorities in order to verify data that I have entered into the electronic case report forms (eCRFs). I will retain the study-related essential documents until the Sponsor indicates that they are no longer needed. I am aware of my responsibilities as an Investigator as per ICH GCP, local regulations, the study protocol, and the clinical trial agreement.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor (or designee).

PROTOCOL SIGNATURE PAGE – INVESTIGATOR (continued)

Investigator:

Print Name	Title
Institution	
Signature	Date

SERIOUS ADVERSE EVENT (SAE), ADVERSE EVENTS OF SPECIAL INTEREST (AESI), PREGNANCY, AND OVERDOSE CONTACT INFORMATION

In the event of an SAE, the Investigator will send a safety report form within 24 hours of becoming aware of the SAE to the contact details below.

Any AESIs, pregnancies, or overdoses will also be reported within 24 hours of becoming aware of the event to the contact details below.

Contract Research Organization

In Europe, Asia-Pacific, and Africa (EAPA):

ICON Drug Safety Center EAPA

Phone +49 621 8782 154

Fax +44 1792 525 720

Email MHGSafety@iconplc.com

In the Americas:

ICON Drug Safety Center Americas

Phone +1 800 772 2215

Fax +1 888 772 6919

Email CHOsafetyfax@iconplc.com

PRODUCT COMPLAINTS

Product complaints will be collected if they occur in the study. A product complaint is any alleged deficiency related to the identity or quality of a study drug, after it is released for distribution to a site or to a patient. This includes all components distributed with the drug, such as packaging, drug containers, labelling, and inserts.

Examples include:

- Packaging that is damaged or broken
- Missing or illegible labelling
- Inability of the enrolled patients to administer the investigational product
- Product with an unexpected color, appearance (eg, broken tablets), or taste

Product complaints should be reported by filling out the Product Complaint Report Form and emailing it to TRANSFORM-prs-DL-CADGS350-productcomplaints@iconplc.com.

Any adverse events (AEs) that are associated with a product complaint should be reported per instructions for AE Reporting in Section 7.3.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Of note, version 2.0 (dated 16 December 2021) has been generated to implement changes mandated by the US Food and Drug Administration (FDA) and some European Regulatory Authorities. This version has only been submitted to the US FDA but has not been shared with any other regulatory authority and has not been implemented in any country.

Thus, version 3.0 (dated 07 April 2022) has been generated from version 1.0 (dated 06 May 2021), to implement all changes described in global amendment 2, as well as those introduced by global amendment 1.

Version 5.0, 27 September 2023

Global Amendment 4 (substantial)

Description of change and rationale for change:

The protocol has been amended to reflect the following key changes, which have been incorporated in the protocol and protocol summary where applicable:

1. This study was initiated as a randomized, placebo-controlled, double-blind, parallel-group, multicenter, adaptive Phase 2b/3 study. The study was planned to consist of a 4-week Screening Period, a 52-week Double-blind Treatment Period, a 52-week Extension Phase Treatment Period, and a 12-week Follow-up Period. The total duration of the study for patients remaining in the study until their final follow-up assessment was planned to be approximately 2 years and 4 months. The feasibility to conduct the study within an acceptable time frame under this design has proved challenging. This is considered to be related to new and more frequently used treatment options, which the current protocol allows for, such as obeticholic acid (OCA) and off-label use of bezafibrates. One consequence of this is that fewer patients than anticipated are meeting the inclusion criteria of alkaline phosphatase (ALP) ≥1.67 and liver stiffness ≥8.0 kPa. Therefore, the study design is revised to a Phase 2b study. The following key changes include:
    a. Revision of primary and secondary objectives, ie, the decrease in ALP from Baseline at 24 weeks as primary objective and no further selection of a key secondary parameter.
    b. Corresponding to the new primary endpoint
        i. A new sample size calculation was performed that resulted in 60 to 70 patients instead of 318, and a reduced number of sites (80 to 130).
        ii. The statistical methods planned to be applied were revised.
    c. Reduction of the Double-blind Treatment Period from 1 year to 24 weeks,

d. The rationale for a 52-week Extension Phase Treatment Period is no longer applicable; therefore, this period as well as the 12-week Follow-up Period have been removed.
e. With the reduction of the Double-blind Treatment Period to 24 weeks, the optional liver biopsy at Week 52 has been removed, it is not expected to find effects at an earlier time point.
f. The rationale for an interim analysis, ie, the assessment of futility and dose selection, is no longer applicable; therefore, the interim analysis has been removed. The study design is no longer adaptive.
g. Corresponding to changes to the overall study design, the statistical methods planned to be applied were revised, including the definition of the Full Analyses Set (FAS) handling of missing data values, the plans for sensitivity and supplementary analyses.

2. To enhance enrollment, the option for a second rescreening (ie, after failure of initial and first rescreening) has been added to Section 4.3.

3. To enhance enrollment by limiting the number of assessments for patients, the magnetic resonance elastography (MRE) to assess liver and spleen stiffness has been removed.

4. Exclusion criterion 18 has been removed. The FDA approved FibroScan® assessments in patients treated with or for planned treatment with a pacemaker, implanted cardioverter defibrillator, or other implanted electronic device.

5. The criterion for premature discontinuation of the investigational medicinal product (IMP) has been amended for patients with a severe cardiac condition or QT prolongation or an increase in QTc greater than 60 milliseconds from Baseline.

6. APPENDIX II – Detection and Management of Suspected or Confirmed Cases of Drug-Induced Liver Injury, has been updated according to FDA recommendations:
   a. Patient are instructed to return to the study center within 24 to 48 hours instead of 48 to 72 hours.
   b. In case of specified laboratory abnormalities the IMP will be discontinued instead of interrupted.
   c. Follow-Up procedures for patient(s) who meet suspected DILI evaluation criteria have been extended.

7. Administrative changes in the address of the Sponsor and the address and safety center of the contract research organization (CRO).

8. Editorial changes to increase readability and consistency.

Special Note: Patients who are following the previous protocol schedule (protocol version 4) and are already beyond Week 24 should permanently discontinue IMP as soon as possible and have an End-of-Treatment Visit 30 days after their last dose.

Version 4.0, 14 March 2023

Global Amendment 3 (substantial)

Description of change and rationale for change:

The protocol has been amended to reflect the following key changes, which have been incorporated in the protocol and protocol summary where applicable:

1. If futility is not met for the setanaxib 1200 mg/day and 1600 mg/day doses, the Independent Data Monitoring Committee (IDMC) will select one dose for Stage 2. Ongoing patients who are receiving the selected dose will continue the study at the same dose. Ongoing patients who are receiving a dose that is discontinued will have their dose escalated/de-escalated to the selected dose. Patients enrolled after the interim analysis will be randomized to setanaxib (dose selected by the IDMC), or placebo, according to a 1:1 randomization ratio, up to full enrollment.

2. An analysis of the proportion of patients with alkaline phosphatase (ALP) reduction of ≥70% reduction from Baseline at Week 52 and changes in markers of cholestasis as assessed by proportion of patients at Week 52 with ALP reduction to <1.5×upper limit of normal (ULN) and total bilirubin ≤1×ULN and with a ≥40% ALP reduction from Baseline have been added following recommendations from the FDA and the European Medicines Agency, respectively.

3. The exploratory endpoint of changes in markers of cholestasis has been upgraded to secondary endpoint (as above mentioned).

4. The list of prohibited medications was updated with regard to corticosteroid use and removal of biologics.

Version 3.0, 07 April 2022

Global Amendment 2 (substantial)

Description of change and rationale for change:

The protocol has been amended to reflect changes to the Concomitant Medication and Procedures Section 6.7 based on a request from the Belgian regulatory authority.

In addition, the following non-substantial revisions and corrections have been incorporated in the protocol and protocol summary where applicable:

1. Genkyotex Suisse SA has been renamed Calliditas Therapeutics Suisse SA effective 01 April 2022.
2. Clarification of Inclusion Criterion #10b
3. The exclusion criteria numbering has been revised to ensure alignment and consistency across all versions of the protocol.
4. Background Section 1.1 includes minor revisions to align with the Investigator Brochure, Edition 12.0.

Version 2.0, 16 December 2021

Global Amendment 1 (substantial)

Description of change and rationale for change:

The protocol has been amended to reflect the following key changes, which have been incorporated in the protocol and protocol summary where applicable:

1. Based on FDA requests, changes have been made to the Patient-Reported Outcome measures used in the study and Key Secondary Endpoints.
2. The 2 errors that had been identified and described in the protocol clarification letter dated 05 Jul 2021 have been corrected.
3. Changes implemented in the local UK, Spanish, Austrian, and German revised protocols have been incorporated in the global amendment. This includes an added on-site visit at Week 4.

4. Language on product complaint reporting was added.

Additionally, the protocol amendment includes minor revisions for consistency/clarification purposes.

Version 1.0, 06 May 2021
Initial creation

PROTOCOL SUMMARY

Protocol number: GSN000350

Protocol title: TRANSFORM: A 24-week, Randomized, Placebo-controlled, Double-blind, Phase 2b Trial of Setanaxib in Patients with Primary Biliary Cholangitis (PBC) and Elevated Liver Stiffness

Short title: A Phase 2b Trial of Setanaxib in Patients with PBC and Elevated Liver Stiffness

Sponsor: Calliditas Therapeutics Suisse SA

Study phase: Phase 2b

Study sites: It is planned to recruit 80 to 130 investigational centers in North America, Europe, Israel, Australia, and New Zealand.

Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
• To evaluate the effect of setanaxib on alkaline phosphatase (ALP) at Week 24 in patients with PBC and with elevated liver stiffness and intolerance or inadequate response to ursodeoxycholic acid (UDCA)	• Change in ALP at Week 24 compared to Baseline
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of setanaxib on fatigue at Week 24	• Change in fatigue at Week 24 compared to Baseline, as assessed by ○ the Patient-Reported Outcomes Measurement Information System (PROMIS) short form-Fatigue 7b Daily ○ the Patient's Global Impression of Severity (PGIS) fatigue ○ the Patient's Global Impression of Change (PGIC) fatigue ○ the PBC-40 questionnaire (PBC-40) fatigue domain
• To evaluate the effect of setanaxib on liver stiffness at Week 24	• Change in liver stiffness at Week 24 compared to Screening, as assessed by transient elastography (FibroScan®)
• To evaluate the effect of setanaxib on ALP, fatigue, and liver stiffness at Week 24, where setanaxib doses are combined	• Change in ALP at Week 24 compared to Baseline, where setanaxib doses are combined • Change in fatigue at Week 24 compared to Baseline, as assessed by the PROMIS short form-Fatigue 7b Daily, the PGIS fatigue, the PGIC fatigue, and the PBC-40 fatigue domain, where setanaxib doses are combined • Change in liver stiffness at Week 24 compared to Screening, as assessed by transient elastography (FibroScan®), where setanaxib doses are combined
• To evaluate the effect of setanaxib on pruritus at Week 24	• Change in pruritus at Week 24 compared to Baseline, as assessed by the Worst Itch Numerical Rating Scale (WI-NRS), the

	PBC-40 itch domain, and the PGIS and PGIC pruritus
• To evaluate the effect of setanaxib on markers of cholestasis at Week 24	• Changes in markers of cholestasis as assessed by proportion of patients at Week 24 with: ○ ALP reduction to <1.67×upper limit of normal (ULN) and total bilirubin ≤1×ULN and a ≥15% or ≥30% or ≥40% or ≥70% ALP reduction from Baseline, respectively ○ ALP reduction to <1.5×ULN and total bilirubin ≤1×ULN and a ≥40% ALP reduction from Baseline ○ ALP <1×ULN and total bilirubin ≤1×ULN ○ Total bilirubin <0.6×ULN
• To evaluate the safety and tolerability of setanaxib over a 24-week Treatment Period	• Adverse events (AEs). Monitoring for AEs at all visits • AEs of special interest (AESIs): ○ Drug-induced liver injury (DILI) ○ Anemia ○ Hypothyroidism • Laboratory tests: ○ Hematology ○ Biochemistry ○ Urinalysis ○ Thyroid function • Vital signs • 12-lead electrocardiograms (ECGs): clinically significant abnormalities

Exploratory Objectives	Exploratory Endpoints
• To evaluate the effect of setanaxib over a 24-week Treatment Period on markers of liver fibrosis, cholestasis, bile acid metabolism, and liver function	• Changes in markers of liver fibrosis, as assessed by the Enhanced Liver Fibrosis (ELF) score, PRO-C3 (released N-terminal propeptide of Type III collagen), C3M (a peptide of helical collagen Type III degradation), and PRO-C3/C3M ratio over 24 weeks compared to Baseline • Changes in total and conjugated bilirubin over 24 weeks compared to Baseline • Changes in markers of bile acid metabolism, as assessed by total bile acids, C4 (7α-OH-4-cholesten-3-one), fibroblast growth factor (FGF)19, and FGF21 over 24 weeks compared to Baseline • Changes in markers of liver function over 24 weeks compared to Baseline, as assessed by: ○ Serum fibrinogen, albumin, and international normalized ratio (INR) ○ Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), high sensitivity C-reactive protein (hsCRP), and immunoglobulin M (IgM) indicating liver inflammation and injury
• To evaluate the effect of setanaxib on adverse clinical outcomes	• Assessment over 24 weeks of: ○ All-cause mortality ○ Proportion of patients requiring a liver transplant (transplant list inclusion) ○ Proportion of patients with a Model for End Stage Liver Disease (MELD) score of ≥15 ○ Proportion of patients with new onset of variceal/portal hypertension bleed and/or hepatic encephalopathy (West Haven criteria), spontaneous bacterial peritonitis, and ascites requiring treatment
• To further evaluate the effect of setanaxib on patient-reported outcomes	• Change over 24 weeks compared to Baseline in: ○ Social isolation symptoms, as assessed by the PBC-40 social domain ○ Overall health-related quality of life, as assessed by the PROMIS-29 questionnaire ○ EuroQol five-dimensional (EQ-5D) Utility Index
• To determine the predose plasma levels of setanaxib and its metabolite GKT138184	• Predose plasma concentrations of setanaxib and GKT138184 over 24 weeks

Study design:

This study is a randomized, placebo-controlled, double-blind, parallel-group, multicenter, Phase 2b study assessing oral setanaxib administered as an add-on therapy in patients with PBC, elevated liver stiffness, and intolerance or inadequate response to UDCA. The safety and efficacy of 1200 mg/day and 1600 mg/day setanaxib will be assessed against matching placebo over 24 weeks of treatment. It is planned to enroll approximately 60 to 70 patients at 80 to 130 investigational centers in North America, Europe, Israel, Australia, and New Zealand.

The study design is outlined in Figure 1, and the visit schedule and planned assessments at each visit are detailed in Table 1.

The study will consist of a 4-week Screening Period, a 24-week Double-blind Treatment Period, and a 4-week Follow-up Period. The total duration of the study for patients remaining in the study until their final follow-up assessment (End-of-Treatment [EoT] Visit 30 days after the last investigational medicinal product [IMP] dose) will be approximately 32 weeks (approximately 8 months).

The Investigator will obtain signed informed consent from the patient before any study procedures are performed. Patients will be assessed for eligibility during the Screening Period. All patients will attend Screening Visit 1. If liver biochemistry (see Footnote i of Table 1) and/or serum pregnancy (see Footnote l of Table 1) retests are required, patients will attend Screening Visit 2. Screening Visit 1 and, if required, Screening Visit 2 should be completed within 4 weeks prior to Randomization. If required, Screening Visit 2 should be conducted by Day -4.

At a subset of study sites that accept referral patients or where sparse transient elastography (FibroScan®) assessments are standard of care, a pre-Screening visit including local laboratory liver function tests and transient elastography can be performed to assess patient eligibility. The Investigator will then obtain signed pre-screening consent. Data obtained at a pre-Screening visit cannot be re-used for screening. Full standard screening must be repeated for patient enrollment.

Baseline assessments will be performed on Day 1 (Visit 3). Post-Baseline assessments will be performed at Weeks 2 (Visit 4), 4 (Visit 5), 8 (Visit 6), 12 (Visit 7), and 24 (Visit 8). In addition, study patients will be contacted by phone by the study site staff at Weeks 16 and 20.

Following permanent IMP discontinuation at any time during the study, patients will undergo an EoT Visit 30 days after their last dose. If IMP is permanently discontinued, the study assessments should continue until completion of the Week 24 Visit (Visit 8). If it is not feasible to complete all the visits, every possible effort should be made to complete the Week 24 Visit.

The Investigator, the site personnel, the Sponsor, and their representatives involved in monitoring and conducting the study, and the patients will be blinded to treatment assignments until the database is locked and the study is unblinded for analysis.

If applicable, patients will continue UDCA, obeticholic acid (OCA), and bezafibrate or fenofibrate treatment at a stable dose during the Double-blind Treatment Period. Patients should not start additional treatments for PBC after Randomization. All medications will be recorded in the electronic Case Report Form (eCRF).

Throughout the study, particular attention will be given to the detection and management of AESIs; suspected cases of DILI, potential cases of bone marrow toxicity, and potential cases of hypothyroidism.

The Independent Data Monitoring Committee (IDMC) will oversee the safety of participating patients. The role and responsibilities of the IDMC will be outlined in an IDMC Charter. An Adjudication Committee, who will remain blinded to patient treatment assignment, will adjudicate the AESIs and the adverse clinical outcomes. The roles and responsibilities of the Adjudication Committee will be outlined in an Adjudication Charter.

Study duration:

The study is expected to be conducted from Q3 2021 to Q2 2024. The start of the study will be the date on which the first patient provides informed consent, and the end of the study will be the last patient's last assessment.

The total study duration for an individual patient is up to approximately 32 weeks (approximately 8 months): A 4-week Screening Period, a 24-week Double-blind Treatment Period, and a 4-week Follow-up Period.

Planned number of patients: It is planned to enroll approximately 60 to 70 patients. Patients will be randomized and allocated to placebo, setanaxib 1200 mg/day, or setanaxib 1600 mg/day according to a 1:1:1 randomization ratio.

This study is designed to detect a >25% reduction in ALP in setanaxib-treated patients versus a 2.5% reduction in the placebo arm with an overall 2-sided $p<0.05$. Standard deviations are assumed to be 19% and 24%, respectively, based on the Phase 2a study with setanaxib and the Phase 3 POISE study with Ocaliva. With approximately 16 evaluable patients per arm (48 patients overall) and using a Hochberg step-up test to control alpha across 2 dose comparisons versus placebo, this study has 88.2% global power to detect at least 1 treatment arm as significantly different from placebo and 68.3% power to detect both treatment arms as statistically significant. Also, for the secondary endpoint of change in fatigue, there will be >80% power to detect a 20% reduction in fatigue versus a 2.5% increase in the placebo arm.

An assumed dropout rate of approximately 25% leads to a target sample size of 66 enrolled patients (22 per arm). A range of approximately 60 to 70 enrolled patients allows for variability in the assumed dropout rate.

Target population: Male or female patients aged ≥18 years with a definite or probable PBC diagnosis, serum ALP levels of ≥1.67×ULN at Screening, and liver stiffness measured by transient elastography (FibroScan®) of ≥8.0 kPa at Screening, will be included. Patients must have taken a UDCA prescriptional dose for the past 6 months (at a stable dose for >3 months prior to Screening) OR be intolerant to UDCA (last dose of UDCA >3 months prior to Screening). Intolerance to UDCA is defined as patients unable to tolerate the full-labeled dose of UDCA in PBC (13-15 mg/kg) due to frequently reported gastrointestinal symptoms such as diarrhea and abdominal pain. Any patients receiving OCA, fenofibrate, or bezafibrate must have been taking the agent(s) for at least 6 months and at a stable dose for >3 months prior to Screening.

Patients with any historical or current hepatic decompensation event, cirrhosis with complications, or competing etiology for liver disease will be excluded, as will patients with total bilirubin levels of >2×ULN or plasma ALT and/or AST levels of >3×ULN. Patients with an INR of >1.2 will also be excluded, unless the patient is on anticoagulant therapy.

Test product:

Name: Setanaxib

Setanaxib film-coated tablets will contain 400 mg setanaxib per tablet formulated with excipients and will be provided in high-density polyethylene (HDPE) bottles.

Dose: 1200 mg/day or 1600 mg/day for 24 weeks.

Mode of administration: Patients will self-administer IMP with food or up to 30 minutes after eating a meal.

- Patients allocated to setanaxib 1200 mg/day will self-administer 2 tablets of setanaxib 400 mg in the morning and 1 tablet of setanaxib 400 mg together with 1 tablet of placebo in the evening (ie, a total of 2 tablets in the morning and 2 tablets in the evening).
- Patients allocated to setanaxib 1600 mg/day will self-administer 2 tablets of setanaxib 400 mg in the morning and 2 tablets of setanaxib 400 mg in the evening (ie, a total of 2 tablets in the morning and 2 tablets in the evening).

Reference therapy:

Name: Placebo

Matching and visually identical placebo film-coated tablets, containing only excipients, will be provided in HDPE bottles.

Dose: Placebo will be self-administered twice daily for 24 weeks.

Mode of administration: Patients will self-administer IMP with food or up to 30 minutes after eating a meal. Patients allocated to placebo will self-administer 2 placebo tablets in the morning and 2 placebo tablets in the evening (ie, a total of 2 tablets in the morning and 2 tablets in the evening).

Statistical methods:

Efficacy Analysis: The Full Analysis Set (FAS) will be the primary set used for all efficacy analyses, along with the summary of disposition, demographics, and Baseline characteristics. Patients will be analyzed according to the treatment group they were randomized to regardless of the actual treatment received.

Primary Efficacy Analysis: Each setanaxib treatment group (1600 mg/day and 1200 mg/day) will be compared with placebo. The primary estimand is to assess the change in ALP (%) over 24 weeks in patients with PBC, elevated liver stiffness, and intolerance or inadequate response to UDCA.

The following intercurrent events will be considered and further detailed in the Statistical Analysis Plan (SAP). Patients who start additional PBC-related medication(s) after Randomization will have their IMP discontinued. These patients will be included in the analysis, but efficacy data collected after the start of the new therapy will be excluded. For all other patients who discontinue from treatment prior to Week 24 but return for the Week 24 Visit (Visit 8), the Week 24 result will be included in the analysis. Patients with a missing Week 24 result will have their value imputed based on observed data.

The primary endpoint will be evaluated using a mixed model for repeated measures (MMRM) with log(ALP) – log(Baseline) as response with log(Baseline) as a continuous covariate, ALP stratification ($<3.0\times$ULN or $\geq 3.0\times$ULN), treatment and visit as categorical covariates and treatment by visit as interaction term. All ALP data captured at Weeks 2, 4, 8, 12, and 24 will be included in the model. The relative mean change from Baseline at Week 24 will be estimated and corresponding 2-sided 95% confidence intervals will be calculated. In the case of outliers in the ALP data, a sensitivity analysis will utilize robust regression; this will be defined in the SAP.

A Hochberg step-up procedure will be used to control type I error across 2 individual dose comparisons versus placebo for the primary endpoint.

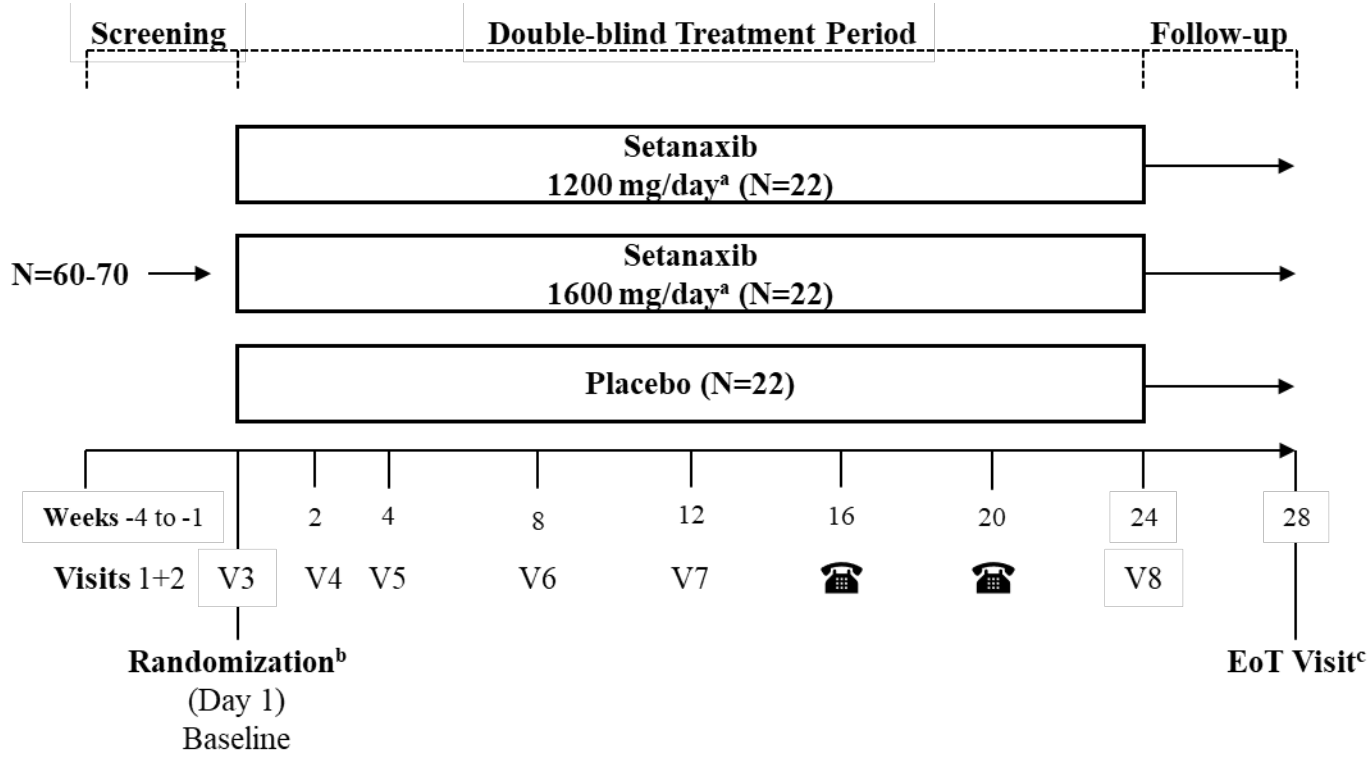
The 2 setanaxib treatment arms also will be combined in a secondary analysis for ALP, fatigue, and liver stiffness.

Safety Analysis: The Safety Analysis Set will be used for the analysis of safety data (AEs, including AESIs, clinical laboratory tests, vital signs, 12-lead ECGs, and physical examination).

Protocol version and date: Version 5.0 (27 September 2023)

STUDY SCHEMATIC

Figure 1 Study Schematic



EoS=End-of-Study; EoT=End-of-Treatment; IDMC=Independent Data Monitoring Committee; V=Visit

[a] The IDMC may recommend change(s) to the setanaxib dose regimen(s), or interruption or discontinuation of an active treatment group(s) based on the regular IDMC safety data reviews (as defined in the IDMC Charter).

[b] Eligible patients will be randomized to oral setanaxib 1200 mg/day, 1600 mg/day, or placebo, according to a 1:1:1 randomization ratio.

[c] Patients who permanently discontinue IMP prior to Week 24 Visit (Visit 8) will have an EoS Visit 30 days after the last IMP dose, after which every possible effort should be made to complete the Week 24 Visit (Visit 8).

SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

Study Period	Screening[a]		Double-blind Treatment Period							Follow-up[b,c,d]
Study Weeks:	-4 to -1		BL	2	4	8	12	16, 20	24	28
Study Days (Visit Window):	-28 to -4		1	15 (±3)	29 (±3)	57 (±7)	85 (±7)	113, 141 (±3)	169 (±14)	last IMP dose+30 (+7)
Visit:	1[a]	2[a]	3	4	5	6	7	Phone[e]	8	EoT
Informed consent	X									
Determination of eligibility[f]	X	X	X[f]							
Randomization			X							
Demographics and relevant medical history	X		X							
Height and body temperature	X									
Body weight	X								X	X
Physical examination[g]	X	X	X	X	X	X	X		X	X
Pulse rate, SBP, and DBP	X	X	X	X	X	X	X		X	X
12-lead ECG	X		X	X	X	X	X		X	X
Liver stiffness using transient elastography[h]	X	X					X		X	X
Blood sampling:										
Liver biochemistry[i]	X	X[i]	X	X	X	X	X		X	X
ELF score, PRO-C3, and C3M			X						X	X
hsCRP, IgM			X	X			X		X	X
Total bile acids, C4, FGF19, FGF21			X						X	X
Autoantibodies,[j] viral serology[k]	X									
Pregnancy test (serum)[l]	X[l]	X[l]								
Hematology and biochemistry[m]	X	X[i]	X	X	X	X	X		X	X
TSH and free T4	X	X[i]	X	X	X	X			X	
PK (morning predose)					X				X	
Biomarker (optional)			X						X	
Optional collection of DNA sample			X							
Urine collection:										
Urine drug screen	X									
Urinalysis[n]	X						X		X	X
Pregnancy test (urine)			X	X	X	X	X		X	X

Table 1 Schedule of Assessments

Study Period	Screening[a]		Double-blind Treatment Period							Follow-up[b,c,d]
Study Weeks:	-4 to -1		BL	2	4	8	12	16, 20	24	28
Study Days (Visit Window):	-28 to -4		1	15 (±3)	29 (±3)	57 (±7)	85 (±7)	113, 141 (±3)	169 (±14)	last IMP dose+30 (+7)
Visit:	1[a]	2[a]	3	4	5	6	7	Phone[e]	8	EoT
Patient questionnaires:										
PBC-40			X		X		X		X	
PROMIS sf-Fatigue 7b Daily, and PGIS fatigue[o]			X		X		X		X	
WI-NRS, and PGIS pruritus[o]			X		X		X		X	
PGIC fatigue and PGIC pruritus[o]					X		X		X	
PROMIS-29			X				X		X	
EQ-5D			X		X		X		X	
Dispense IMP			X		X		X			
Prior and concomitant medications[p,q]	X	X	X	X	X	X	X	X	X	X
MELD score	X		X	X	X	X	X		X	X
Recording of AEs[q]	X	X	X	X	X	X	X	X	X	X

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AMA=antimitochondrial antibodies; AST=aspartate aminotransferase; BL=Baseline; C3M=a peptide of helical collagen Type III degradation; C4=7α-OH-4-cholesten-3-one; DBP=diastolic blood pressure; ECG=electrocardiogram; eCRF=electronic Case Report Form; ELF=Enhanced Liver Fibrosis; EoS=End-of-Study; EoT=End-of-Treatment; EQ-5D=EuroQol-5 dimension; FGF=fibroblast growth factor; GGT=gamma glutamyl transpeptidase; hsCRP=high sensitivity C-reactive protein; IgM=immunoglobulin M; IMP=investigational medicinal product; INR=international normalized ratio; MELD=Model for End Stage Liver Disease; PBC=Primary Biliary Cholangitis; PBC-40=primary biliary cholangitis 40 questionnaire; PGIC=Patient's Global Impression of Change; PGIS=Patient's Global Impression of Severity; PK=pharmacokinetics; PRO-C3=released N-terminal propeptide of Type III collagen; PROMIS=Patient-Reported Outcomes Measurement Information System; RBC=red blood cell; SBP=systolic blood pressure; sf=short form; T4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell; WI-NRS=Worst Itch Numerical Rating Scale

[a] All patients will attend Screening Visit 1. If liver stiffness (see Footnote h) and/or liver biochemistry (see Footnote i) and/or serum pregnancy (see Footnote l) retests are required, patients will attend Screening Visit 2. Screening Visit 1 and, if required, Screening Visit 2 should be completed within 4 weeks prior to Randomization. If required, Screening Visit 2 should be conducted by Day -4. Screening Period extensions of up to 7 days may be considered on a case-by-case basis, if agreed by the Investigator and Medical Monitor.

[b] Patients who permanently discontinue IMP prior to completion of the 24-week Double-blind Treatment Period will have an EoT Visit 30 days after the last IMP dose, after which every possible effort should be made to complete the Week 24 Visit (Visit 8).

[c] Patients who complete the 24-week Double-blind Treatment Period will have an EoT Visit at 30 days after the last IMP dose.

[d] The EoT Visit will be the EoS Visit for a) patients who withdraw from the study before the Week 24 Visit (Visit 8), and b) patients who are following the previous protocol schedule and are already beyond Week 24.

Table 1 Schedule of Assessments

Study Period	Screening[a]		Double-blind Treatment Period							Follow-up[b,c,d]
Study Weeks:	-4 to -1		BL	2	4	8	12	16, 20	24	28
Study Days (Visit Window):	-28 to -4		1	15 (±3)	29 (±3)	57 (±7)	85 (±7)	113, 141 (±3)	169 (±14)	last IMP dose+30 (+7)
Visit:	1[a]	2[a]	3	4	5	6	7	Phone[e]	8	EoT

[e] Patients will be contacted by phone by study site staff at Weeks 16 and 20 to review AEs and any changes to concomitant medications. The phone calls will be documented in the eCRF by the study site.

[f] Eligibility to enter the Double-blind Treatment Period will be determined during Visit 1 and, if required, Visit 2, with a final check before Randomization on Day 1.

[g] A complete physical examination will be performed during Screening Visit 1 and at the Week 24 Visit (Visit 8). Patients who permanently discontinue IMP prior to or at the Week 24 Visit will have a complete physical examination at the EoT Visit. For Visits 2 to 7, when applicable, a symptoms-directed physical examination will be performed.

[h] Liver stiffness measurements using transient elastography (FibroScan®) will be carried out in the morning in the fasting state and at predose.
For assessments carried out on a different day than the study visit, FibroScan® assessments can be performed on any day during the specified visit windows predose or postdose but always after a 3-hour fasting.
During the Screening Period, the FibroScan® assessment can be performed on any day between 28 and 4 days prior to the Randomization/Baseline actual visit, after a 3-hour fasting. One repeat liver stiffness measurement can be performed within the Screening Period (at Screening Visit 2) at the discretion of the Investigator for patients who do not meet the inclusion criterion at the initial screening assessment. FibroScan® images will be read locally.

[i] Liver biochemistry: ALP, ALT, AST, total and conjugated bilirubin, and GGT. One repeat blood sampling (with analysis by the central laboratory) can be performed at the discretion of the Investigator at Screening Visit 2 for patients who do not meet the serum ALP inclusion criterion and/or who meet the total bilirubin and/or ALT/AST and/or TSH exclusion criteria at Screening Visit 1. The INR and creatinine are to be repeated in case the liver biochemistry test panel is taken at Screening Visit 2.

[j] AMA titer, PBC-specific antibodies (anti-GP210, anti-SP100, and antibodies against major M2 components).

[k] Viral serology: HIV antibodies (1 and 2) and, if positive for HIV antibodies, HIV RNA; hepatitis B surface antigen and hepatitis C virus antibodies and, if positive for HCV antibody, HCV RNA.

[l] A blood sample for the serum pregnancy test must be taken within 7 days of Day 1 (female patients of childbearing potential only). Therefore, if Screening Visit 1 is performed more than 7 days prior to Day 1, the serum pregnancy test must be repeated at Screening Visit 2 within 7 days of Day 1.

[m] Hematology: hematocrit, hemoglobin, absolute and relative reticulocyte counts, RBC count, WBC count, differential WBC count, platelet count, absolute neutrophil count, mean cell volume, and INR.
Biochemistry: glucose, total protein, albumin, fibrinogen, creatinine, urea, total cholesterol, triglycerides, sodium, potassium, and chloride.

[n] Quantitative test for urine pH and protein; qualitative tests for glucose, ketones, bilirubin, blood, and microscopic examination of the sediment.

[o] Patient questionnaires PROMIS sf-Fatigue 7b Daily and WI-NRS are completed at home every evening for 7 days prior to the site visits. PGIS and PGIC for fatigue and pruritus, respectively, are completed at home in the evening prior to the site visits.

[p] Prior medication will be recorded during Screening only.

Table 1 Schedule of Assessments

Study Period	Screening[a]		Double-blind Treatment Period							Follow-up[b,c,d]
Study Weeks:	-4 to -1		BL	2	4	8	12	16, 20	24	28
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Visit:	1[a]	2[a]	3	4	5	6	7	Phone[e]	8	EoT

[q] AEs and changes to concomitant medications will be recorded at each visit and each phone contact.

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LIST OF ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibodies
AST	aspartate aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
BID	twice daily
C3M	a peptide of helical collagen Type III degradation
C4	7α-OH-4-cholesten-3-one
CCL4	carbon tetrachloride
CFR	Code of Federal Regulations
CKD-EPI	chronic kidney disease epidemiology collaboration
CRO	Contract Research Organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DBP	diastolic blood pressure
DILI	drug-induced liver toxicity
EAPA	Europe, Asia-Pacific, and Africa
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDISH	evaluation of drug-induced serious hepatoxicity
eGFR	estimated glomerular filtration rate
ELF	Enhanced Liver Fibrosis
EMA	European Medicines Agency
EoS	End of Study
EoT	End-of-Treatment
EQ	EuroQol
EQ-5D	EuroQol 5 dimension
EudraCT	EU Drug Regulating Authorities Clinical Trials

FAS	Full Analysis Set
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
hsCRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IMP	investigational medicinal product
INR	international normalized ratio
IQR/med	interquartile range over median ratio
IRB	Institutional Review Board
IXRS	interactive voice response system/interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End Stage Liver Disease
MMRM	Mixed model repeated measures
MoA	mechanism of action
NADPH	nicotinamide adenine dinucleotide phosphate
NASH	nonalcoholic steatohepatitis
NOAEL	No observed adverse effect level
NOX	nicotinamide adenine dinucleotide phosphate (NADPH) oxidase
OAT	organic anion transporter
OCA	obeticholic acid
OD	once daily
PBC	primary biliary cholangitis
PBC-40	primary biliary cholangitis 40 questionnaire

PGIC	Patient's Global Impression of Change
PGIS	Patient's Global Impression of Severity
PIIINP	amino-terminal propeptide of Type III procollagen
PK	pharmacokinetic(s)
PPS	Per Protocol Set
PRO-C3	released N-terminal propeptide of Type III collagen
PROMIS	Patient-Reported Outcomes Measurement Information System
QTL	quality tolerance limit
RBC	red blood cell
ROS	reactive oxygen species
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
sDILI	suspected drug-induced liver injury
SOC	system organ class
T4	thyroxine 4
TEAE	treatment-emergent adverse event
TIMP-1	tissue inhibitor of metalloproteinase 1
TLR4	Toll-like receptor 4
t_{max}	time to maximum concentration
TSH	thyroid-stimulating hormone
UDCA	ursodeoxycholic acid
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cell
WI-NRS	Worst Itch Numerical Rating Scale

1 INTRODUCTION AND RATIONALE

1.1 Background

1.1.1 Primary Biliary Cholangitis

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is a liver disease caused by autoimmune (T-cell-mediated) attack on the small to medium intralobular bile ducts (Selmi et al 2011, Beuers et al 2015). A continuous assault on the bile duct epithelial cells leads to their gradual destruction and eventual disappearance (ie, ductopenia). Once immune-mediated bile duct injury has been established, the disease progresses due to chronic cholestasis, secondary inflammation, and fibrosis, and may lead to liver cirrhosis and liver failure (Kaplan and Gershwin 2005, Lindor et al 2009). The reasons for the autoimmune attack are not well understood but may involve environmental triggers in genetically-susceptible individuals.

The reported prevalence of PBC ranges from 20 to 400 cases per million of the population with some geographical differences (Sood et al 2004, Peters et al 2007). PBC is more common in women than men (9:1 ratio) and is mostly diagnosed between the ages of 30 and 60 years (Myers et al 2009, Hirschfield et al 2013).

Up to 60% of patients with PBC are asymptomatic at diagnosis. In these cases, PBC is detected through coincidental finding of abnormalities in liver biochemistry tests. The most common symptoms, where present, are fatigue and pruritus. Physical examination is often normal but, where present, common findings are: skin hyperpigmentation, jaundice, excoriations, xanthomata, xanthelasmas and, rarely, hepatosplenomegaly (Balasubramaniam et al 1990, Poupon 2010, Levy et al 2023).

Common laboratory test abnormalities in patients with PBC include elevated alkaline phosphatase (ALP), antimitochondrial antibodies (AMA), antinuclear antibodies, and hyperlipidemia. Other findings may include elevations in serum aminotransferases and bilirubin. Complications of PBC include cirrhosis, hepatocellular carcinoma, metabolic bone disease, and malabsorption (EASL 2017).

PBC is often associated (codiagnosed) with other autoimmune disorders including: Sjogren syndrome, autoimmune thyroid disease (Hashimoto's thyroiditis) and rheumatoid arthritis (EASL 2017).

1.1.1.1 Management and Treatment of Primary Biliary Cholangitis

Management of patients with PBC consists of treatment of the underlying disease and management of its symptoms and complications, including pruritus, fatigue, xanthomata, hypercholesterolemia, vitamin deficiencies, anemia, malabsorption, osteoporosis, etc. (EASL 2017).

PBC is a progressive disease in most patients. The only widely accepted standard of care treatment is ursodeoxycholic acid (UDCA). It is the only treatment recommended in guidelines issued by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver.

Although there is currently no targeted treatment for the autoimmune injury to biliary epithelial cells, in recent years, novel therapies targeting cholestasis have improved outcomes for many patients with PBC. UDCA and more recently obeticholic acid (OCA) have been licensed by the Food and Drug Administration (FDA) and European Medicines Agency (EMA), for treatment of PBC.

UDCA is a synthetic secondary bile acid, given orally at a dose of 13 to 15 mg/kg/day as first-line treatment for PBC. The following mechanisms of action may be involved in the beneficial therapeutic effects of UDCA in PBC and other cholestatic disorders: (a) increase in the hydrophilicity of circulating bile acids; (b) stimulation of hepatocellular and ductular secretions; (c) protection against cellular injury caused by bile acids and cytokines; (d) some degree of immunomodulation and anti-inflammatory effects. Currently, treatment with UDCA represents the global standard of care (Selmi et al 2011, Lindor et al 2009; EASL 2017; Lindor et al 2020), and can delay histologic progression (Sood et al 2004, Kaplan and Gershwin 2005, Peters et al 2007) and improve long-term survival (Myers et al 2009, Hirschfield et al 2013). However, UDCA is not a uniformly effective drug; there is little benefit to symptoms, and approximately 40% of PBC patients have a suboptimal response to UDCA (Corpechot et al 2008, Rudic et al 2012). Patients with an inadequate response to UDCA (assessed biochemically), or those not tolerating UDCA, progress to cirrhosis and liver failure leading to liver transplant or death. Therefore, there is an unmet medical need in PBC patients with inadequate response to UDCA.

OCA is another synthetic secondary bile acid which has been approved by the FDA and EMA for treatment of PBC (Invernizzi et al 2015). OCA is indicated for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. It has a similar mechanism of action as UDCA but has been shown to achieve further reductions in ALP levels in patients with inadequate response to UDCA. This additional anticholestatic effect was associated with a reduction in hepatocellular damage, as shown by decreases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. However, OCA treatment achieved only small reductions in these markers of hepatocellular injury which failed to normalize to below the upper limit of normal (ULN) reference range (Nevens et al 2016). Over time, this sustained hepatocellular injury likely contributes to progressive liver fibrosis and failure. Separately, OCA worsens the severity of pruritus, a key symptom of PBC which significantly impacts patients' quality of life.

The currently approved therapies mainly target cholestasis. However, there is a need for well tolerated therapies able to address additional components of the disease, including autoimmune injury to biliary endothelial cells, bile acid-mediated hepatocellular injury, and fibrogenesis (Dyson et al 2015, Hirschfield et al 2016). Also, there is a need to address symptomatic relief in patients with PBC eg, fatigue and pruritus (Nevens et al 2023).

1.1.2 Setanaxib (Investigational Medicinal Product)

Setanaxib (formerly GKT137831) is a first-in-class inhibitor of the human protein nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) Isoforms 1 and 4. It is a small organic molecule of low molecular weight and a member of the pyrazolopyridine dione chemical class.

The NOX family is a set of transmembrane proteins (Bedard and Krause 2007). NOX enzymes require the stable assembly of transmembrane and cytosolic subunits. Upon assembly of a full enzymatic complex and activation by its substrates NADPH and molecular oxygen, NOX enzymes transport electrons through the cell membrane to produce reactive oxygen species (ROS). In turn, ROS modulate multiple signaling pathways by oxidizing regulatory cysteine residues in target proteins. ROS can also cause other types of posttranslational modification of proteins and can target lipids and nucleic acids.

When exaggerated in duration and/or magnitude, NOX activation participates in the pathogenesis of a broad range of human diseases. In particular, the NOX1 and NOX4 isoforms have been shown to play a key role in a broad range of fibrotic and inflammatory disorders (Krause and Bedard 2008, Paik et al 2014, Liang et al 2016, Teixeira et al 2016). Importantly, studies have revealed that liver tissue expression of NOX1 and/or NOX4 is consistently elevated in patients with fibrotic liver diseases (Bettaieb et al 2015, Lan et al 2015).

Setanaxib is being investigated in several fibrotic and inflammatory disorders, including PBC. Setanaxib's mechanism of action (MoA) differs from that of anticholestatic agents, which are marketed (UDCA, OCA), in late-stage development (seladelpar, elafibranor), or increasingly used off-label (bezafibrate, fenofibrate). Specifically, setanaxib possesses broad antifibrotic and anti-inflammatory effects but does not modulate bile acid metabolism. Phase 2 results indicated that through this novel MoA, setanaxib achieves further reductions in markers of cholestatic injury (ALP, gamma glutamyl transpeptidase GGT]), improves markers of liver fibrosis (liver stiffness, PRO-C3/C3M), and improves quality of life (fatigue and its social and emotional impact). These therapeutic benefits were substantially greater in patients with elevated liver stiffness at Baseline, a population at risk of disease progression. Compounds with novel MoAs are needed, particularly in patients at higher risk or in patients not responding or not tolerating anticholestatic therapies.

1.1.3 Nonclinical Studies

In Vitro and *In Vivo* Pharmacology

Detailed summaries for all studies are given in the Investigator's Brochure (IB).

A set of *in vitro* and *in vivo* pharmacology studies have been conducted with setanaxib to support its proposed use as a NOX1/4 enzyme inhibitor for the treatment of fibrotic and inflammatory disorders including PBC. Investigation of potential effects against a broad range of receptors and enzymes confirmed that setanaxib demonstrated no significant off-target activity, except for significant inhibition of human recombinant

15-lipoxygenase-2. However, a review of available literature did not detect a safety concern.

In *in vitro* studies in isolated cells, setanaxib was shown to attenuate signaling evoked by a number of ligands known to induce and/or drive the fibrogenic process in multiple fibrogenic pathways, including TGF-β1 (transforming growth factor beta 1), PDGF (platelet-derived growth factor), toll-like receptor 4 (TLR4), hedgehog, and angiotensin II (Lan et al 2015). As a result, setanaxib markedly reduced the induction of markers of myofibroblast activation, including αSMA (smooth muscle actin alpha), fibronectin, and procollagen I (Aoyama et al 2012, Jiang et al 2012).

These direct antifibrogenic effects translate into antifibrotic activity in multiple *in vivo* models of liver fibrosis. Specifically, setanaxib attenuated the development of liver fibrosis induced by experimental cholestasis (in the bile duct ligation and MDR2 [multiple drug resistance 2]-/-, mouse models). Setanaxib also prevented liver fibrosis in models of nonalcoholic steatohepatitis (NASH) (in the STAM [stelic animal model] and fast food diet models [Jiang et al 2012, Teixeira et al 2014, Bettaieb et al 2015]) and in toxic hepatitis (in carbon tetrachloride [CCL4]-induced liver injury [Aoyama et al 2012]). Reduced *in vivo* fibrogenesis was associated with a marked reduction in markers of myofibroblast activation.

In addition, setanaxib has shown potent anti-inflammatory effects in a number of biological settings, including metabolic and cholestatic liver injury. Specifically, setanaxib prevented the induction of adhesion molecules, cytokines, and chemokines in CCL4-induced liver injury and fast food diet-induced NASH (Bettaieb et al 2015). These effects on innate immunity resulted in a profound reduction of macrophage infiltration. Available data suggest that these anti-inflammatory effects are mediated through reduced activation of multiple pathways, including TLR4 and NF-κB (nuclear factor kappa B) (Paik et al 2014). In these studies, reduced liver inflammation was associated with a reduction in plasma levels of liver transaminases.

In Vivo and *In Vitro* Safety Pharmacology and Toxicology

To support clinical development of setanaxib via oral administration a series of safety pharmacology studies and a toxicity program designed in accordance with guidelines provided by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) were conducted with setanaxib. This included a standard battery of genotoxicity studies and repeat dose toxicity studies in the rat and dog of up to 26 weeks and 39 weeks duration, respectively.

Setanaxib was shown to be devoid of *in vitro* and *in vivo* genotoxicity and there are no relevant effects on fertility or embryonic/fetal development.

The no observed adverse effect level (NOAEL) in rats was established at 1000 mg/kg/day, the highest dose tested. The dog was the more sensitive species, and the NOAEL was established at 150 mg/kg/day in the 26-week dog study and 300 mg/kg/day in the pivotal 39-week dog study. Treatment-related effects in the dog studies were confined to electrocardiogram (ECG) changes, decreased thyroid hormone

levels, which in some animals correlated to thyroid follicular hypertrophy, and effects on the erythrocyte and reticulocyte counts indicative of effects on bone marrow.

Cardiac disorders: Setanaxib and its main active metabolite GKT138184 had no effect on the hERG channel, with an IC_{50} of >300 μM. There was no significant inhibition of I_{Na} or I_{Ca} with 100 μM of setanaxib or GKT138184. I_{Ks} was inhibited 60% by 100 μM setanaxib and not significantly inhibited by 100 μM of the metabolite, GKT138184. Setanaxib and GKT138184 have no significant inhibitory activity on the I_{Kr} cardiac ion channel at 300 μM.

In dog studies, the chronic administration of setanaxib in the 500/300 mg/kg dose group was associated with reversible QT prolongation and atrioventricular-block events. Cardiovascular effects of setanaxib were examined in conscious dogs using radio telemetry. No effects of setanaxib at doses of up to 1000 mg/kg were observed on blood pressure, heart rate, RR, QRS, and PR intervals or on R wave height, compared to the vehicle-treated group. Significant, but limited, increases in QT interval were observed at 3 to 4 hours postdose in dogs receiving doses of 100 mg/kg or above in this conscious dog using telemetry study. QT/QTc intervals were evaluated at several time points in the 13-, 26- and 39-week dog studies. There were no indications of any ECG changes in the 13-week or 39-week dog studies, in contrast to the 26-week study where variable changes in QTc intervals were limited to the earlier timepoints in the highest setanaxib dose group only (500/300 mg/kg).

The variability of the changes in QT in time and in relation to dose and the lack of consistency within and between animals, the absence of treatment-related ECG alterations at both the NOAEL of 150 mg/kg/day and the highest tolerated dose of 300 mg/kg/day in the 26-week dog study, at the NOAEL of 300 mg/kg in the 39-week dog study, or at any of the doses tested in the already completed clinical studies, did not provide definitive information that setanaxib could prolong QT in a way that indicated a definitive risk to humans.

Thyroid disorders: Findings related to the thyroid, ie, decreased thyroxine (T4) and increased thyroid-stimulating hormone (TSH), in some cases correlating with thyroid hypertrophy, seen in early toxicology studies in dogs were not replicated in the chronic toxicity studies, even though higher exposures were attained. No thyroid follicular cell hypertrophy or changes in thyroid hormones were observed at any dose level up to a dose of 300 mg/kg/day in either the 26-week or 39-week dog studies.

Bone marrow disorders: In dog toxicology studies, the administration of setanaxib in the ≥500/300 mg/kg dose group was associated with a reduction in erythroid precursors in the bone marrow, and reduced reticulocyte and red blood cell (RBC) counts in peripheral blood, leading to severe aplastic anemia in 1 dog, which required euthanasia. By Week 5, ie, prior to the dose reduction from 500 to 300 mg/kg/day in the 26-week dog study, a marked decrease in reticulocyte count (~90% decrease compared with pretest) was detected for 1 female dog. As per protocol, no further hematologic monitoring was conducted until Week 13, at which time reticulocyte counts remained decreased and red cell parameters were markedly decreased. This time course indicates that setanaxib affected erythroid progenitors in 1 dog during the initial dosing period with 500 mg/kg. These findings may be due to a direct effect of setanaxib on erythroid

progenitors because setanaxib was found to be cytotoxic *in vitro* to hematopoietic BFU-E (burst-forming unit-erythroid) progenitor cells derived from canine bone marrow mononuclear cells. This effect was observed only at concentrations greater than 10 μM.

In addition, minor and reversible changes in total plasma bilirubin and other liver function tests were observed but were never associated with signs of hepatocellular injury or liver pathologies and as such were not considered to be adverse.

1.1.4 Clinical Studies

To date, 6 Phase 1 studies in healthy subjects (GSN000108, GSN000109, GSN000198, GSN000199, GSN000299, GSN000310), 2 Phase 2 studies (1 in patients with PBC [GSN000300], 1 in patients with Type 2 diabetes and albuminuria [GSN000200]) have been completed. A Sponsor-led study with setanaxib in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (GSN000400) is ongoing. Ongoing Investigator-initiated studies are evaluating setanaxib in patients with Type 1 diabetes and micro-albuminuria (Study GSN000241), and in patients with idiopathic pulmonary fibrosis (Study GSN000341/Protocol No. IRB-300003198).

Pharmacokinetics

The Phase 1 studies have characterized the clinical pharmacokinetics (PK), safety and tolerability profile of single and multiple ascending doses of setanaxib and the main active metabolite GKT138184 in healthy subjects.

No safety signals or dose-limiting toxicities have been identified up to a maximum single 1800 mg dose or repeated 800 mg twice daily (BID) dose (total daily dose of 1600 mg) for 10 consecutive days.

Potential food and drug interactions have been evaluated. Study GSN000310 assessed the effect of repeated setanaxib administration on the PK of selected cytochrome (CYP) 450 isoenzyme CYP2C9, CYP2C19 and CYP3A4 and transporter substrates, including for OAT1 and OAT3 (organic anion transporters).

Both setanaxib and its main active metabolite (GKT138184) exhibit approximate dose proportional PK across the dose ranges studied. Following both single and multiple dose administration of setanaxib across all doses studied, the main active metabolite exposure is consistently approximately 20% of the corresponding parent exposure. The PK for setanaxib and GKT138184 are similar.

Setanaxib is rapidly absorbed after oral administration (time to maximum concentration [t_{max}] between 0.5 and 3 h post dosing), with a tendency for later t_{max} for both capsules and tablets when setanaxib is administered under fed conditions. Setanaxib dosed in the fasted state is typified by higher inter-subject variability in maximum concentration and area under the curve (AUC). Following single-dose administration of setanaxib tablets, estimates of setanaxib elimination half-life ranged from approximately 8 to 14 h, and 9 to 12 h for the main active metabolite GKT138184. Modest accumulation of both setanaxib and GKT138184 were observed on repeated BID administration of the tablet

formulation (for 1200 and 1600 mg total daily doses), with steady state Day 8 exposures ranging from 2 to 30% higher than corresponding exposures on Day 1.

The main routes of the primary metabolism of setanaxib appear to be uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A9 to GKT289993 (N-glucuronide) and via CYP3A4, principally to the main active metabolite GKT138184 (product of demethylation). Therefore, strong inhibitors and inducers of CYP3A4 and UGT1A9 may affect the plasma exposures of setanaxib.

Setanaxib has been shown to be a weak inhibitor of CYP2C9 and CYP2C19 at the 800 mg BID dose in healthy subjects, increasing the AUC of sensitive probe substrates by 45% and 60%, respectively.

Setanaxib has been shown to be a weak inhibitor of OAT3 at the 800 mg BID dose in healthy subjects, increasing the AUC of a sensitive probe substrate by 33%.

Efficacy in Patients with PBC (Protocol GSN000300)

This completed Phase 2 proof of concept study was an international double-blind, randomized, placebo-controlled clinical study to assess the efficacy and safety of oral setanaxib in patients with PBC, persistently elevated ALP, and elevated levels of GGT who were receiving UDCA. The primary efficacy endpoint was defined as the percent GGT reduction from Baseline to Week 24. Secondary efficacy endpoints included ALP changes, liver stiffness measured by transient elastography (FibroScan®) and quality of life. Statistical significance for all endpoints at Week 24 was set at $p<0.047$ for the first dose level tested and 0.023 for the 2nd dose level tested, according to the Hochberg adjustment method for multiple analyses. A total of 111 eligible patients were randomized to setanaxib (400 mg once daily [OD] or 400 mg BID) or placebo according to 1:1:1 randomization ratio for a total of 24 weeks.

At Week 24, GGT reductions were -8% for placebo, -5% for setanaxib 400 mg OD, and -19% for setanaxib 400 mg BID. These changes did not achieve statistical significance at Week 24, although statistical significance had been achieved at the 6-week interim efficacy analysis ($p<0.01$ for setanaxib 400 mg BID versus placebo). For the 400 mg BID dose, the mean percent change from Baseline in serum GGT was maintained at around -19% from Week 12 to Week 24.

A statistically significant reduction in overall treatment effect was also observed for ALP levels ($p=0.002$) over the course of the Double-blind Treatment Period. At Week 24, setanaxib 400 mg BID achieved meaningful reductions in ALP. Changes were -3% for placebo, −10% for setanaxib 400 mg OD, and -13% for setanaxib 400 mg BID ($p<0.049$ versus placebo). There was a statistically significant change in ALP versus Baseline for the setanaxib 400 mg BID of -16% observed at 6 weeks. No changes were observed for total bilirubin (+11% for placebo, +5% for 400 mg OD, and +15% for setanaxib 400 mg BID). On the composite endpoint of serum ALP <1.67xULN, ALP decrease >15%, and total bilirubin <ULN, the response rates at Week 24 were 5% for placebo, 18% for setanaxib 400 mg OD, and 25% for setanaxib 400 mg BID.

Median percent changes in valid liver stiffness measurements in the intention-to-treat analysis set were +4.1% for placebo, +1.4% for setanaxib 400 mg OD, and −4.9% for

setanaxib 400 mg BID. Patients with advanced liver fibrosis at Baseline (predefined population of patients with liver stiffness ≥9.6 kPa), experienced greater absolute reductions in median liver stiffness from Baseline following 24 weeks of setanaxib 400 mg BID (–3.0 kPa) compared with modest reductions following 24 weeks of setanaxib 400 mg OD (−1.0 kPa) or placebo treatment (−0.7 kPa), corresponding to mean percentage reductions of −16%, −5%, and +4%, respectively (p=0.11 for setanaxib 400 mg BID versus placebo).

The posthoc analyses of the percent change from Baseline to Week 24 in serum GGT and ALP by Baseline liver stiffness subgroup showed that patients with elevated liver stiffness at Baseline who received the setanaxib 400 mg BID dose achieved greater mean reductions in serum GGT and ALP at Week 24 (−32.4% and −24.3%, respectively) than those with normal or marginally elevated liver stiffness at Baseline (−12.9% and −8.7%, respectively).

At Week 24, patients treated with setanaxib 400 mg BID reported greater mean (standard error of mean) absolute reductions from Baseline in PBC-40 fatigue domain score (–3.6 [1.3]) versus those receiving setanaxib 400 mg OD (–0.8 [1.0]) or placebo (0.6 [0.9]). Similar observations were made across all PBC-40 domains except itch. In the setanaxib 400 mg BID arm, patients with moderate to severe fatigue at Baseline had a greater reduction in mean fatigue score at Week 24 (–5.8 [2.1]) versus those with mild fatigue (–0.6 [0.9]); results were similar across all domains. Reduced fatigue was correlated with emotional, social, symptom, and cognitive improvements.

The analysis of the percent change from Baseline to Week 24 in PBC-40 questionnaire showed a statistically significant improvement for the 400 mg BID dose (versus placebo) in the fatigue, social, and emotional domains (p-values equal to 0.027, 0.003, and 0.031, respectively).

The analysis of the percent change from Baseline to Week 24 in pruritus score (using a visual analogue scale [VAS]) showed a statistically significant reduction for the 400 mg OD dose (p-value=0.004) versus placebo. For the 400 mg BID dose, the difference versus placebo is not statistically significant (p-value=0.103).

Safety

In patients with PBC, setanaxib exhibited a favorable safety profile throughout the 24-week Double-blind Treatment Period. No dropouts or treatment interruptions due to pruritus or fatigue were reported. Only 2 serious adverse events (SAEs) were reported, a case of Grade 1 urinary infection requiring hospitalization in the placebo group and a case of multiple bone fractures related to a traffic accident in the setanaxib 400 mg BID group. Both cases were deemed unrelated to study drug by the Investigators. A review of adverse events (AEs), safety laboratory results, vital signs, physical examination, and ECG did not identify any safety signals associated with setanaxib at 400 mg OD or 400 mg BID.

The safety signals identified in toxicology studies (see Section 1.1.3) have not been detected in the completed clinical studies to date. Specifically, there was no evidence of drug effect on thyroid function, bone marrow function, or cardiac conduction:

Thyroid disorders: In clinical studies of setanaxib completed to date, there has been no evidence of thyroid disorders related to setanaxib exposure.

Bone marrow disorders: In clinical studies of setanaxib completed to date, there has been no evidence of bone marrow toxicity related to setanaxib exposure.

Cardiac disorders: In clinical studies of setanaxib completed to date, there has been no evidence of clinically relevant changes in ECGs associated with setanaxib, including QT prolongation.

In this ongoing study, TRANSFORM GSN000350 (data cutoff of 21 August 2023), there was 1 SAE of QTc prolongation that occurred in a patient with atrial fibrillation. The investigational medicinal product (IMP) was discontinued and the patient remained asymptomatic throughout the event duration.

Liver disorders: In clinical studies of setanaxib completed to date, there have been no cases of hepatic disorders related to setanaxib exposure.

In the ongoing TRANSFORM GSN000350 study (data cutoff of 21 August 2023), there have been 4 SAEs in 4 patients associated with mild elevation in liver blood test results that were considered possibly related to the IMP. These 4 SAEs of elevated liver blood test results were the only SAEs of hepatic disorders that were considered related to the IMP in the entire setanaxib clinical program to date. All 4 patients with elevated liver blood test results discontinued IMP and remained asymptomatic throughout the period of the abnormal liver laboratory results.

For further details, refer to the IB.

1.2 Study Rationale

PBC is a chronic disease and without effective treatment it is often progressive, leading to cirrhosis and liver failure, resulting in liver transplantation or death (EASL 2017). This study is being conducted in order to determine the effect of setanaxib on biochemical response based on ALP and fatigue in patients with PBC, elevated liver stiffness, and intolerance or inadequate response to UDCA. Intolerance to UDCA is defined as patients unable to tolerate the full-labeled dose of UDCA in PBC (13-15 mg/kg) due to frequently reported gastrointestinal symptoms such as diarrhea and abdominal pain.

This study will assess the decrease in ALP with daily doses of 1200 mg and 1600 mg versus placebo, whereas the previous PBC setanaxib Phase 2 study (GSN000300) investigated daily doses of 400 mg and 800 mg versus placebo.

Since the initial study design, there has been a significant evolution in the management of patients with PBC. In particular, the use of second-line therapies such as OCA (Ocaliva) and fibrates (eg, bezafibrate) has expanded, and a significant proportion of patients who are intolerant or nonresponders to UDCA are able to receive dual or triple therapy (ie, UDCA plus OCA and/or a fibrate). As a consequence, there appears to have been a general reduction in the level of disease activity observed in patients being

considered for enrolment in the study (allowing for patients on dual or triple therapy), as judged by lower levels of ALP. This has likely decreased the available study population and consequently the rate of enrolment of patients into the study.

Based on the observed low enrolment rate, Calliditas does not consider it feasible to complete the study in its current format within a reasonable timeframe. It is nevertheless acknowledged that there is preliminary evidence of beneficial effects of setanaxib on important clinical aspects of PBC, including ALP, fatigue and related social and cognitive manifestations (Invernizzi et al 2023). Despite the evolution in the therapeutic approach to PBC, there still remain significant unmet needs, in particular with respect to quality of life outcomes such as fatigue, as this is typically unaffected by existing therapies (Jones et al 2023).

Calliditas has therefore decided to amend the protocol changing the study from the current Phase 2b/3 study to a 24-week Phase 2b study of 60 to 70 patients to enable an earlier assessment of the safety and efficacy of setanaxib with the two doses (1600 mg and 1200 mg) versus placebo. With this amended design there is no longer a need for an interim analysis for the assessment of futility and dose selection for a Phase 3 portion, as this is removed. Consequently, the 52-week Extension Phase Treatment Period has been removed.

Given the revision to a Phase 2b study, it is of scientific relevance to focus on an individual endpoint only. Therefore, rather than the originally planned composite endpoint consisting of change in ALP and total bilirubin, the primary endpoint has been amended to evaluate the individual endpoint of change in ALP. The secondary endpoints of change in fatigue and liver stiffness are retained, as is the composite endpoint of changes in markers of cholestasis.

The reduced duration of study treatment from 52 weeks to 24 weeks in combination with the change from a composite primary endpoint to an individual primary endpoint (change in ALP) with fatigue as a secondary endpoint is supported by the preliminary evidence obtained in the Phase 2 study in patients with PBC (GSN000300) as detailed in Section 1.1.4. This study showed statistically significant and clinically meaningful changes in the above mentioned endpoints after 24 weeks of treatment. This is in line with a retrospective investigation, which concluded that measuring ALP at 6 months is of clinical relevance (Murillo Perez et al 2023).

As consequence of the change in primary endpoint, the assumptions for the sample size have been revisited: with approximately 16 evaluable patients per arm (48 patients overall), there will be >80% power to detect a >25% reduction in ALP in setanaxib-treated patients versus a 2.5% reduction in the placebo arm with a 2-sided $p<0.05$. For the secondary endpoint of change in fatigue, there will be >80% power to detect a 20% reduction in fatigue versus a 2.5% increase in the placebo arm. A dropout rate of approximately 25% leads to a target sample size of 66 patients (22 per arm). A range of approximately 60 to 70 patients allows for variability in the assumed dropout rate.

In combination, the revision of treatment duration, primary endpoint, and sample size has statistical validity and an acceptable probability of detecting clinically meaningful changes in ALP and fatigue. During the analysis, the benefit-risk profile of each

setanaxib dose will be assessed and compared to determine the optimal dose for further development.

Given the changes to endpoints, study duration, and statistical analysis of the study, the study will no longer support a direct application for approval in PBC. Rather, the final analysis will permit an assessment of the development pathway for setanaxib in PBC, which will potentially focus on quality of life outcomes such as fatigue. The amended study no longer has an adaptive component and no part of it can be considered Phase 3 in development stage. The description of the study is therefore amended from Phase 2b/3 to Phase 2b. Given that the revisions may allow the 2 doses of setanaxib to be distinguished, it is considered feasible that only 1 additional study may be required for regulatory approval. It should be noted that patients, Investigators, and the Sponsor have remained blind to randomized treatment and no unblinded data have been reviewed prior to this amendment.

Details regarding the rationale for setanaxib dose selection are provided in Section 3.2.1.

1.3 Benefit/Risk Assessment

Potential Benefits

Patients included in this study will have PBC with elevated liver stiffness, despite treatment with first-line and potentially second-line treatments for PBC. Participation in this study provides the patient with a potential opportunity to take setanaxib, which is being evaluated for efficacy in this clinical study. Patients included in the study will have a 2/3 chance of receiving setanaxib. While NOX1/4 inhibition represents an attractive therapeutic strategy in patients with PBC, therapeutic benefits in patients with PBC have yet to be demonstrated.

During this study patients will undergo the regular medical evaluations and assessments for PBC, as part of the study procedures.

Potential Risks

As summarized in Section 1.1.3 and Section 1.1.4, setanaxib has been extensively investigated in nonclinical and clinical studies.

In the completed Phase 1 and Phase 2 studies, the safety profile of setanaxib has been shown to be favorable, with no clinical safety signal and no dose-limiting toxicity identified (see Section 1.1.4). The safety signals identified in the toxicology studies (thyroid function, ECG abnormalities, hematological changes) have been carefully monitored in all clinical studies completed to date. No treatment-related clinical or pathological findings have been observed, irrespective of dose, treatment duration or type of clinical study.

The doses of setanaxib under investigation in this study are 1200 mg/day and 1600 mg/day. The highest dose regimen to be evaluated in this study constitutes a dose doubling compared to the previous study in patients with PBC where there were no safety signals of concern (see the setanaxib dose rationale and justification of safety

margins in Section 3.2.1). Due to the higher setanaxib doses being evaluated in the current study, there is a potential risk of new safety signals that have not been observed to date in the previous clinical studies. Patients included in this study will undergo regular safety assessments. In addition, given the findings from the toxicology studies (see Section 1.1.3), and the characteristics of the disease, appropriate exclusion criteria and safety endpoints for regular monitoring have been built into this study as precautions.

- Thyroid disorders (hypothyroidism): Patients with TSH levels >ULN at Screening will be excluded from this clinical study. The levels of TSH and free T4 will be regularly monitored during the study. In the case of TSH ≥10 mIU/L, IMP administration will be interrupted while the patient undergoes evaluation for hypothyroidism.

- Bone marrow disorders (anemia): Patients with a history of bone marrow disorder, including aplastic anemia, or any current marked anemia defined as hemoglobin <10.0 g/dL will be excluded from the study. Reticulocyte counts will be regularly monitored during the study. In case of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 anemia, IMP administration will be interrupted while the patient undergoes further evaluation.

- Cardiac disorders: Patients with certain cardiac conduction abnormalities as well as patients with a second- or third-degree atrioventricular block will be excluded from the study. Patients included in the study will undergo regular monitoring for evidence of cardiac disorders by 12-lead ECGs. If the patient develops a QT prolongation (QTc Fridericia interval >450 milliseconds for males and >470 milliseconds for females), or an increase in QTc greater than 60 milliseconds from Baseline, whichever comes first, or if the patient develops other severe cardiac conditions per the Investigator's judgment, the IMP will be discontinued.

- Liver disorders (DILI): Patients with total bilirubin >2×ULN and/or plasma ALT and/or AST >3×ULN will be excluded from the study. Liver biochemistry tests will be regularly monitored during the study. As noted in Appendix II, if prespecified levels of AST, ALT, total bilirubin, or international normalized ratio (INR) are met during the study, IMP administration will be interrupted while the patient undergoes further evaluation.

Drug-induced liver injury (DILI), anemia, and hypothyroidism will be AEs of special interest ([AESIs], see Section 7.1.5) in this study and will be reported within 24 hours of the Investigator becoming aware of the event.

An Adjudication Committee will remain blinded to patient treatment assignment and will adjudicate the AESIs and the adverse clinical outcomes (see Section 5.4). An unblinded Independent Data Monitoring Committee (IDMC) will oversee the safety of participating patients. The IDMC will regularly review an aggregated list of events adjudicated by the Adjudication Committee (see Section 9.4).

The medications being taken by a patient will be carefully evaluated by the Investigator before the patient is enrolled into the study, and concomitant medications will be

recorded throughout the study. The main routes of the primary metabolism of setanaxib appear to be UGT1A9 to GKT289993 (N-glucuronide) and via CYP3A4, principally to the main active metabolite GKT138184 (product of demethylation). Therefore, strong inhibitors and inducers of UGT1A9 or CYP3A4 may affect the plasma exposures of setanaxib. Setanaxib is a weak inhibitor of CYP2C9, CYP2C19 and OAT3.

In vitro, setanaxib inhibited breast cancer resistance protein (BCRP) and MDR1 (P-glycoprotein) and also suggests that setanaxib is an inducer of CYP2B6. Therefore, setanaxib may increase the plasma concentration of drugs which are primarily eliminated through these enzymes and transporters. Caution should be exercised during concomitant use of the drug with setanaxib. Based on a literature search, and nonclinical and clinical safety data, it is the Sponsor's position that setanaxib does not have immunosuppressive properties. All approved COVID-19 vaccines are allowed in setanaxib studies. It is important that the COVID-19 vaccinations are not delayed.

At least one-third of patients included in this study will not receive setanaxib. Therefore, there is a risk of disease progression without the possibility of trying any other new potential treatments for PBC.

More detailed information about the known and expected benefits, risks, and reasonably expected AEs of setanaxib can be found in the IB.

Considering the measures taken to minimize risk to the patients participating in this study, the potential risks identified in association with setanaxib are justified by the anticipated benefits that may be afforded to patients with PBC.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Endpoint

Primary Objective	Primary Endpoint
• To evaluate the effect of setanaxib on ALP at Week 24 in patients with PBC and with elevated liver stiffness and intolerance or inadequate response to UDCA	• Change in ALP at Week 24 compared to Baseline

Information about the corresponding estimand is provided in Section 8.4.1.1.

2.2 Secondary Objectives and Endpoints

Secondary Objective	Secondary Endpoint
• To evaluate the effect of setanaxib on fatigue at Week 24	• Change in fatigue at Week 24 compared to Baseline, as assessed by ○ the Patient-Reported Outcomes Measurement Information System (PROMIS) short form-Fatigue 7b Daily ○ the Patient's Global Impression of Severity (PGIS) fatigue ○ the Patient's Global Impression of Change (PGIC) fatigue ○ the PBC-40 questionnaire (PBC-40) fatigue domain
• To evaluate the effect of setanaxib on liver stiffness at Week 24	• Change in liver stiffness at Week 24 compared to Screening, as assessed by transient elastography (FibroScan®)
• To evaluate the effect of setanaxib on ALP, fatigue, and liver stiffness at Week 24, where setanaxib doses are combined	• Change in ALP at Week 24 compared to Baseline, where setanaxib doses are combined ○ Change in fatigue at Week 24 compared to Baseline, as assessed by the PROMIS short form-Fatigue 7b Daily, the PGIS fatigue , the PGIC fatigue, and the PBC-40 fatigue domain, where setanaxib doses are combined ○ Change in liver stiffness at Week 24 compared to Screening, as assessed by transient elastography (FibroScan®), where setanaxib doses are combined

• To evaluate the effect of setanaxib on pruritus at Week 24	• Change in pruritus at Week 24 compared to Baseline, as assessed by the Worst Itch Numerical Rating Scale (WI-NRS), the PBC-40 itch domain, and the PGIS and the PGIC pruritus
• To evaluate the effect of setanaxib on markers of cholestasis at Week 24	• Changes in markers of cholestasis as assessed by proportion of patients at Week 24 with: ○ ALP reduction to <1.67×ULN and total bilirubin ≤1×ULN and a ≥15% or ≥30% or ≥40% or ≥70% ALP reduction from Baseline, respectively ○ ALP reduction to <1.5×ULN and total bilirubin ≤1×ULN and a ≥40% ALP reduction from Baseline ○ ALP <1×ULN and total bilirubin ≤1×ULN ○ Total bilirubin <0.6×ULN
• To evaluate the safety and tolerability of setanaxib over a 24-week Treatment Period	• AEs. Monitoring for AEs at all visits • AESIs: ○ DILI ○ Anemia ○ Hypothyroidism • Laboratory tests: ○ Hematology ○ Biochemistry ○ Urinalysis ○ Thyroid function • Vital signs • 12-lead ECGs: clinically significant abnormalities

2.3 Exploratory Objectives and Endpoints

Exploratory Objectives	Exploratory Endpoints
• To evaluate the effect of setanaxib over a 24-week Treatment Period on markers of liver fibrosis, cholestasis, bile acid metabolism, and liver function	• Changes in markers of liver fibrosis, as assessed by the Enhanced Liver Fibrosis (ELF) score, PRO-C3 (released N-terminal propeptide of Type III collagen), C3M (a peptide of helical collagen Type III degradation), and PRO-C3/C3M ratio over 24 weeks compared to Baseline • Changes in total and conjugated bilirubin over 24 weeks compared to Baseline • Changes in markers of bile acid metabolism, as assessed by total bile acids, C4 (C4=7α-OH-4-cholesten-3-one), fibroblast growth factor (FGF)19, and FGF21 over 24 weeks compared to Baseline • Changes in markers of liver function over 24 weeks compared to Baseline, as assessed by: ○ Serum fibrinogen, albumin, and INR ○ ALT, AST, GGT, high sensitivity C-reactive protein (hsCRP), and immunoglobulin M (IgM) indicating liver inflammation and injury
• To evaluate the effect of setanaxib on adverse clinical outcomes	• Assessment over 24 weeks of: ○ All-cause mortality ○ Proportion of patients requiring a liver transplant (transplant list inclusion) ○ Proportion of patients with a Model for End Stage Liver Disease (MELD) score of ≥15 ○ Proportion of patients with new onset of variceal/portal hypertension bleed and/or hepatic encephalopathy (West Haven criteria), spontaneous bacterial peritonitis, and ascites requiring treatment

Exploratory Objectives	**Exploratory Endpoints**
• To further evaluate the effect of setanaxib on patient-reported outcomes	• Change over 24 weeks compared to Baseline in: ○ Social isolation symptoms, as assessed by the PBC-40 social domain ○ Overall health-related quality of life, as assessed by the PROMIS-29 questionnaire ○ EuroQol five-dimensional (EQ-5D) Utility Index
• To determine the predose plasma levels of setanaxib and its metabolite GKT138184	• Predose plasma concentrations of setanaxib and GKT138184 over 24 weeks

3 STUDY PLAN

3.1 Overall Study Design and Plan

This study is a randomized, placebo-controlled, double-blind, parallel-group, multicenter, Phase 2b study assessing oral setanaxib administered as an add-on therapy in patients with PBC, elevated liver stiffness, and intolerance or inadequate response to UDCA. The safety and efficacy of 1200 mg/day and 1600 mg/day setanaxib will be assessed against matching placebo over 24 weeks of treatment. It is planned to enroll approximately 60 to 70 patients at 80 to 130 investigational centers in North America, Europe, Israel, Australia, and New Zealand.

The study design is outlined in Figure 1 (Study Schematic), and the visit schedule and planned assessments at each visit are detailed in Table 1.

The study will consist of a 4-week Screening Period, a 24-week Double-blind Treatment Period, and a 4-week Follow-up Period. The total duration of the study for patients remaining in the study until their final follow-up assessment (End-of-Treatment [EoT] Visit 30 days after the last IMP dose) will be approximately 32 weeks (approximately 8 months).

The Investigator will obtain signed informed consent from the patient before any study procedures are performed. For further details regarding the informed consent process, see Section 9.3. Patients will be assessed for eligibility during the Screening Period. All patients will attend Screening Visit 1. If liver biochemistry (see Footnote i of Table 1) and/or serum pregnancy (see Footnote l of Table 1) retests are required, patients will attend Screening Visit 2. Screening Visit 1 and, if required, Screening Visit 2 should be completed within 4 weeks prior to Randomization. If required, Screening Visit 2 should be conducted by Day -4.

At a subset of study sites that accept referral patients or where sparse transient elastography (FibroScan®) assessments are standard of care, a pre-Screening visit including local laboratory liver function tests and transient elastography can be performed to assess patient eligibility. The Investigator will then obtain signed pre-screening consent. Data obtained at a pre-Screening visit cannot be re-used for screening. Full standard screening must be repeated for patient enrollment.

Eligible patients will be randomized to oral setanaxib 1200 mg/day, 1600 mg/day, or placebo, according to a 1:1:1 randomization ratio, stratified by Screening serum ALP < or ≥3.0×ULN. See Section 6.3 for further details on the method of assigning patients to the treatment groups, and see Section 6.4 for further details on the dose and administration of setanaxib and placebo.

Baseline assessments will be performed on Day 1 (Visit 3). Post-Baseline assessments will be performed at Weeks 2 (Visit 4), 4 (Visit 5), 8 (Visit 6), 12 (Visit 7), and 24 (Visit 8). In addition, study patients will be contacted by phone by the study site staff at Weeks 16 and 20.

Special Note: Patients who are following the previous protocol schedule (protocol version 4) and are already beyond Week 24 should permanently discontinue IMP as soon as possible and have an EoT Visit 30 days after their last dose.

Following permanent IMP discontinuation at any time during the study, patients will undergo an EoT Visit 30 days after their last dose. If IMP is permanently discontinued, the study assessments should continue until completion of the Week 24 Visit (Visit 8). If it is not feasible to complete all the visits, every possible effort should be made to complete the Week 24 Visit.

The Investigator, the site personnel, the Sponsor and their representatives involved in monitoring and conducting the study, and the patients will be blinded to treatment assignments until the database is locked and the study is unblinded for analysis (see Section 6.2). Also see Section 6.2 for details on access to the treatment codes in the event of emergency unblinding.

If applicable, patients will continue UDCA, OCA, and bezafibrate or fenofibrate treatment at a stable dose during the Double-blind Treatment Period. Patients should not start additional treatments for PBC after Randomization. All medications will be recorded in the electronic Case Report Form (eCRF).

Throughout the study, particular attention will be given to the detection and management of AESIs, suspected cases of DILI (see Section 5.3.2.1 and Appendix II), potential cases of bone marrow toxicity (see Section 5.3.2.2), and potential cases of hypothyroidism (see Section 5.3.2.3).

The IDMC will oversee the safety of participating patients (see Section 9.4.2). The role and responsibilities of the IDMC will be outlined in an IDMC Charter. An Adjudication Committee, who will remain blinded to patient treatment assignment, will adjudicate the AESIs and the adverse clinical outcomes (see Section 9.4.1). The roles and responsibilities of the Adjudication Committee will be outlined in an Adjudication Charter.

3.2 Discussion of Study Design

This study will be randomized, placebo-controlled, and double-blinded. Study randomization will prevent bias in treatment allocation. In addition, stratification by Screening serum ALP will help to ensure that the treatment groups are balanced in terms of population characteristics, thereby minimizing factors that could confound the interpretation of study results. The double-blinding of the study with regard to setanaxib and placebo treatment assignments will minimize bias in the assessment of treatment effect. Although Investigators are blinded to treatment assignments, the Investigators will review the laboratory reports, which will include ALP, the primary endpoint parameter, and bilirubin. It is acknowledged that access to the values might essentially unblind the Investigators to the treatment assignment of their patients. However, knowledge of ALP and bilirubin is required to inform the appropriate medical management of the patient from a safety perspective.

The patients included in this study will have PBC with elevated liver stiffness, despite treatment with first-line, and potentially second-line, treatments for PBC.

All patients included in this study will continue treatment on their stable prescriptional dose of UDCA, unless the patient is intolerant to UDCA. Second-line therapies for PBC are also permitted for patients who have been on a stable dose for >3 months prior to Screening. Therefore, setanaxib or placebo will be given as add-on therapy to first and/or second-line therapies. Due to the lack of alternative effective treatments for this population of patients with PBC, a placebo-controlled study design is most appropriate.

The doses of setanaxib under investigation in this study are 1200 mg/day and 1600 mg/day. The highest dose regimen to be evaluated in this study constitutes a dose doubling compared to the previous study in patients with PBC where there were no safety signals of concern. Please refer to Section 3.2.1 for the setanaxib dose rationale and justification of safety margins.

Management of patients with PBC includes monitoring of laboratory parameters (including ALP, bilirubin, AST, albumin, and platelet count) and elastography (EASL 2017). Abnormally high ALP levels typically occur in patients with PBC, and ALP values are associated with disease progression (EASL 2017). Bilirubin is a prognostic marker of a poor outcome in patients with PBC and is generally elevated at late stages of the disease (EASL 2017). Patients included in this study will have an ALP level ≥1.67×ULN and a total bilirubin level of ≤2×ULN at Screening. If the total bilirubin elevation is >ULN at Screening, the albumin level must be within the reference range.

This Phase 2b study has as the primary endpoint change in ALP (%), with daily doses of 1200 mg and 1600 mg versus placebo, whereas the previous PBC setanaxib Phase 2 study (GSN000300) investigated daily doses of 400 mg and 800 mg versus placebo. A central laboratory analyzes the levels of ALP and other laboratory parameters in order to standardize the analysis methodology and minimize sources of error from samples taken at the different study sites.

The feasibility to conduct a study within an acceptable time frame under an adaptive Phase 2b/3Phase 2b study design, has proved challenging. This is considered to be related to new and more frequently used treatment options, which the study (all protocol versions) allows for, such as OCA and off-label use of bezafibrates. One consequence of this is that fewer patients than anticipated are meeting the inclusion criteria of ALP ≥1.67×ULN or liver stiffness ≥8.0 kPa. Therefore, the study design is revised to a Phase 2b study, with the primary objective to assess the decrease in ALP. Please also see Section 1.2.

Patients included in this study will have an EoT Visit 30 days after the last dose of IMP.

Cholestasis often manifests with symptoms including fatigue and pruritus, which are significant causes of impaired quality of life (EASL 2017). In this study, fatigue and pruritus will be assessed as secondary endpoints. A structured approach to quantify fatigue and pruritus will be undertaken through the completion of validated questionnaires.

Safety is being assessed in this study as a secondary endpoint. The safety assessments included in this study are standard.

3.2.1 Setanaxib Dose Rationale and Justification of Safety Margins

Given the experience of nonclinical and clinical data, the present study is designed to show efficiency in a safely conducted study.

In the completed Phase 1 and Phase 2 studies, the safety profile of setanaxib has been shown to be favorable, with no clinical safety signal and no dose-limiting toxicity identified.

The previous clinical study in patients with PBC (GSN000300) evaluated setanaxib 400 mg BID for 24 weeks. This dosing regimen was considered safe and well tolerated, but the observed clinical efficacy was considered insufficient. Therefore, there is an interest in studying higher doses up to 800 mg BID for 24 weeks.

The highest dose regimen to be evaluated in this study constitutes a dose doubling compared to the previous study in patients with PBC where there were no safety signals of concern. Although the expected exposures will be around the defined NOAEL for both the parent (setanaxib) and the main active metabolite (GKT138184), all the NOAEL defining toxicology signals can and will be monitored and were not observed neither in the healthy volunteers at 800 mg BID for 8 days or patients at 400 mg BID for 24 weeks.

For the proposed maximal dose (setanaxib 800 mg BID [total daily dose 1600 mg]), toxicology studies in the dog, the most sensitive species, provide a safety margin of ≥1, when the combined concentration of setanaxib and its main active metabolite (GKT138184) is considered. The safety margin for setanaxib alone is also ≥1. However, for the main active metabolite GKT138184, the safety margin is calculated to be 0.7. Refer to the Setanaxib Investigator Brochure for further details on the safety margins.

Given the findings from the toxicology studies and the characteristics of the disease, appropriate exclusion criteria and safety endpoints for regular monitoring have been built into this study, as precautions. Please refer to Section 1.3 for further details.

3.3 End of Study

A patient is considered to have completed the study if he/she has completed all study visits.

The end of the study is defined as the date of the last visit or last procedure of the last patient in the study.

4 STUDY POPULATION

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

4.1 Inclusion Criteria

The following inclusion criteria must be met for a patient to be eligible for inclusion in the study:

1. Male or female patient aged ≥18 years, inclusive at the time of informed consent.

2. Willing and able to give written informed consent and to comply with the requirements of the study.

3. Definite or probable PBC diagnosis as demonstrated by the presence of ≥2 of the following 3 diagnostic factors:

    a. Documented history of elevated ALP levels ≥1.67×ULN of the local reference range.

    b. Documented history of positive AMA titer or positive PBC-specific antibodies (anti-GP210 or anti-SP100 or antibodies against the major M2 components [PDC-E2, 2-oxo-glutaric acid dehydrogenase complex]).

    c. Historical liver biopsy consistent with PBC.

4. Serum ALP ≥1.67×ULN at Screening.

    One repeat blood sampling (with analysis by the central laboratory) can be performed at the discretion of the Investigator at Screening Visit 2 for patients who do not meet this inclusion criterion at Screening Visit 1. If this inclusion criterion is then met at Screening Visit 2, the patient may be eligible for the study.

5. Liver stiffness measured by transient elastography (FibroScan®) of ≥8.0 kPa and an interquartile range over median ratio (IQR/med) of ≤30% at Screening, are taken with the results expressed in kilopascals [kPa]).

    One repeat liver stiffness measurement can be performed within the Screening Period at the discretion of the Investigator for patients who do not meet the inclusion criterion at the initial screening assessment. If the inclusion criterion is then met, the patient may be eligible for the study.

6. UDCA prescriptional dose use for the past 6 months (at a stable dose for >3 months prior to Screening) OR intolerant to UDCA (last dose of UDCA >3 months prior to Screening). Intolerance to UDCA is defined as patients unable to tolerate the full-labeled dose of UDCA in PBC (13-15 mg/kg) due to frequently reported gastrointestinal symptoms such as diarrhea and abdominal pain.

7. For patients receiving OCA, fenofibrate, or bezafibrate treatment for at least 6 months and stable dose for >3 months prior to Screening.

8. For patients intolerant to OCA, OCA must have been discontinued >3 months prior to Screening.

9. For patients previously treated with bezafibrate or fenofibrate, and these agents were discontinued prior to Screening, they must have been discontinued >3 months prior to Screening.

10. Female patients of childbearing potential must use a highly effective method of contraception to prevent pregnancy for ≥4 weeks before Randomization and must agree to continue strict contraception up to 90 days after the last dose of IMP.

    a. For the purposes of this study, women of childbearing potential are defined as "Fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy."

    b. Postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In female patients who are not using hormonal contraception or hormonal replacement therapy but with suspected menopause and less than 12 months of amenorrhea, a high follicle-stimulating hormone (FSH) level in the postmenopausal range will be required at Screening to confirm a postmenopausal state. Confirmation with more than one FSH measurement is required.

    c. Highly effective contraception is defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. These methods are:

        (1) Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)

        (2) Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)

        (3) Intrauterine device

        (4) Intrauterine hormone-releasing system

        (5) Bilateral tubal occlusion

        (6) Vasectomized partner

        (7) Sexual abstinence (refraining from heterosexual intercourse during the entire period of risk associated with the study treatments). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception). Female condom and male condom should not be used together.

11. Female patients of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization/Baseline before dosing.

12. Male patients with female partners of childbearing potential must be willing to use a condom and require their partner to use a highly effective contraceptive method (as defined in the list in item 10c). This requirement begins at the time of informed consent and ends 90 days after receiving the last dose of IMP.

13. Male patients must be willing not to donate sperm, and female study patients must be willing not to donate eggs, from Baseline until 90 days after the last dose of IMP.

4.2 Exclusion Criteria

A patient who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

1. A positive pregnancy test or breastfeeding for female patients.

2. Any historical or current hepatic decompensation event defined as variceal/portal hypertension bleed and/or hepatic encephalopathy, spontaneous bacterial peritonitis, ascites requiring treatment, or liver transplantation list inclusion.

3. History of liver transplantation, current placement on a liver transplant list or current MELD score of ≥12 unless the patient is on anticoagulant therapy, or a Child-Pugh Score of ≥6.

4. Cirrhosis with complications, including history or presence of hepatocellular carcinoma.

5. Total bilirubin >2×ULN. In case of total bilirubin elevation >ULN the Screening serum albumin must be within the reference range.

   One repeat blood sampling (with analysis by the central laboratory) can be performed at the discretion of the Investigator at Screening Visit 2 for patients who meet this exclusion criterion at Screening Visit 1. If this exclusion criterion is not met at Screening Visit 2, the patient may be eligible for the study.

6. Plasma ALT >3×ULN and/or AST >3×ULN.

   One repeat blood sampling (with analysis by the central laboratory) can be performed at the discretion of the Investigator at Screening Visit 2 for patients who meet this exclusion criterion at Screening Visit 1. If this exclusion criterion is not met at Screening Visit 2, the patient may be eligible for the study.

7. INR >1.2 unless patient is on anticoagulant therapy.

   One repeat blood sampling (with analysis by the central laboratory) can be performed at the discretion of the Investigator at Screening Visit 2 for patients who meet this exclusion criterion at Screening Visit 1. If this exclusion criterion is not met at Screening Visit 2, the patient may be eligible for the study.

8. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, as calculated by the central laboratory using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation.

9. TSH >ULN at Screening.

   One repeat blood sampling (with analysis by the central laboratory) can be performed at the discretion of the Investigator at Screening Visit 2 for patients who meet this exclusion criterion at Screening Visit 1. If this exclusion criterion is not met at Screening Visit 2, the patient may be eligible for the study.

10. Competing etiology for liver disease (eg, hepatitis C, as defined by positive hepatitis C virus antibody and positive hepatitis C RNA [unless effectively cured of hepatitis C (HCV antibody positive and negative HCV RNA) with a sustained virologic response for at least 6 months prior to Screening], active hepatitis B [HBsAg positive], NASH, alcoholic liver disease, autoimmune hepatitis, autoimmune hepatitis-PBC overlap syndrome, primary sclerosing cholangitis, Gilbert's Syndrome).

11. Medical conditions that could cause nonhepatic increases in ALP (eg, Paget's disease).

12. Known history of HIV infection. If the anti-HIV antibody test is positive, HIV RNA negativity has to be confirmed by the central laboratory.

13. Surgery (eg, stomach bypass) or medical condition that might significantly affect absorption of medicines (as judged by the Investigator).

14. Positive urine drug screen (if not due to prescriptional use of a concomitant medication, as confirmed by the Investigator) at Screening. Patients on stable methadone or buprenorphine maintenance treatment for at least 6 months prior to Screening Visit 1 may be included in the study. Medicinal cannabis and cannabidiol products are not allowed.

15. Patients receiving prohibited medications within 3 months of Screening Visit 1 as specified in Section 6.6 and 6.7.

16. Treatment with any investigational agent within 12 weeks of Screening Visit 1 or 5 half-lives of the IMP (if known) (whichever is longer) or current enrollment in an interventional clinical study.

17. Evidence of any of the following cardiac conduction abnormalities: A QTc Fridericia interval >450 milliseconds for males or >470 milliseconds for females, as calculated by the central reader. Patients with a second- or third-degree atrioventricular block are to be excluded.

18. History of a malignancy within 5 years of Screening with the following exceptions:

    a. Adequately treated carcinoma in situ of the cervix

    b. Adequately treated basal or squamous cell cancer or other localized nonmelanoma skin cancer.

19. The occurrence of any acute infection requiring systemic antibiotic therapy within the 2 weeks prior to Screening Visit 1.

20. A history of bone marrow disorder including aplastic anemia, or any current marked anemia defined as hemoglobin <10.0 g/dL.

21. Prior treatment with setanaxib or participation in a previous setanaxib clinical study.

22. Unstable cardiovascular disease as defined by any of the following:

    a. Unstable angina within 6 months prior to Screening

    b. Myocardial infarction, coronary artery bypass graft surgery, or coronary angioplasty within 6 months prior to Screening

    c. Cerebrovascular accident within 6 months prior to Screening

    d. New York Heart Association Class III or IV heart failure

23. Presence of any laboratory abnormality or condition that, in the opinion of the Investigator, could interfere with or compromise a patient's treatment, assessment, or compliance with the protocol and/or study procedures.

24. Any other condition which, in the opinion of the Investigator, constitutes a risk or contraindication for the participation of the patient in the study, or that could interfere with the study objectives, conduct, or evaluation.

25. Hypersensitivity or intolerance to setanaxib or to any of its excipients or placebo compounds.

4.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but who do not meet one or more criterion required for participation and are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Note that one repeat blood sampling (with analysis by the central laboratory) can be performed at Screening Visit 2 for patients who do not meet the serum ALP inclusion criterion and/or who meet the INR, TSH, total bilirubin and/or ALT/AST exclusion criteria at Screening Visit 1 at the Investigator's discretion, if the Investigator believes that the result was spurious, confounded, or not in line with the historical values of the patient. In these cases, the repeat assessment is allowed without the patient being considered a screen failure. Screening Period extensions of up to 7 days may be considered on a case-by-case basis, if agreed by the Investigator and Medical Monitor.

Patients who are screen failures may undergo **full** rescreening once at the discretion of the Investigator if there is a reasonable expectation that the patient is potentially eligible for the study. In these cases, the rescreened patient should be assigned a new unique screening number. A second full rescreening at the discretion of the Investigator if there is a reasonable expectation and rationale provided that the patient is potentially eligible for the study can be done if agreed by the Medical Monitor. Again, the rescreened patient should be assigned a new unique screening number.

4.4 Premature Discontinuation

4.4.1 Premature Discontinuation of Investigational Medicinal Product

Patients should discontinue the IMP if any of the following occurs:

1. The patient withdraws his/her consent to participate in the study.

2. The patient develops an illness that would interfere with his/her continued participation in the study, at the Investigator's discretion.

3. The patient is noncompliant with study procedures or medication, which in the opinion of the Investigator, impacts patient safety and/or the integrity of the study results.

4. The patient takes prohibited medication that warrants the IMP discontinuation at the discretion of the Investigator. The introduction of any standard of care PBC treatment (OCA, fenofibrate, or bezafibrate) is allowed, but warrants IMP discontinuation (see Section 6.7). Dose modifications of concomitant PBC treatments initiated before Randomization do not require IMP discontinuation.

5. The patient is confirmed to be pregnant.

6. The Sponsor or regulatory agency requests withdrawal of the patient.

7. The patient has suspected drug-induced liver injury (sDILI) meeting Criteria C in Appendix II.

8. The patient has CTCAE Grade ≥2 anemia AND the retest absolute reticulocyte count is below 50% of the Baseline value, IMP will not be resumed and will be permanently discontinued.

9. The patient has a retest TSH level of ≥10 mIU/L if overt biological hypothyroidism is confirmed (ie, TSH ≥10 mIU/L and reduced free T4) (see Section 5.3.2.3).

10. The patient has one or more adverse clinical outcome listed in Section 5.4.

11. The patient has a severe cardiac condition per the Investigator's judgment, QT prolongation (QTc Fridericia interval >450 milliseconds for males and >470 milliseconds for females), or an increase in QTc greater than 60 milliseconds from Baseline, whichever comes first.

Patients who permanently discontinue IMP prior to completion of the Week 24 Visit (Visit 8) will have an EoT Visit 30 days after the last IMP dose, after which every possible effort should be made to complete the Week 24 study assessments (Visit 8) (see Table 1).

Patients who discontinue IMP prematurely will not be replaced.

4.4.2 Premature Discontinuation from the Study

Participation in the study is strictly voluntary. A patient has the right to withdraw from the study at any time for any reason, without any reprisal.

The Investigator has the right to terminate participation of a patient for any of the following reasons:

- Violation of the protocol jeopardizing patient safety and/or integrity of study results
- Any other reason relating to the patient's safety
- Any other reason relating to the integrity of the study data

Investigators should make every effort to discuss with the study monitor/Sponsor before discontinuing a patient from the study; it should be considered if IMP discontinuation, with completion of the Week 24 Visit (Visit 8) may be appropriate (see Section 4.4.1).

If a patient is withdrawn from the study, the study monitor/Sponsor will be informed immediately. If there is a medical reason for withdrawal, the patient will remain under the supervision of the Investigator until satisfactory health has returned.

If the patient withdraws consent for disclosure of further information, the Sponsor may retain and continue to use any collected data before such a withdrawal of consent. If a patient 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.

Although a patient is not obliged to give his/her reason(s) for withdrawing prematurely from a study, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights.

At the time of premature study discontinuation, the Investigator should make every effort to ensure the patient completes the assessments indicated at the EoT Visit, which will be the End of Study (EoS) Visit for the patient; see Table 1.

Patients who prematurely discontinue from the study cannot subsequently rejoin the study.

For details on the discontinuation of study sites or the study as a whole, see Section 14.

4.4.3 Lost to Follow-up

A patient will be considered lost to follow-up if he/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 patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.

- Before a patient is deemed lost to follow-up, the Investigator (or designee) must make every effort to regain contact with the patient (where possible, at least 2 phone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical notes.

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

5 DESCRIPTION OF STUDY ASSESSMENTS

Refer to Table 1 for the schedule of assessments.

Patients will be asked to fast from 10 pm on the day prior to study visits until after the study procedures have been completed. Patients will be reminded to bring the IMP and their PBC medications with them to each study visit. On visit days, patients will take their morning doses of IMP and their usual PBC medications with food (or up to 30 minutes after eating a meal) after the study procedures have been completed. In cases where the FibroScan® assessment is carried out on a different day than the study visit, refer to Section 5.2.2 for fasting and IMP instructions.

In general, the assessments at the site visits will be conducted in the following order:

- Patient-reported outcomes (see Section 5.2.3 for the order of patient-reported outcomes assessments)
- AEs/concomitant medications recording
- Physical examinations/vital signs/ECGs
- Laboratory assessments/FibroScan®
- Dispense IMP
- Patient takes morning dose of IMP with food (or up to 30 minutes after eating a meal), as well as any morning doses of their usual medications for PBC (see Section 6.7)

5.1 Demographics and Other Screening Assessments

All patients will attend Screening Visit 1. If serum pregnancy (see Footnote l of Table 1) retests are required, patients will attend Screening Visit 2. Screening Visit 2 is also performed at the discretion of the Investigator to retest liver stiffness, liver biochemistry and/or TSH when eligibility criteria are not met at Screening Visit 1 (see Footnotes h and i of Table 1). Screening Visit 1 and, if required, Screening Visit 2 should be completed within 4 weeks prior to Randomization. If required, Screening Visit 2 should be conducted by Day -4. Screening Period extensions of up to 7 days may be considered on a case-by-case basis, if agreed by the Investigator and Medical Monitor.

Demographics will be collected as described in Section 5.1.2. The assessment of medical history is described in Section 5.1.1.

Safety assessments, including laboratory assessments, which are also part of the screening assessments are described in Section 5.3. The eGFR will be calculated as described in Section 5.1.3.

The screening assessment of liver stiffness by transient elastography (FibroScan®) will be assessed as described in Section 5.2.2.

Prior medications will be assessed at Screening, as described in Section 6.6.

5.1.1 Medical History

Relevant medical history, including any ongoing illnesses, will be recorded in the eCRF, with the start date and stop date (if applicable) of the illness/condition.

Any prestudy procedures will be recorded in the eCRF as part of the medical history assessment.

5.1.2 Demographics

Demographic data, including year of birth/age, sex, and race, will be recorded in the eCRF.

5.1.3 Estimated Glomerular Filtration Rate

The CKD-EPI formula for adults will be used to calculate eGFR (mL/min/1.73 m^2) from the biochemistry and demographic data collected at Screening Visit 1. The eGFR will be calculated by the central laboratory according to the equation included in the central laboratory manual.

5.1.4 Child-Pugh Score

The Child-Pugh Score will be calculated from the total bilirubin, serum albumin, and INR central laboratory test results from blood samples collected at Screening Visit 1, together with the clinical criteria of hepatic encephalopathy and ascites. In case retesting of liver function tests, TSH, and INR are performed at Screening Visit 2, then the Screening Visit 2 results are used for calculating the Child-Pugh Score. The formulas to calculate the Child-Pugh Score are provided in Appendix V.

5.2 Efficacy Assessments

5.2.1 Biochemical Response

Liver biochemistry blood samples for the assessment of biochemical response (based on ALP and total bilirubin levels) will be collected as described in Section 5.3.2. Biochemical response will be assessed at each post-Baseline visit for which a liver biochemistry blood sample is collected.

5.2.2 Liver Stiffness, Transient Elastography (FibroScan®)

Transient elastography (FibroScan®) will be used to assess the degree of liver stiffness. The assessments will be conducted by a health professional trained, qualified, and experienced in the use of FibroScan® and in accordance with the manufacturer's manual and the study specific site operations manual.

FibroScan® will be carried out in the morning in fasting state, and hence predose, with fasting from 10 pm on the day prior to the study visit. For assessments carried out on a different day than the study visit, FibroScan® assessments can be performed on any day

during the specified visit windows predose or postdose but always after a 3-hour fasting.

During the Screening Period, the FibroScan® assessment can be performed on any day between 28 and 4 days prior to the Randomization/Baseline actual visit, after a 3-hour fasting. One repeat liver stiffness measurement can be performed within the Screening Period at the discretion of the Investigator for patients who do not meet the inclusion criterion at the initial screening assessment. If the inclusion criterion is then met, the patient may be eligible for the study. The FibroScan Screening assessment meeting the inclusion criterion will serve as the Baseline value.

It is recommended that the patient's FibroScan® assessment is done by the same person using the same type of probe at each study visit. The results from FibroScan® assessments will be expressed in kPa. FibroScan® images will be read locally. Investigators will printout the results of the FibroScan® assessments and file the printouts in the patient notes. The results, the FibroScan® software version and probe used will be recorded in the eCRF.

Both non-SmartExam and SmartExam software versions can be used. Every effort should be made to not mix the use of non-SmartExam and SmartExam versions for the assessments in individual patients. FibroScan® acquisition files from SmartExam assessments should be downloaded from the FibroScan® and stored in accordance with the Study Operational Manual. Those files will be used to a posteriori compute the liver stiffness values obtained without SmartExam algorithm.

Patients eligible for the study are required to have liver stiffness of ≥8.0 kPa and an IQR/med of ≤30% at Screening. At each subsequent FibroScan® assessment an IQR/med of ≤30% for liver stiffness measurement is required (Boursier et al 2013; Corpechot et al 2022).

5.2.3 Patient-reported Outcomes

Patient-reported outcome questionnaires will be completed on paper at time points specified in Table 1. The Sponsor or designee will provide the questionnaires to the study sites. Site staff should refer to the site operation manual for guidance on the administration of the patient-reported outcomes. The completed questionnaires will be maintained at the study site as source documents. The results will be transcribed into the eCRF by site personnel. The eCRF entry guidelines include questionnaire-specific instructions on how to manage any ambiguous responses to individual items.

- Fatigue will be assessed using the PROMIS short form-Fatigue 7b Daily (Section 5.2.3.1), and the PGIS fatigue, PGIC fatigue (Section 5.2.3.5) and the PBC-40 fatigue domain (Section 5.2.3.1).

- Pruritus will be assessed using the WI-NRS (Section 5.2.3.3), the PBC-40 itch domain (Section 5.2.3.1), and the PGIS and PGIC pruritus (Section 5.2.3.5).

- Social isolation symptoms will be assessed using the PBC-40 social domain (Section 5.2.3.1).

- Health-related quality of life will be assessed using PROMIS-29 (Section 5.2.3.4)
- Health utility data will be computed using the EQ-5D Utility Index (Section 5.2.3.6).

The patient-reported outcome questionnaires PBC-40, PROMIS-29, and EQ-5D are completed at the site. The completion of questionnaires at the site visits should be performed before any of the other study procedures, including the collection of blood for laboratory assessments. At study site visits, the patient will be asked to read and complete the questionnaires independently. The patient will be given sufficient time to complete the assessments. If a patient is unable to read, the site staff will administer the questionnaires by reading aloud the content of the questionnaires to the patient and recording the patient's verbal response. The questionnaires will be administered in the following order:

- PBC-40
- PROMIS-29
- EQ-5D

The patient questionnaires PROMIS short form-Fatigue 7b Daily and WI-NRS are completed at home every evening for 7 days prior to the site visits. PGIS and PGIC for fatigue and pruritus, respectively, are completed at home in the evening prior to the site visits (ie, Day 7 of each of the diary completion weeks). The questionnaires are provided as booklets where the questionnaires are placed in the order specified below. Detailed completion instructions are included in the booklets.

- PROMIS short form-Fatigue 7b Daily
- WI-NRS
- PGIS fatigue
- PGIC fatigue
- PGIS pruritus
- PGIC pruritus

5.2.3.1 Primary Biliary Cholangitis-40 Questionnaire

The PBC-40 is a disease-specific health-related quality of life measure validated for use in patients with PBC (Jacoby et al 2005). The questionnaire comprises 40 questions in 6 domains related to fatigue, emotional, social, and cognitive function, general symptoms, and itch, and 3 additional questions related to general health and well-being. Patients will be asked to select his/her most appropriate response for all questions applying a 1-week recall period.

5.2.3.2 Patient-Reported Outcomes Measurement Information System Short Form-Fatigue 7b Daily

The PROMIS short form-Fatigue 7b Daily is a generic fatigue scale designed to measure daily fatigue. The instrument comprises 7 items and is completed daily using a recall period of 'since waking up'. This measure will be completed at home by the patient via daily diary over 7 consecutive days prior to the study visits.

5.2.3.3 Worst Itch Numerical Rating Scale

The 11-point WI-NRS will be completed at home and collected via daily diary over 7 days prior to the visits.

5.2.3.4 Patient-Reported Outcomes Measurement Information System Questionnaire

The PROMIS-29 Profile (v2.1) comprises 7 domains (anxiety, depression, fatigue, pain interference, physical function, sleep disturbance, and ability to participate in social roles and activities) and a single pain intensity item (Cella et al 2010). Each of the 7 domains contains 4 items. Patients will be asked to respond to each question or statement by marking the box underneath the most appropriate response.

5.2.3.5 Patient's Global Impression of Severity and Patient's Global Impression of Change Fatigue and Pruritus

PGIS and PGIC fatigue and PGIS and PGIC pruritus will be recorded at the times indicated in Table 1.

5.2.3.6 EuroQoL 5-Dimension Utility Index

The 5-level version of the EQ-5D (EQ-5D-5L) comprises a descriptive system with 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the EQ-VAS (Herdman et al 2011; EuroQoL Research foundation 2019).

Each of the 5 dimensions in the descriptive system has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient will be asked to indicate his/her health by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions will be combined into a 5-digit number that describes the patient's health state.

The EQ-VAS is a vertical VAS numbered from 0 to 100, where 0=The worst health you can imagine, and 100=The best health you can imagine. The patient will be asked to mark an X on the scale to indicate how his/her health is today, and to write the number he/she marked on the scale in the box next to the scale.

5.2.4 Laboratory Markers of Liver Fibrosis, Cholestasis, and Liver Function

5.2.4.1 Liver Fibrosis

Blood samples for the assessment of ELF score, which is based on tissue inhibitor of metalloproteinase 1 (TIMP-1), amino-terminal propeptide of Type III procollagen (PIIINP), and hyaluronic acid, will be collected as described in Section 5.3.2.

These blood samples will also be used for the assessment of the other PBC-related biomarkers PRO-C3 and C3M.

5.2.4.2 Cholestasis and Bile Acid Metabolism

The liver biochemistry blood sample, collected as described in Section 5.3.2, will be used for the assessment of markers of cholestasis based on ALP levels and total bilirubin.

Blood samples for the assessment of markers of bile acid metabolism, based on total bile acids, C4, FGF19, and FGF21, will be collected as described in Section 5.3.2.

5.2.4.3 Liver Function

The biochemistry blood sample, collected as described in Section 5.3.2, will be used for the assessment of serum fibrinogen and albumin levels; the hematology blood sample will be used for the assessment of INR; and the liver biochemistry sample will be used for the assessment of total and conjugated bilirubin, ALP, ALT, AST, and GGT.

The MELD score will be calculated based on the results from the liver biochemistry (total bilirubin), biochemistry (creatinine, and sodium if MELD score >11), and hematology (INR) blood samples (see Appendix III). The MELD score is provided by the central laboratory.

Blood samples for the assessment of hsCRP and IgM will be collected as described in Section 5.3.2.

5.3 Safety Assessments

5.3.1 Adverse Events

AEs will be followed, recorded, and reported in line with the procedures described in Section 7. AESIs are defined in Section 7.1.5.

Particular attention will be given to the detection and management of potential bone marrow toxicity (Section 5.3.2.1), cases of DILI (Section 5.3.2.2), and potential cases of hypothyroidism (see Section 5.3.2.3). In the event that a patient has any clinical signs or symptoms that are, in the opinion of the Investigator, consistent with hepatitis (such as right upper quadrant discomfort, fever, fatigue, nausea, vomiting, jaundice, rash, or eosinophilia >5%) or drug-induced hepatoxicity, please refer to Appendix II.

5.3.2 Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory, unless otherwise specified. The central laboratory will analyze the samples or send them to reference laboratory(ies) for analysis, as indicated in the central laboratory manual. Laboratory assessments of PK and sampling for future biomarker and genetic research are described in Section 5.5, Section 5.6, and Section 5.7, respectively.

Blood and urine samples will be collected predose under fasting conditions (see Section 5) at the times indicated in Table 1. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. The blood volumes to be collected per patient during the study will be provided in the ICF and/or in the central laboratory manual. For further details, refer to the central laboratory manual.

Sampling for the analysis of clinical laboratory parameters will be performed before the administration of IMP.

The following parameters will be assessed:

Liver biochemistry: ALP, ALT, AST, total and conjugated bilirubin, and GGT

One repeat blood sampling for ALP, total bilirubin and/or ALT/AST (with analysis by the central laboratory) can be performed at the discretion of the Investigator at Screening Visit 2 for patients who do not meet an inclusionary laboratory value at Screening Visit 1.

Note that biochemical response is assessed based on the liver biochemistry sample (Section 5.2.1).

ELF score and other PBC-related biomarkers: TIMP-1, PIIINP, and hyaluronic acid for calculation of the ELF score; and the other PBC-related biomarkers PRO-C3 and C3M

Other markers of liver function: hsCRP and IgM

Markers of bile acid metabolism: Total bile acids, C4, FGF19, FGF21

Autoantibodies: AMA titer, PBC-specific antibodies (anti-GP210, anti-SP100, antibodies against major M2 components [PDC-E2, 2-oxo-glutaric acid dehydrogenase complex])

A sample for the assessment of autoantibodies will be collected at Screening Visit 1 only. Central laboratory results will not be used to confirm patient eligibility at Baseline.

Viral serology: HIV antibodies (1 and 2) and, if positive for HIV antibodies, HIV RNA; hepatitis B surface antigen and hepatitis C virus antibody and, if positive for HCV antibody, HCV RNA

A sample for the assessment of viral serology will be collected at Screening Visit 1 only.

Pregnancy test (serum): See Section 5.3.3.

Hematology: hematocrit, hemoglobin, absolute and relative reticulocyte counts, RBC count, white blood cell (WBC) count, differential WBC count, platelet count, absolute neutrophil count, mean cell volume, and INR

One repeat blood sampling for INR (with analysis by the central laboratory) can be performed at the discretion of the Investigator at Screening Visit 2 for patients who do not meet the inclusionary laboratory value at Screening Visit 1.

Biochemistry: glucose, total protein, albumin, fibrinogen, creatinine, urea, total cholesterol, triglycerides, sodium, potassium, and chloride

Serum creatinine data will be used to calculate eGFR at Screening Visit 1 (see Section 5.1.3).

Thyroid function: TSH and free T4

One repeat blood sampling for TSH (with analysis by the central laboratory) can be performed at the discretion of the Investigator at Screening Visit 2 for patients who do not meet the inclusionary laboratory value at Screening Visit 1.

Drug screen (urine): a urine screen for amphetamines, cocaine or opiates (ie, heroin and morphine) will be performed at Screening. Patients on stable methadone or buprenorphine maintenance treatment for at least 6 months prior to Screening Visit 1 may be included in the study. Patients with a positive urine drug screen due to prescription opioid-based medication are eligible if the prescription and diagnosis are reviewed and approved by the Investigator. Patients with a positive urine drug screen, if not due to prescriptional use of a concomitant medication, as confirmed by the Investigator, will be excluded from the study. Medicinal cannabis and cannabidiol products are not allowed.

Urinalysis: quantitative test for urine pH and protein; qualitative tests for glucose, ketones, bilirubin, blood, and microscopic examination of the sediment

Pregnancy test (urine): See Section 5.3.3.

Refer to the central laboratory manual for details regarding the collection, processing, and shipping of the blood and urine samples.

The Investigator must review the laboratory report and assess results for clinical significance, including ALP values, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Refer to Section 7.1.4. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during the patient's participation in the study or within 30 days after the last dose of IMP, whichever is later, should be repeated until the values return to normal, to Baseline levels, or have stabilized and are no longer clinically significant, as determined 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, then the etiology should be identified, and the Sponsor (or designee) notified.

If required due to COVID-19-related restrictions, laboratory samples to follow-up an AE, including the retests for DILI (see Appendix II), absolute reticulocyte count (see Section 5.3.2.2), or TSH and free T4 (see Section 5.3.2.3), may be collected by a qualified healthcare professional at a location other than the study site. For other circumstances pertaining to patient safety during COVID-19-related restrictions, follow-up with the Sponsor (or designee).

Laboratory samples taken to follow-up an AE, including, absolute reticulocyte count, or TSH and free T4 noted above, may be tested locally so that the results are communicated to the Investigator's site promptly. If required due to COVID-19-related restrictions, the results of local safety laboratory tests may be provided to the Investigator by phone. Local laboratory results will not be entered into the eCRF. However, where unscheduled central laboratory confirmation is not possible for protocol-specified retests for evaluation of anemia, or hypothyroidism, the retest results may be requested.

For cases of suspected DILI (Appendix II), the retesting as well as close monitoring will be done by central laboratory only.

5.3.2.1 Suspected Drug-induced Liver Injury

During the study, the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether the patient meets DILI criteria at any point during the study.

In the event that a patient has any of the following laboratory results, please refer to Appendix II for details regarding the detection and management of suspected or confirmed cases of DILI, including instructions for retesting, close monitoring, and action to take regarding the IMP:

- AST or ALT ≥3×ULN
- AST or ALT >2×Baseline
- Total bilirubin >2×ULN
- INR >1.5 (except for patients on anticoagulant therapy).

Baseline values for liver tests (ALT and AST) are determined by averaging the values obtained at Screening and Baseline/Day 1 to determine the arithmetic mean.

Details of the IMP stopping criteria relating to suspected or confirmed DILI are provided in Section 4.4 and Appendix II.

Any suspected or confirmed DILI events meeting the criteria for an AESI, as defined in Section 7.1.5, will be reported to the Sponsor (or designee) following the same procedure as for SAEs (see Section 7.4).

5.3.2.2 Detection and Management of Potential Bone Marrow Toxicity

Particular attention will be given to the detection and management of potential cases of bone marrow toxicity. In case of Grade ≥2 severity anemia, the Investigator will instruct the patient to interrupt IMP administration and to return to the study center within 7 days so that the absolute reticulocyte count can be retested. If the retest value is below 50% of the Baseline value, IMP will not be resumed and will be permanently discontinued. IMP administration will be resumed, only if the retest value for the absolute reticulocyte count is ≥50% of the Baseline value and a Grade ≤1 of anemia, and an alternative cause for the anemia can be documented. The patient will continue to be closely monitored (at least weekly) until normalization of the reticulocyte count, ie, return to Baseline values.

Anemia will be reported to the Sponsor (or designee) as an AESI, as defined in Section 7.1.5, following the same procedure as for SAEs (Section 7.4).

5.3.2.3 Detection and Management of Hypothyroidism

Particular attention will be given to the detection and management of potential cases of hypothyroidism. In case of TSH ≥10 mIU/L, based on the regular TSH laboratory follow-up and/or based on unscheduled TSH test due to change of the thyroid hormone replacement dose for patients on thyroid hormone replacement therapy, or initiation of thyroid hormone replacement therapy, the Investigator will instruct the patient to interrupt IMP administration and to return to the study center within 5 days so that TSH and free T4 values can be retested at the central laboratory. If the retest value is ≥10 mIU/L with reduced free T4, IMP will not be resumed. If hypothyroidism is not confirmed (ie, central laboratory TSH <10 mIU/L and normal free T4), IMP administration will be resumed as per protocol. The patient will continue to be closely monitored by at least their clinical status and TSH/free T4 levels (at least weekly) until normalization of the TSH and free T4 values, ie, return to Baseline values.

Hypothyroidism will be reported to the Sponsor (or designee) as an AESI, as defined in Section 7.1.5, following the same procedure as for SAEs (Section 7.4).

5.3.3 Pregnancy

All patients are required to meet the requirements relating to pregnancy and use of contraception described in the inclusion and exclusion criteria (see Section 4.1 and Section 4.2, respectively).

For female patients who are considered postmenopausal but have less than 12 months of amenorrhea and who are not on concomitant estrogen replacement therapy, a high

FSH level in the postmenopausal range will be required at Screening. Confirmation with more than one FSH measurement is required.

Serum (beta human chorionic gonadotrophin) or urine pregnancy tests will be performed for female patients of childbearing potential at the time points indicated in Table 1.

Female patients of childbearing potential must have a serum pregnancy test at Screening Visit 1. The blood sample for the serum pregnancy test must be taken within 7 days of Day 1. Therefore, if Screening Visit 1 is performed more than 7 days prior to Day 1, the serum pregnancy test must be repeated at Screening Visit 2 within 7 days of Day 1. The result must be negative for the patient to be eligible for the study. If the test result is positive, the patient must be excluded from the study. The serum pregnancy tests will be analyzed by the central laboratory. A negative urine pregnancy test result is required at Randomization/Baseline before dosing. Urine pregnancy tests will be analyzed locally.

Monitoring for pregnancies in female patients and the partners of male patients will continue from the patient's inclusion in the study until 30 days after the last dose of IMP. Male patients will be required to inform the Investigator if their partner becomes pregnant during the study and up to 30 days after the last dose of IMP. The Investigator should inform the Sponsor (or designee) within 24 hours of learning of the pregnancy or partner pregnancy by completing and submitting a pregnancy report form (refer to the SAE contact information at the beginning of this protocol) to the Sponsor (or designee).

If a patient becomes pregnant, she will permanently discontinue IMP and attend an EoT Visit 30 days after the last dose of IMP, after which the patient will be encouraged to continue study assessments until completion of the Week 24 Visit (Visit 8). Any pregnant patient and the fetus will be closely followed-up throughout the duration of the pregnancy to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality). The Investigator will ask the patient to provide informed consent to record information on the health of the baby. Generally, follow-up will be required for no longer than 6 to 8 weeks beyond the estimated delivery date.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) will be considered SAEs.

For any male study patient's partner who becomes pregnant, the Investigator will attempt to collect pregnancy information on the male patient's partner while the male patient is in this study until 30 days after the last dose of IMP. The Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor (or designee) within 24 hours of learning of the partner's pregnancy. The Investigator will obtain informed consent from the female partner to collect information about the pregnancy and its outcome. Information on the status of the mother and child will be

forwarded to the Sponsor (or designee). Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) will be considered SAEs.

5.3.4 Breastfeeding

Breastfeeding women will be excluded from the study.

5.3.5 Vital Signs

Vital signs will be measured as outlined in Table 1 with the patient in a sitting position after 5 minutes' rest and will include pulse rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP). Body temperature will be measured at Screening Visit 1 according to local standard of care. Method of temperature measurement will be recorded in the patient notes and in the eCRF.

5.3.6 12-lead Electrocardiogram

An ECG device with a built-in printer will be provided by Clario and will be used for all study ECG assessments. Triplicate 12-lead ECGs will be obtained as outlined in Table 1.

The ECGs will be conducted in the supine position after 5 minutes' rest. At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

The ECG tracing printout should be signed and dated by the person who made the interpretation locally (for purposes of patient safety management); the tracing printout will be archived at the study site. The machines will provide heart rate, PR, QRS, QT, QTc intervals, and abnormal findings.

Electrocardiograms obtained throughout the study will be electronically transferred for central reading.

The central reader will analyze the patient's ECG results. The ECG analysis from the central reading, including HR (bpm), RR, QT, QRS, QTc Bazett, and QTc Fridericia intervals (milliseconds), and interpretation (abnormalities, rhythm, conduction), will be sent to the study site. The mean QTc Fridericia interval calculated by the central reader and based on triplicate ECGs, will be used for the assessment of eligibility.

If there is any evidence of the cardiac conditions or abnormalities as described in Section 4.4.1, IMP is to be permanently discontinued.

Further details regarding the ECG assessments are provided in the site operations manual or manual provided by the vendor.

5.3.7 Physical Examination, Including Height and Body Weight

Patients will undergo complete physical examinations and symptoms-directed physical examinations, as indicated in Table 1.

The complete physical examination will include assessments of the standard physical examination items, including general appearance, skin, eyes, ears, nose, throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, and other body systems, if applicable, for describing the status of the patient's health.

Body weight and height (height at Screening Visit 1 only) will also be measured and recorded. The patient should be dressed in light clothing, without shoes.

Investigators should pay special attention to clinical signs related to previous serious illnesses. Any new abnormalities or worsening of existing abnormalities that are associated with signs and/or symptoms (except for PBC-related pre-existing conditions [see Section 7.3]) should be reported as AEs or SAEs, as appropriate (see Section 7.1.4).

5.4 Adverse Clinical Outcomes

The following adverse clinical outcomes will be captured during the study:

- All-cause mortality
- Patients requiring a liver transplant (transplant list inclusion)
- MELD score of ≥15 (confirmed at repeat testing at least 14 days apart), as calculated by the central laboratory, according to the formulas in Appendix III

  The MELD score will be calculated based on the results from the liver biochemistry (total bilirubin), biochemistry (creatinine, and sodium if MELD score >11), and hematology (INR) blood samples, collected as described in Section 5.3.2.
- Variceal bleed
- Portal hypertension bleed
- Hepatic encephalopathy (West Haven criteria), see Appendix IV
- Spontaneous bacterial peritonitis
- Uncontrolled ascites requiring treatment

In the event of any of these outcomes, IMP will be permanently discontinued, as noted in Section 4.4.1, and the patient may continue study visits.

Investigators will record the AEs in the Adverse Event page of the eCRF and will indicate on the Adverse Event page if it meets the criteria for an SAE. If the event meets

the criteria of an SAE, it will be reported using the paper safety report form within 24 hours of becoming aware of the event.

The adverse clinical outcomes will be adjudicated by the Adjudication Committee (see Section 9.4.1).

Investigators will indicate on the eCRF Adverse Event page if the event meets the criteria for adjudication. If the event meets the criteria for adjudication, the Investigator will then complete the Adjudication Event eCRF.

Please refer to the Investigator adjudication manual for further information.

5.5 Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of setanaxib and GKT138184 at the visits specified in Table 1. The PK blood volumes to be collected during the study will be provided in the ICF and/or in the central laboratory manual. Samples will be collected predose in the morning.

Instructions for the collection and handling of biological samples will be provided by the Sponsor (or designee) and will be included in the central laboratory manual. The actual date and time that each sample is collected will be recorded.

The measurement of plasma setanaxib and GKT138184 concentrations will be performed by a central laboratory.

5.6 Future Biomarker Research

Patients will have the option to accept or decline additional blood sampling for future biomarker research.

Patients who consent to future biomarker research will have a blood sample collected at Baseline and Week 24. The optional biomarker blood volumes to be collected during the study will be provided in the ICF and/or in the central laboratory manual.

The blood samples will be used for analyses of biomarkers related to liver fibrosis and/or PBC. The biomarker analyses results may be used to explore potential relationship with setanaxib response and/or disease progression data obtained in this study.

The results of the biomarker analyses will be reported separately from the clinical study report (CSR) and individual biomarker analysis results will not be reported to the Investigator or the Site.

Details on processes for collection, shipment and destruction of the samples can be found in the central laboratory manual.

5.7 Future Genetic Research

Where local regulations and Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)allow, a blood sample for DNA isolation will be collected at Baseline from patients who have consented to participate in the genetic analysis component of the study. The blood volume of this optional sample will be provided in the ICF and/or in the central laboratory manual. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

DNA samples will be used for research related to setanaxib and/or PBC and related diseases. They may also be used to develop tests/assays, including diagnostic tests related to setanaxib and/or IMPs of this drug class and PBC. The genetic research may consist of the analysis of one or more candidate gene(s) or the analysis of genetic markers throughout the genome or analysis of the entire genome.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to setanaxib or IMPs of this class to understand study disease or related conditions.

The results of genetic analyses will be reported separately from the CSR and will not be communicated to study sites.

The Sponsor or designee will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

Details on processes for collection, shipment, and destruction of these samples can be found in the central laboratory manual.

6 TREATMENTS

6.1 Investigational Product(s)

6.1.1 Description of Investigational Product(s)

Test Product	
IMP/non-IMP:	IMP
Name:	Setanaxib
Doses:	• Setanaxib 1200 mg/day group • Setanaxib 1600 mg/day group
Mode of administration:	Oral film-coated tablets Setanaxib film-coated tablets will contain 400 mg setanaxib per tablet formulated with excipients.
Manufacturer:	Aptuit Via Alessandro Fleming, 4 37135 Verona VR Italy

Placebo	
Substance:	Matching placebo film-coated tablets, containing only excipients, will be provided. The placebo film-coated tablets will be visually identical to setanaxib film-coated tablets in order to maintain the blind.
Doses:	Not applicable
Mode of administration:	Matching oral tablets
Manufacturer:	Aptuit Via Alessandro Fleming, 4 37135 Verona VR Italy

6.1.2 Preparation, Handling, and Storage

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. The bottles containing setanaxib and placebo film-coated tablets will be stored under controlled conditions according to the storage requirements described on the label(s). The IMP is to be stored at room temperature or below. The film-coated tablets must not be frozen or stored above 25ºC or 77ºF. The Investigator (or designee) will instruct the patients to store the IMP in accordance with the instructions on the label(s).

6.1.3 Packaging, Labelling, and Shipment

Setanaxib and placebo will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines.

Setanaxib and placebo will be provided in high-density polyethylene (HDPE) bottles containing:

- Setanaxib 400 mg film-coated tablets for morning dosing
- Matching placebo film-coated tablets for morning dosing
- Setanaxib 400 mg film-coated tablets for evening dosing
- Matching placebo film-coated tablets for evening dosing.

Each bottle will contain 70 film-coated tablets.

The packaging of the placebo will be the same as the IMP in order to maintain the blind.

Setanaxib and placebo will be shipped and stored under controlled conditions according to the storage requirements. The IMP must be stored at room temperature or below (the film-coated tablets must not be frozen or stored above 25ºC or 77ºF).

Refer to the pharmacy manual for full details for packaging, labelling, and shipment of the IMP.

Almac UK will label and package the IMP bottles and will supply the IMP to local depots/study sites on behalf of the Sponsor (or designee).

6.2 Blinding

This study is double-blinded. The Investigator, the site personnel, the Sponsor and their representatives involved in monitoring and conducting the study, the Adjudication Committee, and the patients will be blinded to treatment assignments.

Randomization data will be kept strictly confidential, accessible only to authorized staff and the IDMC until the time of unblinding. Authorized staff may include the randomization statistician, who will store the master randomization list in a secure system, an unblinded statistician, and unblinded programmers, who will provide the IDMC with unblinded data for review in accordance with the procedures described in the IDMC Charter. The randomization will be performed by the external interactive voice response system/interactive web response system (IXRS) provider, Almac. The blinded statistician supporting the study will have no access to the unblinded randomization schedule. All authorized unblinded staff must be documented.

The setanaxib and placebo film-coated tablets are visually identical in order to maintain the blind. Setanaxib and placebo bottles will be coded and labeled in a manner that protects blinding. The coding system will permit rapid identification of the product (in case of medical emergencies), that does not permit undetectable breaking of the blind.

Breaking of the blind is only allowed in the case of an emergency, when knowledge of the IMP is essential for the clinical management of the patient. In such emergency situations, the responsibility to break the treatment code resides solely with the Investigator. The Investigator will have immediate access to break the blind through

IXRS. The Investigator must contact the Sponsor within 1 working day after the event, without revealing to the Sponsor (or contract research organization [CRO]) the results of the code break, except to the designated global patient safety representative. The Investigator must document the date of unblinding and the reason.

Emergency unblinding will be organized through IXRS. The Investigator must record the date of unblinding and the reason. All breaks of the blind must be adequately documented.

If an SAE is reported, the designated global patient safety representative may unblind the treatment assignment for the individual patient through IXRS in order to meet regulatory reporting requirements.

Although Investigators are blinded to treatment assignments, the Investigators will review the laboratory reports, which will include ALP and bilirubin values. This is required to ensure the appropriate medical management of the patient from a safety perspective.

6.3 Method of Assigning Treatment

Each patient will have a unique screening number obtained from the IXRS. This will be assigned at Screening Visit 1. If a patient is rescreened (see Section 4.3), the rescreened patient should be assigned a new unique screening number. The Investigator will keep a record (the patient screening log) of patients who enter Screening.

Once the patient has been successfully screened and the Investigator has determined that the patient is eligible, the patient will be confirmed as enrolled within the IXRS.

Randomization will be performed via a centralized IXRS.

The randomization codes will be prepared by the randomization statistician. The randomization statistician will store the master randomization list in a secure system.

If a patient withdraws from study participation, his/her unique identification number(s) cannot be re-used for another patient.

On Day 1, eligible patients will be assigned to setanaxib 1200 mg/day, setanaxib 1600 mg/day, or placebo according to a 1:1:1 randomization ratio, stratified by Screening serum ALP $<$ or $\geq$3.0×ULN. Each patient will receive a unique randomization number when he/she is assigned IMP. Patients will be allocated to IMP according to the randomization code.

6.4 Dose and Administration

Patients will be assigned to IMP as described in Section 6.3.

At each dispensing visit (Table 1), patients will receive kit(s) comprising 4 bottles (see Table 2). Each bottle contains 70 film-coated tablets. Patients will be dispensed 1 or

2 IMP kits at dispensing visits, as described in the site operations manual, to ensure that the patient has sufficient IMP to last until the next scheduled visit.

Table 2 Investigational Medicinal Product Kits

IMP	Bottles for morning dosing		Bottles for evening dosing	
	Bottle 1	Bottle 2	Bottle 3	Bottle 4
Setanaxib 1200 mg/day	Setanaxib 400 mg tablets	Setanaxib 400 mg tablets	Setanaxib 400 mg tablets	Placebo tablets
Setanaxib 1600 mg/day	Setanaxib 400 mg tablets	Setanaxib 400 mg tablets	Setanaxib 400 mg tablets	Setanaxib 400 mg tablets
Placebo	Placebo tablets	Placebo tablets	Placebo tablets	Placebo tablets

Patients will take 4 tablets per day, 1 tablet from each bottle. Two tablets will be taken in the morning and 2 tablets will be taken in the evening (see Table 2), for 24 weeks.

- Patients allocated to setanaxib 1200 mg/day will self-administer 2 tablets of setanaxib 400 mg in the morning, 1 tablet of setanaxib 400 mg in the evening, and 1 tablet of placebo in the evening.

- Patients allocated to setanaxib 1600 mg/day will self-administer 2 tablets of setanaxib 400 mg in the morning and 2 tablets of setanaxib 400 mg in the evening.

- Patients allocated to placebo will self-administer 2 placebo tablets in the morning and 2 placebo tablets in the evening.

Patients will be instructed not to take their morning IMP dose on visit days until after the study assessments have been completed.

The tablets should be taken orally with food or up to 30 minutes after eating a meal. Each tablet should be taken separately and swallowed whole with water. The patients will be instructed to distribute their morning and evening doses as even as possible.

For BID administration, the dosage interval should be at least 4 hours. A missed morning dose can therefore be taken up until 4 hours prior to the evening dose. Patients will be provided with a patient IMP dosing card. Patients will be instructed to record the date and time of each tablet that they take on the dosing card straight after they have taken the tablet.

Patients will be reminded to bring the IMP (including any empty bottles and packaging) and the patient IMP dosing card with them to each study visit.

The IMP dosing card will be considered as a source document. Site personnel will record the date and time of the IMP dose prior to PK Visits in the eCRF.

6.4.1 Dose Modification

No dose modifications are permitted on a patient-basis in this study. Dose interruptions are required in case of DILI, anemia, and hypothyroidism, when the events meet the

criteria as defined in Appendix II, Section 5.3.2.2, and Section 5.3.2.3, respectively. Events that require permanent discontinuation of IMP are listed in Section 4.4.1.

6.4.2 Intervention After the End of the Study

Continued access to IMP is not planned beyond the completion of the study.

6.5 Precautions and/or Lifestyle Considerations

Patients will be asked to fast from 10 pm on the day prior to study visits until after the study procedures have been completed. In cases where the FibroScan® assessments are carried out on a different day than the study visit, refer to Section 5.2.2 for fasting instructions.

6.6 Prior Medication

The requirements regarding prior use of UDCA and second-line therapies for PBC, including OCA, fenofibrate, or bezafibrate, are provided in the inclusion criteria (Section 4.1). The recording requirements for prior medications are included in Section 6.7.

Prohibited Medications

The following medications are prohibited within 3 months of Screening Visit 1, and during the study: oral and systemic corticosteroids, colchicine, mycophenolate mofetil, azathioprine, methotrexate, sulfasalazine, leflunomide, cyclophosphamide, valproate, or isoniazid. Note: nonsystemic corticosteroids, ie, topical/nasal/inhaled/other corticosteroids are allowed provided used in recommended doses, and up to 7 days of low doses up to up to 10 mg prednisone or equivalent of oral/parenteral corticosteroids are allowed.

Treatment with any investigational agent within 12 weeks of Screening Visit 1 or 5 half-lives of the IMP (if known) (whichever is longer) is prohibited, as is current enrollment in another interventional clinical study.

6.7 Concomitant Medication and Procedures

The use of a UDCA at a prescriptional dose is required during the study, unless the patient is intolerant to UDCA (see Inclusion Criterion 6). Second-line therapies for PBC, including OCA, fenofibrate, or bezafibrate, are also permitted during the study. For patients receiving these agents, all efforts should be made to maintain the dose of UDCA, OCA, and fenofibrate or bezafibrate stable during the Double-blind Treatment Period. The reasons for considering a dose change should be clearly documented in the study documentation. Patients should not start additional treatments for PBC after Randomization. If PBC treatments are started it will lead to IMP discontinuation. Dose modifications of concomitant PBC treatments initiated before Randomization do not require IMP discontinuation.

Patients will be instructed not to take their usual PBC medications on visit days until after the study assessments have been completed. Patients will be reminded to bring their medications for PBC with them to each study visit.

Regarding COVID-19 vaccination, as setanaxib does not have immunosuppressive properties based on nonclinical and clinical safety data, the Sponsor considers that study patients may undergo COVID-19 vaccination during the study.

Concomitant Medications to be Used with Caution

Setanaxib has been shown to be a weak inhibitor of OAT3, CYP2C9 and CYP2C19 in a clinical study. In addition, setanaxib inhibited BCRP and P-glycoprotein *in vitro*. This may result in increased exposures of applicable concomitant medications, and hence caution should be exercised with use of:

- Medications that are primarily eliminated through OAT3
- Sensitive CYP2C9 and CYP2C19 substrates that have a narrow therapeutic range such as warfarin and phenytoin (CYP2C9) and S-mephenytoin (CYP2C19)
- Sensitive substrates of BCRP and P-glycoprotein such as digoxin

In vitro data suggests that setanaxib is an inducer of CYP2B6. This may result in decreased exposures and therefore reduced efficacy of applicable concomitant medications, and hence caution should be exercised with use of:

- Sensitive CYP2B6 substrates, such as tamoxifen, valproic acid, and cyclophosphamide

Prohibited Concomitant Medications

The prohibited (prior) medications and devices listed in Section 6.6 are also prohibited during the Double-blind Treatment Period.

In addition, the following medications are prohibited during the Double-blind Treatment Period:

- Potent CYP3A4 inhibitors (itraconazole, lopinavir/itonavir, telaprevir, clarithromycin, ritonavir, ketoconazole, indinavir/ritonavir, conivaptan, and voriconazole)
- Potent UGT1A9 inhibitors and inducers: such as belumosudil, cannabidiol, cannabinol, deferasirox, diflunisal, eltrombopag, fosphenytoin/phenytoin, isavuconazole, medical cannabis, mefenamic acid, methylene blue, morniflumate, niflumic acid, perampanel, regorafenib, rifampicin, sorafenib, umifenovir)

If patients receive a prohibited medication, Investigators should consider if IMP administration should be temporarily interrupted or permanently discontinued. Additionally, if a patient has taken a prohibited medication (eg, short-term antifungal therapy) and the Investigator learns about it later, this might not lead to the permanent

discontinuation of IMP. In this case, there should be no signs of drug-drug interaction and continuation of IMP administration will be left to the Investigator's discretion.

Medication Recording Requirements

Prior and concomitant medications taken for PBC, including UDCA, OCA, fenofibrate or bezafibrate, will be recorded up to the end of the EoT Visit in the appropriate section of the eCRF.

All other medication (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken from 3 months (90 days) before Screening Visit 1 until the end of the EoT Visit will also be recorded in the appropriate section of the eCRF.

The following details must be recorded in the eCRF:

- Medication name, ideally the generic name
- Reason for use
- Start and end date of administration
- The dose and frequency of administration

In addition, the following details of medications taken for PBC, will be recorded in the eCRF:

- Prior use of OCA (yes/no), fenofibrate (yes/no), bezafibrate (yes/no)
- Reason for dose change (only concomitant medications taken for PBC)
- Reason for discontinuing prior or concomitant medications taken for PBC

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

6.8 Overdose

For this study, a single intake of 5 or more setanaxib tablets and/or a total daily dose of 7 or more tablets will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose with setanaxib.

Decisions regarding dose interruptions will be made by the Investigator based on the clinical evaluation of the patient.

In the event of an overdose, patients should be closely observed/hospitalized for close observation and appropriate symptomatic/supportive medical care and be followed until resolution/stabilization of any clinical issues.

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved setanaxib) must be communicated to the Sponsor (or a specified designee) using the overdose report form within 24 hours of becoming aware of its occurrence.

Any overdose associated with clinical symptoms will be recorded as an AE or SAE, as appropriate. Note that an overdose without clinical symptoms will not be recorded as an AE or SAE, even if the patient was hospitalized for observation. Details of any signs or symptoms and their management should be recorded, including details of any treatments administered for the overdose. All overdoses with clinical symptoms meeting the SAE criteria must be reported as described in Section 7.4.

6.9 Compliance

The Investigator (or designee) will explain the correct use of the IMP to each patient and will check that each patient is following the instructions properly. Patients will document the IMP doses that they take on a patient IMP dosing card.

Compliance will be assessed at each visit by counting the returned tablets and will be documented in the source documents and eCRF. Any deviation from the correct use of the IMP will be recorded in the eCRF.

A record of the number of IMP tablets dispensed to and taken by each patient will be maintained and reconciled with IMP and compliance records. The IMP start and stop dates, including dates for IMP interruptions, will also be recorded in the eCRF.

6.10 Accountability

The IMP must not be used for any purpose other than that defined in this protocol. All supplies of IMP will be accounted for in accordance with Good Clinical Practice (GCP).

The pharmacist (or designee) should maintain accurate records of all IMP supplies received during the study. These records should include the dates and amounts of IMP that were received at the site, dispensed, and destroyed or returned to the Sponsor (or designee). The records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the IMP and study patients. If errors or damage in the IMP shipments occur, the Investigator should contact the Sponsor (or its designee) immediately. Copies of the IMP accountability records will be provided by each Investigator for inclusion in the trial master file. The study monitor will periodically check the supplies of IMP held by the Investigator or pharmacist to verify accountability of the IMP used.

The Investigator (or designee) will dispense the IMP only to the identified patients in this study, according to the procedures described in this study protocol. Details of IMP dispensed to patients, will be recorded in the eCRF. Investigators should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all IMP received from the Sponsor (or designee).

After the end of the study, all unused IMP and all medication containers should be destroyed at the study center or returned to the drug depot for destruction, as instructed

in the pharmacy manual. In either instance, complete documentation will be returned to the Sponsor (or designee). The IMP resupply will be managed by the IXRS.

7 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

7.1.2 Serious Adverse Events

An SAE is any event that meets any of the following criteria:

- Results in death (Investigators should identify 1 SAE that is the leading cause of death).
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization. The event will be considered an SAE when, based upon appropriate medical and scientific judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Definition of Terms

Life-threatening: an AE is life-threatening if the patient was at immediate risk of death from the event as it occurred, i.e,, it does not include a reaction that, if it had occurred in a more severe form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery, or for procedures planned prior to the patient providing informed consent, or routine clinical procedures that are not the result of an

AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

In general, hospitalization signifies that the patient 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. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Disability/incapacity: an AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

7.1.3 Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction is defined as an untoward and unintended response to a study drug, which is not listed in the applicable product information (eg, IB for an unapproved IMP or the SmPC [Summary of Product Characteristics] for an authorized medicinal product), and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or is an important medical event that may not result in death, be life-threatening, or require hospitalization; and is assessed as causally related to the IMP. For suspected unexpected serious adverse reactions, the blind will be broken for safety reporting purposes.

7.1.4 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities without clinical significance should not be recorded as AEs or SAEs. However, clinically significant laboratory abnormalities as per the Investigator's assessment (eg, clinical chemistry, hematology, and urinalysis abnormalities) that require medical or surgical intervention or lead to IMP interruption or discontinuation must be recorded as an AE or SAE, as applicable. In addition, laboratory or other abnormal assessments (eg, in ECGs, X-rays, or vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. Any worsening of existing abnormalities that are associated with signs and/or symptoms (except for PBCrelated- pre-existing conditions [see Section 7.3]) should be reported as AEs or SAEs, as appropriate. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia) as the AE or SAE, not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities, see Section 5.3.2.

7.1.5 Adverse Events of Special Interest

The AESIs for this study are DILI, anemia, and hypothyroidism.

AESIs of DILI will be defined as any DILI event that meets the criteria in **A**, **B**, or **C** of Appendix II. Please refer to Section 5.3.2.1 and Appendix II for details regarding the detection and management of cases of DILI.

AESIs of anemia will be defined as CTCAE Grade ≥2 anemia AND absolute reticulocyte counts of <50% of the Baseline value, which is confirmed by repeat testing. Please refer to Section 5.3.2.2 for details regarding the detection and management of potential cases of bone marrow toxicity.

AESIs of hypothyroidism will be defined as TSH levels of ≥10 mIU/L, which is confirmed by repeat testing at the central laboratory (ie, TSH ≥10 mIU/L and reduced free T4). Please refer to Section 5.3.2.3 for details regarding the detection and management of hypothyroidism. The AESI should be reported by the investigative site to the ICON Drug Safety Center within 24 hours of learning about the event by completing the paper safety report form and sending it via email or fax. The documentation and processing of AESIs is further detailed in the Investigator Site File.

The AESIs will be adjudicated by the Adjudication Committee (see Section 9.4.1).

Investigators will indicate on the relevant Adverse Event eCRF page if the event meets the criteria for an AESI. If the event meets the criteria for an AESI, the Investigator will inform the Sponsor (or designee) of the AESI utilizing the safety report form (refer to the SAE contact information at the beginning of this protocol) and will then complete the Adjudication Event eCRF.

Please refer to the Investigator adjudication manual for further information.

7.2 Assessment of Adverse Events

7.2.1 Severity

The terms serious and severe are not synonymous. The general term “severe” is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is usually associated with events that pose a threat to a patient’s life or ability to function (see Section 7.1.2). A severe AE (classified as Grade 3) does not necessarily need to be considered serious. For example, a WBC count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

Investigators will grade all AEs by severity using CTCAE (version 4.03).

If an AE is not listed in the CTCAE criteria, a corresponding grading is to be performed by the Investigator based on his/her best medical judgment as follows:

- Mild (Grade 1): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

- Moderate (Grade 2): minimal, local, or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living (ADL)

- Severe (Grade 3): medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care ADL

- Life-threatening (Grade 4): life-threatening consequences; urgent intervention indicated

- Death (Grade 5): death related to an AE

7.2.2 Causality

Investigators are required to systematically assess the causal relationship between the AEs and SAEs and the exposure to the IMP using the following definitions:

Related:

- The AE has a reasonable possibility of an association with the product because:

    - The AE follows a reasonable temporal sequence to IMP administration and cannot be reasonably explained by the patient's clinical state or other risk factors (eg, disease under study, concurrent diseases, or concomitant medications).

    - The AE follows a reasonable temporal sequence to IMP administration, and it is a known reaction to the drug under study or a related chemical group or is predicted by known pharmacology or nonclinical safety.

Not Related:

- The AE does not follow a reasonable sequence from IMP administration, or it can be reasonably explained by the patient's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

7.3 Documenting and Reporting Adverse Events

Reporting of AEs will begin when the patient has provided informed consent and will continue up to 30 days after the last IMP administration.

Occurrence of AEs may be volunteered spontaneously by the patient; discovered as a result of general, nonleading verbal questioning by the study staff; or determined by physical examination or other safety assessments. All AEs will be monitored and recorded in the eCRF throughout the entire study. Note that worsening of PBC-related pre-existing conditions will not be reported as AEs. Worsening of other existing abnormalities that are associated with signs and/or symptoms should be reported as AEs (or SAEs), as appropriate.

For all AEs, the Investigator must pursue and obtain adequate information (a description of the event, severity, time of occurrence, including whether the AE onset was before, during, or after the IMP administration if the AE started on a dosing day, duration, and any action, eg, treatment/follow-up tests). The outcome of the event should be provided along with the Investigator's assessment of the relationship to the IMP. The Investigator must also assess whether the event meets the criteria for classification as an SAE.

It is the Investigator's responsibility to review all documentation (eg, hospital notes, laboratory reports, and diagnostic reports) related to an AE. Wherever possible, the Investigator's diagnosis, not the individual signs and symptoms, will be documented as the AE.

Investigators are not obligated to actively seek AEs or SAEs after the patient's conclusion of study participation. However, if the Investigator learns of any SAE, including death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the IMP or study participation, the Investigator must promptly notify the Sponsor (or designee).

7.4 Reporting of Serious Adverse Events

For SAEs with an onset inside the reporting period (ie, onset after provision of informed consent and up to 30 days after the last IMP administration), the Investigator must immediately, without undue delay but under no circumstances no later than 24 hours after becoming aware of the event, inform the Sponsor (or designee) of the SAE utilizing the safety report form (refer to the SAE contact information at the beginning of this protocol).

The Investigator is obliged to respond to any request for follow-up information (eg, additional information, event outcome, final evaluation, or other records where needed) or to any question the Sponsor (or designee) may have concerning the SAE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor (or designee) and, as applicable, to allow the Sponsor to meet strict regulatory timelines associated with expedited reporting obligations for events of this nature.

7.5 Adverse Event and Serious Adverse Event Follow-up

During the study (and after the patient's participation in the study has ended), all AEs and SAEs should be followed proactively by the Investigator until the event resolves or the condition stabilizes to a level acceptable to the Investigator, until the event is otherwise explained, or until the patient is lost to follow-up. At the time the patient's study participation ends, all ongoing AEs and SAEs should be evaluated for resolution. New or updated information will be recorded in the originally completed eCRF and the Investigator will submit any updated SAE/AESI information to the Sponsor (or designee) within the same timelines as those noted above for initial reports after receipt of the information.

7.6 Safety Reporting Oversight

In accordance with ICH GCP, the Sponsor (or designee) will inform Investigators of "findings that could affect adversely the safety of patients, impact the conduct of the study, or alter the IEC/IRB's approval/favorable opinion to continue the trial."

The Sponsor (or designee) has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The Sponsor (or designee) will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators. To support compliance with these requirements, the Investigator must provide requested information in a timely manner.

An Investigator who receives an Investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor (or designee) will file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

8 STATISTICS

8.1 General Procedures

With the exception of the unblinded statistician and programmers supporting the IDMC, all personnel involved with the analysis of the study will remain blinded until database lock and identification of protocol deviations. Analyses will be performed using SAS® (SAS Institute, Cary, NC, US) by the Sponsor or its representatives.

A detailed description of all statistical analyses to be performed for this study and any deviations from the analysis detailed in the protocol will be outlined in the Statistical Analysis Plan (SAP). A first version of the SAP will be prepared prior to the inclusion of the first study patient and the SAP will be approved prior to database lock.

All data will be presented by treatment group. Descriptive statistics (number of observations, mean, SD, median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables.

For the primary endpoint of change in ALP (%), Baseline is defined as the last nonmissing measurement prior to the first administration of study drug, or, if multiple pretreatment measurements are available, the arithmetic mean of the last (up to) 3 measurements preceding the first administration of study drug. This includes unscheduled and screening visits. For rescreened patients, the value associated with their screen failure record will not be considered for Baseline. If a patient has a Screening Visit 2 due to a retest for ALP, the last nonmissing measurement prior to the first administration of study drug will be used as Baseline for the efficacy analyses.

For other endpoints, Baseline will be defined as the last nonmissing measurement before or on the date of first administration of IMP, unless otherwise stated in the SAP.

The primary analysis will include data collected over a 24-week Double-blind Treatment Period. Any data collected after Week 24 (and a 4-week Follow-up Period) will be listed and, where sufficient data are available, may be summarized.

8.2 Analysis Populations

The Full Analysis Set (FAS) will include all patients who are randomized to a treatment group and receive at least 1 tablet of IMP or placebo and have at least 1 post-Baseline value for the primary endpoint. This analysis set will be the primary set used for all efficacy analyses, along with the summary of disposition, demographics, and Baseline characteristics. Patients will be analyzed according to the treatment group they were randomized to regardless of the actual treatment received.

The Safety Analysis Set will include all randomized patients who receive at least 1 tablet of IMP or placebo. Patients will be analyzed according to the treatment they actually received. This analysis set will be used for summaries of safety data.

For supplementary analysis purposes, primary and secondary efficacy analyses will be repeated utilizing a Per Protocol Set (PPS), including all patients who do not have any

major protocol deviations that would potentially affect the efficacy of the study drug. Major protocol deviations and any other reasons for exclusion from the PPS will be defined in the SAP and this analysis set will be finalized in a blinded manner prior to database lock. The PPS will be analyzed as actually treated.

The PK Analysis Set will include all patients who receive at least 1 dose of setanaxib and have at least 1 measured concentration at a scheduled PK time point postdose. Patients may be excluded if they have an important AEs or protocol deviations that may impact PK.

8.3 Sample Size

The primary efficacy endpoint is the change in ALP (%) over 24 weeks.

It is planned to enroll approximately 60 to 70 patients. Patients will be randomized and allocated to placebo, setanaxib 1200 mg/day, or setanaxib 1600 mg/day according to a 1:1:1 randomization ratio.

This study is designed to detect a >25% reduction in ALP in setanaxib-treated patients versus a 2.5% reduction in the placebo arm with an overall 2-sided $p<0.05$. Standard deviations are assumed to be 19% and 24%, respectively, based on the Phase 2a study with setanaxib and the Phase 3 POISE study with Ocaliva. With approximately 16 evaluable patients per arm (48 patients overall) and using a Hochberg step-up test to control alpha across 2 dose comparisons versus placebo, this study has 88.2% global power to detect at least 1 treatment arm as significantly different from placebo and 68.3% power to detect both treatment arms as statistically significant. Also, for the secondary endpoint of change in fatigue, there will be >80% power to detect a 20% reduction in fatigue versus a 2.5% increase in the placebo arm.

An assumed dropout rate of approximately 25% leads to a target sample size of 66 enrolled patients (22 per arm). A range of approximately 60 to 70 enrolled patients allows for variability in the assumed dropout rate.

8.4 Statistical Methods

8.4.1 Analysis of Efficacy

Efficacy data will be presented and analyzed using the FAS and a supplementary analysis will be performed using the PPS.

8.4.1.1 Primary Endpoint Analysis

The primary endpoint is listed in Section 2.1.

For the primary efficacy analysis, each setanaxib treatment group (1600 mg and 1200 mg) will be compared with placebo. The primary estimand is to assess the change in ALP (%) over 24 weeks in patients with PBC, elevated liver stiffness, and intolerance or inadequate response to UDCA.

The following intercurrent events will be considered and further detailed in the SAP. Patients who start additional PBC-related medication(s) after Randomization will have their IMP discontinued (Section 6.7). These patients will be included in the analysis, but efficacy data collected after the start of the new therapy will be excluded. PBC-related medication(s) will be identified through blinded medical review prior to database lock. For all other patients who discontinue from treatment prior to Week 24 but return for the Week 24 Visit (Visit 8), the Week 24 result will be used regardless of the occurrence of the intercurrent event. Patients with missing results will have their values imputed based on observed data. Further details will be defined in the SAP.

The primary endpoint will be evaluated using a mixed model for repeated measures (MMRM) with log(ALP) – log(Baseline) as response with log(Baseline) as a continuous covariate, ALP stratification (<3.0×ULN or ≥3.0×ULN), treatment and visit as categorical covariates and treatment by visit as interaction term. All ALP data captured at Weeks 2, 4, 8, 12, and 24 will be included in the model. The relative mean change from Baseline at Week 24 will be estimated and corresponding 2-sided 95% confidence intervals will be calculated. The relative mean change and confidence interval will also be converted to the percentage scale, for presentation purposes.

An unstructured covariance matrix will be used to model the within-patient correlation of data. The Kenward-Roger's degrees-of-freedom adjustment will be used. Restricted maximum likelihood will be used to obtain parameter estimates. The least squares means will be estimated by visit along with the associated 95% confidence intervals and p-values with the analysis taken from the estimate at 24 weeks. In the case of insufficient patients at either level of the stratification, the stratification factor will be removed from the model.

Model assumptions of the MMRM will be assessed using residual plots (such as q-q plots, histograms, box plots, and scatter plots). If the model above does not converge, heterogeneous Toeplitz covariance structure will be used instead of the unstructured covariance matrix. If convergence still does not meet, the Toeplitz structure then will be used.

8.4.1.2 Multiplicity

The null hypothesis is no difference in change in ALP (%) between setanaxib and placebo over 24 weeks. The alternative hypothesis is that setanaxib demonstrates a difference in change in ALP (%) over placebo.

In order to control the study-wise error rate, that is, the probability of rejecting the true null hypothesis for the primary endpoint at 1-sided 0.025, a Hochberg step-up procedure will be applied to adjust for 2 dose comparisons versus placebo.

For the analysis of secondary and exploratory endpoints, "nominal" p-values will be presented and will not be considered as part of the study-wise control of type I error. This is considered appropriate for an exploratory Phase 2b study.

8.4.1.3 Sensitivity Analysis

Sensitivity analyses to test the intercurrent strategy and the assumption of missing at random for the MMRM model will be defined in the SAP.

In the case of outliers in the ALP data, a further sensitivity analysis will utilize robust regression; this will be defined in the SAP.

8.4.1.4 Supplementary Analysis

The primary and secondary efficacy analyses will be repeated using the PPS, as defined in Section 8.2.

8.4.1.5 Secondary Endpoints

The secondary efficacy endpoints, as appropriate, will be analyzed using the same approach as the primary analysis.

As additional secondary endpoints, the 2 setanaxib dose arms will be combined for the analysis of change in ALP (%), change in fatigue, and change in liver stiffness and will be analyzed per the primary endpoint.

8.4.1.6 Exploratory Endpoints

The exploratory endpoints are listed in Section 2.3.

The analyses of the exploratory endpoints will be defined in the SAP.

8.4.2 Analysis of Safety

The safety endpoints are listed in Section 2.2.

The Safety Analysis Set will be used for the analysis of safety data (AEs, including AESIs, clinical laboratory tests, vital signs, 12-lead ECGs, and physical examination).

AEs that occur, having been absent before the date and time of the first dose of the IMP, or have worsened in severity or seriousness after initiating the IMP until 30 days after the date and time of last dose of IMP will be classified as treatment-emergent AEs (TEAEs). The number of TEAEs and number and percentage of patients experiencing TEAEs will be summarized by treatment group, severity, and relation to IMP. TEAEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. All AEs will be listed by patient.

SAEs will be listed by patients and summarized by treatment group, MedDRA SOC, and preferred term. Summaries will also be presented by severity and relationship to IMP.

Laboratory data (hematology, serum chemistry, and urinalysis) will be converted to Système International units for reporting and processing purposes. Absolute values and changes from Baseline will be presented descriptively. Laboratory data outside study-specific reference ranges will be listed.

Abnormal laboratory values will be listed by patient and summaries of the incidence and frequency by treatment group, scheduled visit, severity, and relationship to IMP will be presented. Shift tables of CTCAE (version 4.03) graded labs will be presented. WBC and reticulocyte counts will be expressed in absolute values. Differential count will be expressed as both absolute count and percentage of WBCs. Evaluation of drug-induced serious hepatotoxicity (eDISH) analysis will be conducted in order to explore potential liver toxicity signals by treatment group.

Vital signs and ECG parameters will be presented descriptively. Vital signs including pulse rate, SBP, and DBP and 12-lead ECG data will be summarized by treatment group and listed by patient.

A summary of abnormal physical examination findings by treatment group and scheduled visit will be presented.

8.4.3 Demographic and Baseline Characteristics

Demographic characteristics (including age, sex, ethnicity, and race) and Baseline characteristics (including height, weight, and disease characteristics) will be presented descriptively, overall and by treatment group.

Discrepancies between randomization stratification information (obtained from IXRS) and strata formed based on Screening factors collected on eCRFs will be tabulated and listed.

8.4.4 Pharmacokinetic Analysis

The PK Analysis Set will be used for PK Analyses.

Plasma concentrations of setanaxib and GKT138184, along with blood sampling dates and actual blood sampling time relative to previous dosing time, will be listed by patient, dose group (ie, actual treatment), and nominal sampling time. Samples with time deviation from nominal time will be identified and listed. Plasma concentrations of setanaxib and GKT138184 will be summarized with descriptive statistics by actual treatment and nominal sampling time, and dose normalized, as appropriate. The descriptive statistics will include N, mean, standard deviation, coefficient of variation, geometric mean, median, Q1, Q3, minimum, and maximum. Mean plasma setanaxib and GKT138184 concentrations (dose normalized as appropriate) versus study visit will be plotted as a box plot.

8.4.5 Handling of Missing Values

If there are missing ALP or fatigue data, imputation methods will be utilized. These will be described in the SAP.

Imputation for missing partial dates of AEs and concomitant medication will be specified in the SAP.

9 ETHICS AND RESPONSIBILITIES

9.1 Good Clinical Practice

This study will be conducted in accordance with the Note for Guidance on GCP ICH Harmonised Tripartite Guideline E6 (R1)/Integrated Addendum E6 (R2); US FDA Code of Federal Regulations (CFR) (Title 21 Parts 50, 56, 312), requirements for the conduct of clinical studies as provided in the EU Directive 2001/20/EC; the general guidelines indicated in the Declaration of Helsinki; and all applicable regulatory requirements.

9.2 Institutional Review Board/Independent Ethics Committee

Before initiating a study, the Investigator/institution must have written and dated approval/favorable opinion from the IRBs/IECs for the study protocol/amendment(s), written ICF(s), any ICF updates, patient recruitment procedures (eg, advertisements), and any written information to be provided to patients and a statement from the IRBs/IECs that these comply with GCP requirements (if applicable). A current copy of the IB should be included as part of the written application to the IRB/IEC.

The IRB/IEC approval(s) must identify the protocol version as well as the documents reviewed. Any amendments to the protocol will require IRB/IEC approval before the implementation of the changes made to the study, except for changes necessary to eliminate an immediate hazard to the study patients.

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/IEC

- Notifying the IRB/IEC of SAEs or other significant safety findings, including adverse drug reactions that are both serious and unexpected, as required by IRB/IEC procedures

- Providing oversight of the conduct of the study at the site and adherence to the requirements of all applicable regulations

- Promptly reporting deviations from, or changes to, the protocol to eliminate immediate hazards to the study patients

9.3 Informed Consent

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the Investigator should have the IRB/IEC's written approval/favorable opinion of the written ICF and any other written information to be provided to study patients.

- The Investigator or his/her representative will explain the purpose and nature of the study as well as possible adverse effects to the patient or his/her legally acceptable representative and answer all questions regarding the study.

- Patients must be informed that their participation is voluntary, and consent can be withdrawn at any point.

- Patients or their legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of US FDA CFR Title 21 Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements in the US, and the IRB/IEC or study site.

- Prior to a patient's participation in the study, the written ICF should be signed and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion.

- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained.

- The original copy of the signed ICF will be retained at the study site.

- A copy of the ICF and any other written information must be provided to the patient or the patient's legally acceptable representative.

- If the ICF is revised, the revised ICF must have received the IRB/IEC's approval/favorable opinion in advance of its use. Patients must be informed of the changes to the ICF and must re-consent to the most current version during their participation in the study. The patient or the patient's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. The communication of this information should be documented.

In addition, patients will be required to document agreement for optional future genetic research. The patients will be informed about its purpose, confidentiality of test results, and will be asked for their authorization to perform the test. If the patient does not consent to the blood sample for future genetic testing, they may still participate in the study but will not have a blood sample taken for the future genetic testing.

Patients will also be required to document agreement for optional future biomarker research. The Investigator (or authorized designee) will explain to each patient the objectives of the future biomarker research and will be asked for their authorization to collect the blood samples. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. If the patient does not consent to the blood samples for future biomarker research, they may still participate in the study but will not have the blood samples taken for the future biomarker research.

Patients will be required to document agreement for the use of remaining mandatory PK back-up samples for optional exploratory research. The Investigator (or authorized designee) will explain to each patient the objectives of the exploratory research. The samples will be used for research related to setanaxib and/or PBC and related diseases. They may also be used to develop tests/assays, including diagnostic tests related to setanaxib and/or IMPs of this drug class and PBC. The research may include genetic research and may consist of the analysis of one or more candidate gene(s) or the analysis of genetic markers throughout the genome or analysis of the entire genome. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient's agreement to allow any remaining PK back-up samples to be used for exploratory research. Patients who decline to participate in this optional research will not provide this separate signature.

If a patient is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. The witness should sign and personally date the ICF after:

- The written ICF and any other written information to be provided to patients is read and explained to the patient or the patient's legally acceptable representative
- The patient or the patient's legally acceptable representative has orally consented to the patient's participation in the study
- The patient or the patient's legally acceptable representative has signed and personally dated the ICF, if they are capable of doing so

By signing the ICF, the witness attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the patient or the patient's legally acceptable representative, and that informed consent was freely given by the patient or the patient's legally acceptable representative.

9.4 Adjudication Committee and Independent Data Monitoring Committee

9.4.1 Adjudication Committee

The Adjudication Committee, who will remain blinded to patient treatment assignment, will adjudicate the AESIs (DILI, anemia, and hypothyroidism), and the following adverse clinical outcomes, which will require permanent IMP discontinuation: all-cause mortality, transplant list inclusion, MELD score of ≥15 (confirmed at repeat testing at least 14 days apart), variceal bleed, portal hypertension bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, and uncontrolled ascites requiring treatment. These events will be adjudicated as defined in an Adjudication Charter.

Expert adjudication of cases will be conducted using the CIOMS/RUCAM (Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method) score, as well as detection of Hy's Law cases. Data from eDISH analysis will be provided to the Adjudication Committee.

An aggregated list of adjudicated events will be regularly provided to the IDMC for review.

The roles and responsibilities of the Adjudication Committee will be outlined in the Adjudication Charter.

9.4.2 Independent Data Monitoring Committee

The IDMC will oversee the safety of participating patients.

The IDMC will regularly review an aggregated list of events adjudicated by the Adjudication Committee. The frequency of review will be specified in the IDMC Charter.

An eDISH analysis will be conducted for each predefined IDMC meeting in order to explore potential liver toxicity signals at the study cohort level.

The IDMC may recommend change(s) to the setanaxib dose regimen(s), or interruption or discontinuation of an active treatment group(s) based on the regular IDMC safety data reviews, as defined in the IDMC Charter.

The IDMC will include independent consultants, including an unblinded statistician and physicians, and will be supported by an IDMC Specialist and programmers, as well as any other functions detailed in the IDMC Charter.

The role and responsibilities of the IDMC will be outlined in the IDMC Charter.

9.5 Financing and Insurance

9.5.1 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the CRO and/or Sponsor (or designee) will sign a clinical trial agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly.

9.5.2 Insurance, Indemnity, and Compensation

The Sponsor will maintain an appropriate clinical study insurance policy.

9.5.3 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.

10 RECORDS MANAGEMENT

All clinical study information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. This principle applies to all records referenced in this protocol, irrespective of the type of media used.

An eCRF will be used to store and transmit patient information. Information from the medical records (progress notes) and other source documents is to be promptly entered into the appropriate section of the eCRF. The eCRF must be reviewed and electronically signed and dated by the Investigator on an ongoing basis. The Investigator is responsible for verifying that the data entries are accurate and correct by signing the eCRF.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (eg, Investigators and the Study Coordinator). The eCRF must be completed as soon as possible after any patient evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

During each study visit, a physician participating in the study will maintain progress notes in the patient's medical records to document all significant observations. At a minimum, these notes are to contain:

- The date of the visit and the corresponding day or visit in the study schedule
- General condition and status remarks by the patient, including any significant medical findings. The severity, frequency, duration, and resolution of any reported AE, and the Investigator's assessment as to whether the reported AE is related to IMP
- Changes (including dosages) in concomitant medications/therapies (including medical foods) or procedures
- A general reference to the procedures completed
- Protocol deviations identified that could potentially affect safety and/or study results
- The signature or initials of all physicians making an entry in the medical record (progress notes)

In addition, any contact with the patient via phone or other means that provides significant clinical information is to also be documented in the medical record (progress notes), as described above.

Changes to information in the medical record (progress notes) and other source documents are to be initialed and dated on the day the change is made by the Investigator (or designee). If the reason for the change is not apparent, a brief

explanation for the change is to be written adjacent to the change. Changes to the eCRF will be electronically tracked.

The ICON data management department will write a Data Management Plan, which will be finalized prior to performing any data validation.

10.1 Source Documentation

Source documents contain the results of original observations and activities of a clinical investigation. They are the original records in which raw data are first recorded. Source documents include, but are not limited to, medical records (progress notes), ECG and computer printouts, screening logs, completed scales, quality of life questionnaires, and recorded data from automated instruments.

The Investigator/site personnel should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

All source documents from this study are to be maintained by the Investigator and made available for inspection by authorized persons. The Investigator will provide direct access to source documents/data for study-related monitoring, audits, IRB/IEC review, and regulatory inspections. The Sponsor should verify that each patient has consented, in writing, to direct access to his/her original medical records for study-related monitoring, audit, IRB/IEC review, and regulatory inspection.

10.2 Case Report Form Completion and Data Management

An eCRF will be used to store and transmit patient information. The file structure and format for the eCRF will be provided by the Sponsor or its representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed and dated by the Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (eg, Investigators and the Study Coordinator). The eCRF must be completed as soon as possible after any patient evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track the changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors. Changes to the eCRF will be electronically tracked.

Data will be entered/loaded into a validated electronic database using a clinical data management system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

10.3 Study Files and Record Retention

All data derived from the study will remain the property of the Sponsor. The Sponsor assumes accountability for actions delegated to other individuals, eg, the CRO.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents, including records of study patients, source documents, eCRFs, and the IMP inventory, must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of setanaxib. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Investigator when these documents no longer need to be retained.

The Investigator is not to dispose of any records relevant to this study without written permission from the Sponsor and is to provide the Sponsor the opportunity to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate source documents of all observations and data generated during this study, including hard copy source documents and electronic imaging files, as applicable. Such documentation is subject to inspection by the Sponsor, its representatives, and regulatory authorities.

If an Investigator moves, withdraws from a study, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

11 AUDITING AND MONITORING

Sponsor-assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study, such as verifying that the ICFs were signed and dated before any study-specific procedure was performed, assessing patient enrollment, compliance with protocol procedures, completeness and accuracy of data entered into the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The Investigator must agree to Sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) to ensure compliance with applicable regulations, and the Investigator will assist with the Sponsor's monitoring activities.

Quality control will occur at each stage of data handling to ensure that all data are reliable and have been processed correctly. The Sponsor should ensure oversight of any study-related duties and functions carried out on its behalf, including study-related duties and functions that are subcontracted to another party by the Sponsor's contracted CRO(s).

The eCRFs should be completed in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Details describing the strategy, responsibilities, and requirements of the study monitoring are provided in the study Medical Monitoring Plan.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are being fulfilled. The Sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator (or designee) should contact the Sponsor/CRO immediately if this occurs. All medical records (progress notes) must be available for audit. The Investigator must agree to participate with audits conducted at a convenient time in a reasonable manner.

11.1 Risk and Quality Tolerance Limits

Perceived risks and quality tolerance limits (QTLs) will be identified and documented in the Protocol Risk Evaluation Plan before the start of the study.

The Sponsor will review risk control measures periodically to ascertain whether the implemented quality management activities remain effective and relevant. The quality management approach and any important deviations from the predefined QTLs (and remedial actions adopted) will be described in the CSR.

11.2 Protocol Adherence and Deviations

The Investigator and site personnel should conduct the study in compliance with the protocol and should use continuous vigilance to identify and report protocol deviations.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol that may be on the part of the Investigator, the site personnel, or the patient.

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. For example, important protocol deviations may include enrolling patients in violation of key eligibility criteria designed to ensure a specific patient population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study.

The Investigator should not implement any deviation from the protocol without agreement from the Sponsor and prior review and approval from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard to a study patient, or when the change involves only logistical or administrative aspects of the study, such as a change in a monitor or phone number.

In the event of an important protocol deviation, the Investigator will discuss the deviation with the Sponsor’s Medical Monitor and will come to an agreement as to whether the patient should be withdrawn from the study due to the important protocol deviation.

12 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by the Sponsor. A protocol change intended to eliminate an apparent immediate hazard to patients should be implemented immediately.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC, and the Investigator must await approval before implementing the changes. The Sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

The current version of the ICF will require similar modification if the IRB/IEC, Investigator, and/or Sponsor, judge the amendment to the protocol to substantially change the study design and/or increase the potential risk to the patient and/or impact the patient's involvement as a study patient. In such cases, the ICF will be renewed for enrolled patients before their continued participation in the study.

13 STUDY REPORT AND PUBLICATIONS

This study will be registered on ClinicalTrials.gov in accordance with applicable laws or publication policy and may also be registered on other publicly accessible websites, such as EudraCT (EU Drug Regulating Authorities Clinical Trials), as necessary.

Two CSRs will be prepared. The first CSR will contain all results from this study, except for the results of genetic analyses, which will be reported separately. The Sponsor is responsible for preparing and providing the appropriate regulatory authorities with the CSRs according to the applicable regulatory requirements. The Sponsor should ensure that the CSRs meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).

The publication policy of the Sponsor is discussed in the Investigator's clinical trial agreement.

14 STUDY START AND TERMINATION

The study start date is the date on which the first patient provides informed consent.

The end of the study is defined as the last patient's last assessment.

Both the Sponsor and the Investigator reserve the right to terminate the study or the participation in the study at an Investigator's site at any time. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the patients' interests.

If the study is prematurely terminated or suspended for any reason, the Sponsor/Investigator/site personnel should promptly inform the study patients and should assure appropriate therapy and follow-up for the patients. Where required by the applicable regulatory requirements, the IRB/IEC should be informed promptly and be provided with a detailed written explanation of the termination or suspension.

If the Investigator terminates or suspends a study without prior agreement of the Sponsor, the Investigator should inform the site personnel. The Investigator/site personnel should promptly inform the Sponsor and the IRB/IEC. The Investigator/site personnel should also provide the Sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

15 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IRB/IEC personnel, the Sponsor and its authorized representatives are allowed full access to the records.

All study patients must be informed that their 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 patient, who will be required to give consent for their data to be used as described in the ICF. The patients must be informed that their medical records may be examined by auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. In case of any data security breach, this will be reported to authorities in line with local requirements.

Identification of patients and eCRFs shall be by unique patient identification numbers (such as screening or randomization numbers) only. All personal identifiers according to applicable regulations (eg, name, phone number) must be redacted permanently by the site personnel and replaced with the patient's unique identification number in all records and data before transfer to the Sponsor (or designee).

All personal details will be treated as confidential by the Investigator and staff at ICON.

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17 APPENDICES

17.1 APPENDIX I – Study Administrative Structure

Sponsor:	Calliditas Therapeutics Suisse SA Chemin des Aulx 14 1228 Plan-les-Ouates Switzerland The Sponsor assumes the responsibilities of the trial Sponsor for regulatory purposes and will provide for required insurance.
Operationally Responsible for Study conduct, Including Certain Sponsor Obligations:	The Sponsor is a controlled subsidiary of Calliditas Therapeutics AB, a Swedish corporation with its registered office and mailing address at PO Box 70351, SE-107 24 Stockholm, Sweden and its principal office and address for courier delivery at Kungsbron 1, SE11122 Stockholm, Sweden ("Calliditas" and, with its controlled affiliates, the "Calliditas Group"). As such, the Sponsor applies standard operating procedures relating to clinical development, medical affairs, manufacturing, quality assurance, quality control, and pharmacovigilance of the Calliditas Group. Certain Calliditas Group managers, including the Calliditas Group Chief Medical Officer, have been delegated responsibility by Sponsor for Sponsor's activities within their functional areas.
Sponsor's medical expert:	Chief Medical Officer c/o Calliditas Therapeutics AB Mailing address: PO Box 70351, SE-107 24 Stockholm, Sweden Principal office and address for courier delivery: Kungsbron 1, SE11122 Stockholm, Sweden Phone:
CRO:	ICON plc Corporate Headquarters South County Business Park Leopardstown, Dublin 18 Ireland Phone (IRL): +353 1 291 2000 Phone (US): +1 215 616 3000 Fax: +353 1 247 6260
Medical Monitor(s)	The names and contact details of the study Medical Monitor(s) will be provided in the Key Study Team Contact List.
Central Laboratory:	Cerba Research Industriepark-Zwijnaarde 3 9052 Ghent Belgium Phone: Refer to the central laboratory manual
Pharmacokinetics Laboratory	Unilabs York Bioanalytical Solutions Cedar House Northminister Business Park Upper Poppleton York Y026 6QR UK
PBC-Related Biomarker (PRO-C3 and C3M) Laboratory	Nordic Biosciences Herlev Hovedgade 207 DK-2730 Herlev Denmark

Central Reader for Electrocardiogram	ERT Clinical Peterborough Business Park Lynch Wood Peterborough PE2 6FZ UK
Central Reading for Imaging (MRE)	Perspectum Ltd Gemini One 5520 John Smith Drive Oxford OX4 2LL UK
Central Pathologist Review (Liver Biopsy)	Cerba Research Industriepark-Zwijnaarde 3 9052 Ghent Belgium
Setanaxib and placebo manufacturer:	Aptuit Via Alessandro Fleming, 4 37135 Verona VR Italy
Setanaxib and placebo Distributor of Drug Supplies:	Almac Clinical Services 9 Charlestown Road Seagoe Industrial Estate Craigavon BT63 5PW UK
IXRS	Almac 25 Fretz Road Souderton PA 18964 US
eCRF	Medidata 12 Hammersmith Grove, 9th Floor Hammersmith, London W6 7AP UK

A log of the name and title of the Investigators who are responsible for conducting the study, and the address and phone numbers of the study sites will be maintained.

The names and addresses of any other laboratories involved in the study (further to those stated above) will be provided in the laboratory manual.

17.2 APPENDIX II – Detection and Management of Suspected or Confirmed Cases of Drug-Induced Liver Injury

Particular attention will be given to the detection and management of suspected or confirmed cases of DILI.

If any of the following laboratory results or clinical signs or symptoms are obtained during the study, the Investigator will instruct the patient to return to the study center within 24 to 48 hours of receipt of the laboratory test results to undergo a retest.

- AST or ALT ≥3×ULN
- AST or ALT >2×Baseline
- Total bilirubin >2×ULN
- INR >1.5 (except for patients on anticoagulant therapy)
- Clinical signs or symptoms that are, in the opinion of the Investigator, consistent with hepatitis (such as right upper quadrant discomfort, fever, fatigue, nausea, vomiting, jaundice, rash, or eosinophilia >5%) or drug-induced hepatotoxicity. Isolated eosinophilia >5% without clinical signs or symptoms that are consistent with hepatitis or hepatotoxicity by the Investigator's medical judgment, should not be considered suspected DILI (sDILI). Retesting of eosinophilia (>5%) will only be required in case this is observed in combination with at least one of the other criteria listed above.

Baseline values for liver tests (ALT, AST, and total bilirubin) are determined by averaging the values obtained at Screening and Baseline/Day 1 to obtain the arithmetic mean.
The results of the Test and Retest will be checked to determine if they meet the criteria in **A** or **B**, which are based on the patient's ALT and AST levels at Baseline, or **C** below:

17.2.1 Criteria for Close Monitoring of Liver Biochemistry and IMP Action

A) For patients with **ALT and/or AST <ULN at study start** (Baseline Values), unless an alternative cause for the combination of laboratory abnormalities is immediately apparent (and documented) at the time of the laboratory test elevations in the opinion of the Investigator, close monitoring for sDILI (as described in Appendix II, Section 17.2.2) will be performed in patients with any of the following criteria (all confirmed by repeat testing):

a. ALT or AST >3×ULN

b. Total bilirubin >2×ULN

c. INR >1.5 (except for patients on anticoagulant therapy)

d. Clinical signs or symptoms that are, in the opinion of the Investigator, consistent with hepatitis (such as right upper quadrant discomfort, fever, fatigue, nausea, vomiting, jaundice, rash, or eosinophilia >5% provided the latter is in combination with any of the other criteria listed under A-a, b, c or d).

B) For patients with **ALT and/or AST between ≥ULN and <3×ULN at study start** (Baseline Values), unless an alternative cause for the combination of laboratory abnormalities is immediately apparent at the time of the laboratory test elevations in the opinion of the Investigator (and documented), close observation for DILI (as described in Appendix II, Section 17.2.2) will be performed in patients with any of the following criteria (all confirmed by repeat testing):

a. ALT or AST >2×Baseline at any time (see Figure 2 for illustration)

b. Total bilirubin >2×ULN

c. INR >1.5 (except for patients on anticoagulant therapy)

d. Clinical signs or symptoms that are, in the opinion of the Investigator, consistent with hepatitis (such as right upper quadrant discomfort, fever, fatigue, nausea, vomiting, jaundice, rash, or eosinophilia >5% provided the latter is in combination with any of the other criteria listed under A-a, b, c or d).

During the close monitoring period in **A** and **B**, IMP can be continued, unless:

- The patient is symptomatic in addition to having elevated laboratory parameters
- Close Monitoring is not possible
- Criteria **C** of Appendix II (see below) are met and no other cause for laboratory abnormalities is clinically apparent and documented by the Investigator in the study documents
- At the discretion of the Investigator

C) For patients meeting any of the following events, IMP will be discontinued when no other cause for the combination of laboratory abnormalities is immediately apparent:

a. ALT or AST >5×Baseline

b. ALT or AST >10×ULN

c. ALT or AST >3×Baseline (see Figure 3 for illustration) with 1 or more of the following:

i. Total bilirubin >2×ULN

ii. Total bilirubin >1.5×Baseline and >ULN

iii. INR >1.5 (except for patients on anticoagulant therapy)

iv. Appearance of clinical signs or symptoms that are, in the opinion of the Investigator, consistent with drug-induced hepatotoxicity

d. ALT or AST >Baseline with any 2 or more of the following:

i. Total bilirubin >2×ULN or 1.5×Baseline

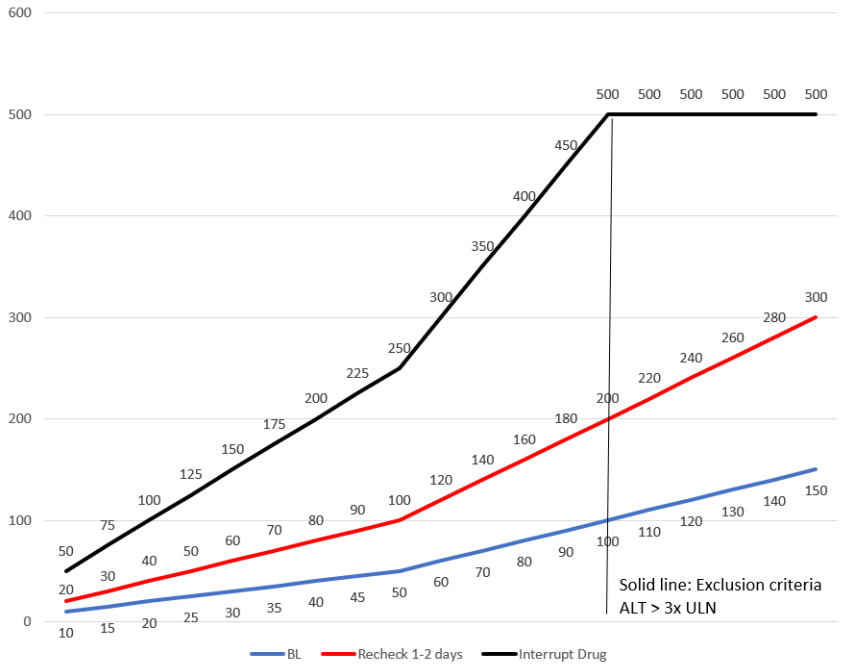
ii. INR>1.5 (except for patients on anticoagulant therapy)

iii. Appearance of clinical signs or symptoms that are, in the opinion of the Investigator, consistent with drug-induced hepatotoxicity

If the above criteria in **C** are met, the Investigator will instruct the patient to discontinue IMP administration and return to the study center within 2 days of receipt of the laboratory test results to undergo a retest and additional investigations (ie, close monitoring) to assess for sDILI. IMP cannot be reintroduced.

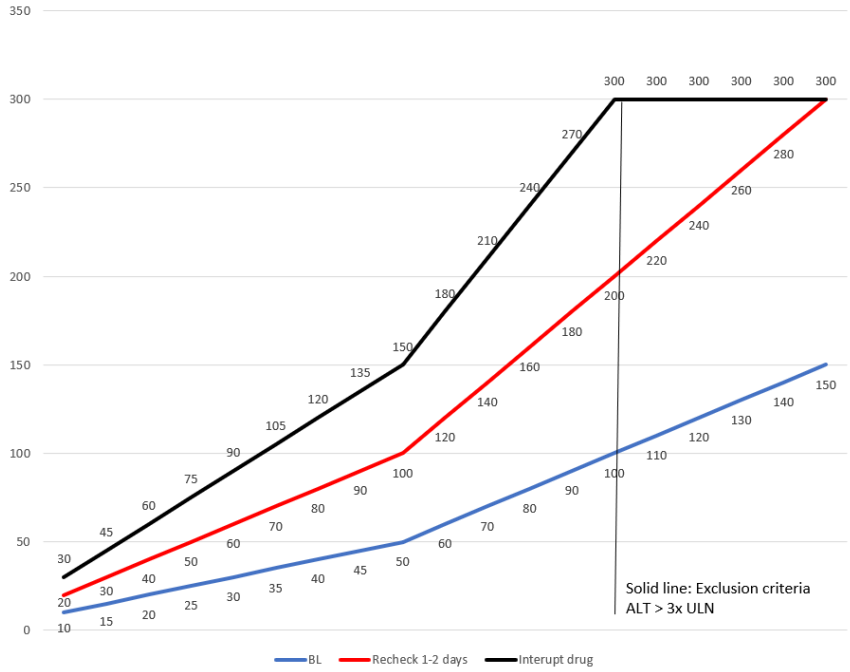
Any suspected or confirmed DILI event, defined as events meeting the criteria in **A**, **B**, or **C** above, will be closely monitored by the Investigator and the IDMC and reported to the Sponsor as an AESI following the same procedure as for SAEs.

Figure 2 Triggers to Recheck and Interrupt Drug in Patients With ALT ≤3×ULN at Baseline and No Symptoms



ALT=alanine aminotransferase; ULN=upper limit of normal

Figure 3 Triggers to Interrupt Drug in Patients With ALT ≤3×ULN at Baseline, and if (+) Symptoms or Abnormal INR or Bilirubin



ALT=alanine aminotransferase; ULN=upper limit of normal

17.2.2 Close Monitoring

1. Monitor patient twice or 3 times weekly until liver biochemistries (ALT, AST, ALP, total bilirubin), and coagulation profile (INR) resolve, stabilize or return to within Baseline values. Additional tests (eg, conjugated bilirubin) should also be obtained, as appropriate, at the discretion of the Investigator.

2. Monitor liver biochemistries and coagulation profile once a week or less according to the Investigator's judgment if the abnormalities stabilize, resolve or return to within Baseline values, or IMP has been discontinued and the patient is asymptomatic.

3. Close Monitoring can be stopped based on the Investigator's clinical judgment once the abnormalities stabilize, resolve or return to within Baseline values; or when there is an alternative documented cause to explain the deterioration.

4. Obtain a detailed history for symptoms assessment: appearance or worsening of clinical symptoms of hepatitis (such as right upper quadrant discomfort, fever, fatigue, nausea, vomiting, jaundice, rash, or eosinophilia >5%). If a patient is symptomatic in addition to having elevated laboratory parameters, the drug must be discontinued immediately, and a suspected DILI evaluation must be performed.

5. Obtain a more detailed history of prior or concomitant diseases.

6. Obtain a history for concomitant medications, acetaminophen, dietary supplements, herbal remedies, other over-the-counter medications, recreational drug use, and special diets.

7. If possible, quantify the alcohol consumption to assess for alcoholic hepatitis.

8. Obtain a history of exposure to environmental chemical agents.

9. If INR is also elevated, a trial of intravenous vitamin K administration may be considered, especially in cholestatic patients.

Follow-Up procedures for patient(s) who meet suspected DILI evaluation criteria in **A**, **B**, or **C** (laboratory analyses are performed at the central laboratory):

Viral hepatitis serology including:

1. Hepatitis A IgM antibody.

2. Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).

3. Hepatitis C RNA.

4. Hepatitis E IgM antibody.

5. Cytomegalovirus IgM antibody.

6. Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); however, IgM antibodies must be sent out as soon as possible.

Follow-up signs and symptoms consistent with potential immune mediated injury and, if relevant, monitor until the abnormalities resolve and to EoT Visit.

1. Fever, malaise, pruritus, etc.

2. Rash.

3. Edema.

4. Lymphadenopathy.

5. Hematological changes (leukopenia, anemia, thromobocytopenia, etc.), urinalysis, ECG etc.

6. Other organ involvement, in addition to liver (kidney, heart, lungs, etc.).

Other laboratory tests and assessments including:

1. Serum Creatine phosphokinase and lactate dehydrogenase.

2. Fractionate bilirubin, if total bilirubin >2×ULN.

3. A liver biopsy at the discretion of the Investigator.

4. Assess for peripheral eosinophilia. Investigators are also encouraged to obtain a skin biopsy in subjects who have liver enzyme elevation together with eosinophilia.

5. Assess for hypoxic/ischemic hepatopathy, and biliary tract disease.

As long as Criteria A, B or C are met WITHOUT identification and documentation of an alternative cause, these abnormal liver tests will be considered suspected DILI and be reported to the Sponsor as AESI and go for adjudication. Once an alternative cause has been identified and documented, for the laboratory abnormalities qualifying Criteria **A**, **B**, or **C** of Appendix II, the alternative clinical event is to be reported as an AE/SAE.

In addition, undertake the following for patients who meet the stopping criteria for both ALT and total bilirubin OR experiences clinical symptoms of hepatitis:

1. Antinuclear antibody, antismooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins). Analyses are performed at the central laboratory.

2. If required, evaluation of competing undiagnosed liver disease (hemochromatosis, Wilson's disease, alpha-1 anti-trypsin deficiency).

3. Serum acetaminophen levels OR serum acetaminophen adducts by high performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in patients with definite or likely acetaminophen use in the preceding week).

4. Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease at the discretion of the Investigator.

17.3 APPENDIX III – MELD Score

The MELD score will be calculated based on the results from the liver biochemistry (total bilirubin), biochemistry (creatinine, and sodium if MELD score >11), and hematology (INR) blood samples, according to the following formulas:

a. **MELD** = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43

b. **When MELD>11: MELD–Na** = MELD + 1.32×(137 – Na (mmol/L) – (0.033×MELD×(137 – Na (mmol/L))))

17.4 APPENDIX IV – West Haven Criteria and Clinical Description

WHC including MHE	Description	Suggested Operative Criteria	Comment
Unimpaired	No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis Local standards and expertise required
Grade I	• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his or her standard on clinical examination or to the caregivers	Clinical findings usually not reproducible
Grade II	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least 3 of the followings are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms	Clinical findings variable, but reproducible to some extent
Grade III	• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least 3 of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV	Coma	Does not respond even to painful stimuli	Comatose state usually reproducible

HE=hepatic encephalopathy; MHE=minimal hepatic encephalopathy; WHC=West Haven Criteria
All conditions are required to be related to liver insufficiency and/or portosystemic shunting.
Source: Vilstrup et al 2014

17.5 APPENDIX V – Child-Pugh Classification of Severity of Cirrhosis

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy is assessed as described in the table below.

A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease), 7 to 9 is class B (significant functional compromise), and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100% and 85%; class B: 80% and 60%; and class C: 45% and 35%.

Parameter	**Points assigned**		
	1	**2**	**3**
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 µmol/L)	2 to 3 mg/dL (34.2 to 51.3 µmol/L)	>3 mg/dL (>51.3 µmol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time (seconds over control) or	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

INR=international normalized ratio.
Source: https://www.uptodate.com/contents/image?imageKey=GAST%2F78401