

CLINICAL STUDY PROTOCOL

A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of the NOX1/4 Inhibitor Setanaxib in Patients with Alport Syndrome

Investigational Product: Setanaxib

Protocol Number: GSN000500

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Sponsor:

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SIGNATURE PAGE

STUDY TITLE: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of the NOX1/4 Inhibitor Setanaxib in Patients with Alport Syndrome

We, the undersigned, have read this Protocol and agree that it contains all necessary information required to conduct the study.

Signature

PPD

Date

24-Apr-2024

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INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this Protocol. I approve this document, and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this Protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this Protocol and access to all information furnished by Calliditas to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Calliditas and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Calliditas, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation guidelines for Good Clinical Practice, and applicable regional regulations.

Investigator's Signature

Date

Investigator's Printed Name

Institution Name

SYNOPSIS

TITLE: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of the NOX1/4 Inhibitor Setanaxib in Patients with Alport Syndrome

PROTOCOL NUMBER: GSN000500

INVESTIGATIONAL PRODUCT: Setanaxib

PHASE: 2a

INDICATION: Alport syndrome

OBJECTIVES AND ENDPOINTS:

The objectives and endpoints of this study are provided in Table S1.

Table S1. Objectives and Endpoints

Primary Objective	Primary Endpoints
To evaluate the safety and tolerability of setanaxib compared to placebo in patients with Alport syndrome.	<ul style="list-style-type: none"> Percentage of patients with SAEs; and Percentage of patients with treatment-emergent AESIs, ie, anemia.
Safety Objectives	Safety Endpoints
To assess the effect of setanaxib on vital signs compared to placebo.	Percentage of patients with clinically significant changes in heart rate and blood pressure.
To evaluate the effect of setanaxib on 12-lead ECGs compared to placebo.	Percentage of patients with clinically significant changes in 12-lead ECG.
To evaluate the effect of setanaxib on physical examinations compared to placebo.	Percentage of patients with clinically significant changes in physical examination.
To evaluate the effect of setanaxib on clinical laboratory parameters compared to placebo.	Percentage of patients with clinically significant changes in hematology, serum chemistry, urinalysis, and thyroid function.
To evaluate the effect of setanaxib on hearing compared to placebo.	Percentage of patients with clinically significant changes in hearing audiometric testing (bone- and air-conduction).
Secondary Objectives	Secondary Endpoints
To assess the effect of setanaxib on UPCR compared to placebo.	<ul style="list-style-type: none"> The ratio of UPCR at 24 weeks compared to baseline; and Percentage of patients with a 25% reduction in UPCR at 24 weeks, compared to baseline.
To assess the effect of setanaxib on eGFR compared to placebo.	The ratio of eGFR at 24 weeks compared to baseline.
To assess the plasma exposure of setanaxib and its active metabolite GKT138184.	<p>Pre-dose and post-dose plasma concentrations of setanaxib and GKT138184 at steady state. The following PK properties will be calculated:</p> <ul style="list-style-type: none"> Area under the concentration-time curve over 24 hours at steady state ($AUC_{0-24-ss}$); Minimum plasma concentration at steady state (C_{min-ss}); and Maximum plasma concentration at steady state (C_{max-ss}).

Table S1. Objectives and Endpoints (Continued)

Exploratory Objectives	Exploratory Endpoints
To assess the effect of setanaxib on biomarkers of inflammatory pathways, fibrosis, or disease progression compared to placebo.	Change from baseline at 24 weeks in the following parameters: Urine-based biomarkers: MCP-1/Cr, EGF, Cystatin-C, TGF-β1, NGAL, KIM-1, B2-M, and osteopontin; Serum-based biomarkers: MCP-1, BUN, Cystatin-C, B2-M, TGF-β1, CCL3, IL1B, TIMP1, TNFα, VEGF, and YKL-40; and Plasma-based biomarkers: NGAL, MMP9, SPP1, and CCN2.
Potential optional future analysis to assess the effect of setanaxib on additional biomarkers of inflammatory pathways, fibrosis, or disease progression compared to placebo.	Where allowed per local regulations, IEC approval and patient consent (and assent, where applicable), optional exploratory blood and urine samples will be collected. The samples will be used to assess additional biomarkers of Alport syndrome, inflammatory pathways, fibrosis, or disease progression compared to placebo. This may include, but will not be limited to, ADMA, TIMP-2, IGFBP7, and COL1A1.
AESI = adverse event of special interest; BUN = blood urea nitrogen; C _{max} = maximum plasma concentration; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; IEC = Independent Ethics Committee; PK = pharmacokinetic(s); SAE = serious adverse event; UPCR = urine protein to creatinine ratio.	

POPULATION:

The target population for this study is male and female patients aged 12 to 50 years, inclusive, with Alport syndrome at risk of disease progression despite receiving maximum-tolerated renin-angiotensin system (RAS) inhibitor therapy. For sites in the European Union (EU), patients aged 18 to 50 years, inclusive, will be enrolled.

Inclusion criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Male or female patients aged 12 to 50 years, inclusive, at the time of informed consent/assent;
For sites in the EU: Male or female patients aged 18 to 50 years, inclusive, at the time of informed consent;
2. Diagnosis of Alport syndrome by genetic testing (documented mutation in a gene associated with Alport syndrome [ie, COL4A3, COL4A4, or COL4A5]). Patients with a variant of uncertain significance should not be included in the study;
Note: Genetic test results are to be available prior to initiating other Screening procedures. In cases where genetic testing results are not available but the patient is likely to fulfill the other inclusion and exclusion criteria and has provided consent/assent, a sample for genetic testing should be processed locally and the Screening Period duration can be prolonged with the time it takes to receive the genetic test results. All other Screening assessments must be completed within 4 weeks (±7 days) prior to randomization.
3. Weight ≥40 kg;
4. Willing and able to give informed consent (and assent, where applicable), in accordance with local age requirements, and to comply with the requirements of the study;

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5. 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 (as specified in 5c) up to 90 days after the last dose of investigational medicinal product (IMP);
- For the purposes of this study, women of childbearing potential (WOCBP) are defined as “fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy”;
 - 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 level in the postmenopausal range will be required at Screening to confirm a postmenopausal state; and
 - 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 include the following:
 - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal);
 - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable);
 - Intrauterine device;
 - Intrauterine hormone-releasing system;
 - Bilateral tubal occlusion;
 - Vasectomized partner; and
 - Sexual abstinence (refraining from heterosexual intercourse during the entire period of risk associated with the study treatments, ie, up to 90 days after the last dose of IMP). 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, or post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.
6. Female patients of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Visit 3 (after randomization and before dosing);
7. 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 inclusion criterion 5c). Female condom and male condom should not be used together. This requirement begins at the time of informed consent/assent and ends 90 days after receiving the last dose of IMP;
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8. 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;
 9. Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m² at Study Visit 1 or 2, calculated at the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for patients ≥ 18 years of age and the revised bedside Schwartz formula for patients 12 to 17 years of age;
 10. Proteinuria (urine protein to creatinine ratio [UPCR] ≥ 90 mg/mmol [0.8 g/g]) at 2 consecutive measurements (24-hour urine sampling), separated by at least 2 weeks and calculated by the central laboratory;
 11. Receiving maximum allowed dose or maximum-tolerated daily dose of an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin II type I receptor blocker (ARB) that has been stable for at least 8 weeks prior to consent/assent; and

Note: A stable dose is defined as a dose within 25% of the dose at randomization.

Note: Patients with proven intolerance to ACEi and ARB are allowed in the study.

Note: Sodium/glucose co-transporter 2 inhibitors are allowed provided they have been given at the same dose for at least 8 weeks prior to Screening and are given at the same dose during the study.

12. Systolic and diastolic blood pressure ≤ 95 th percentile, based on the patient's age and weight for patients 12 to 17 years of age or with ≤ 130 mmHg systolic blood pressure and ≤ 80 mmHg diastolic blood pressure for patients ≥ 18 years of age.

Note: At least 1 blood pressure measurement during Screening (Study Visit 1 or 2) should be within these limits. Blood pressure will be measured after resting in the supine position for at least 5 minutes and will be measured 3 times with each measurement separated by at least 1 minute (the lowest value will be recorded on the electronic case report form).

Exclusion criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Has ongoing chronic hemodialysis or peritoneal dialysis;
 2. Has a history of kidney transplant;
 3. Has other causes of chronic kidney disease (CKD) (even if not yet on hemodialysis), including but not limited to other heritable disorders leading to CKD, diabetic nephropathy, hypertensive nephropathy, lupus nephritis, and immunoglobulin A nephropathy;
 4. Has been treated with any investigational agent within 12 weeks of signing informed consent/assent or 5 half-lives of the investigational agent (if known), whichever is longer, or current enrollment in an interventional clinical study;
 5. Has had prior treatment with setanaxib;
 6. Has known malignancy that is progressing or requires active treatment, with the exception of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer that has undergone potentially curative therapy, or malignancy treated with curative intent and
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with no known active disease ≥ 2 years before the first dose of study drug and of low potential risk for recurrence;

7. Positive urine drug screen (if not due to prescription 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 exclusionary and may be allowed if the prescription and diagnosis are reviewed and approved by the Investigator;
8. Has an active HIV infection or acute or chronic hepatitis B or C infection, confirmed at Screening;
9. Has had a surgery (eg, gastric bypass) or medical condition that might significantly affect absorption of medicines (as judged by the Investigator);
10. Has a positive pregnancy test at Study Visit 2 (Screening) and/or Study Visit 3 (Day 1) (WOCBP only) or is breastfeeding;

Note: If a randomized patient has a positive pregnancy test at Study Visit 3 (Day 1), they will be considered a patient withdrawn for non-safety reasons.

11. Has evidence of any of the following cardiac conduction abnormalities at Screening or Day 1 (pre-dose): a QTcF interval >450 milliseconds for male patients or >470 milliseconds for female patients, or a PR interval ≥ 220 milliseconds;

Note: Patients with a second or third degree atrioventricular block are to be excluded.

12. Has a history of aplastic anemia, or any current marked anemia, defined as hemoglobin <10.0 g/dL;
 13. Has uncontrolled hypothyroidism. Patients with subclinical hypothyroidism may be included. Subclinical hypothyroidism is defined biochemically as a normal serum free thyroxine (T4) concentration in the presence of an elevated serum thyroid-stimulating hormone (TSH) concentration;
 14. Has 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;
 15. Has any other condition that, 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;
 16. Uses medications known to be potent cytochrome P450 (CYP) 3A4 inhibitors (itraconazole, lopinavir/ritonavir, telaprevir, clarithromycin, ritonavir, ketoconazole, indinavir/ritonavir, conivaptan, and voriconazole), potent CYP3A4 inducers (avasimibe, carbamazepine, enzalutamide, mitotane, nevirapine, phenobarbital, phenytoin, rifabutin, rifampicin, rifapentine, and St John's wort), or potent uridine 5'-diphospho-glucuronosyltransferase 1A9 inhibitors and inducers (mefenamic acid and rifampicin) within 21 days prior to study drug administration;
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17. Has known psychiatric illness/social situations that would limit compliance with study requirements, substantially increase risk of incurring adverse events (AEs), or compromise the ability of the patient to give written informed consent/assent;
 18. Has known hypersensitivity or intolerance to setanaxib or to any of its excipients;
 19. Has a history of chronic liver disease (eg, primary biliary cholangitis, alcoholic liver disease, chronic viral hepatitis including hepatitis B and C, non-alcoholic fatty liver disease, and hemochromatosis);
 20. Has plasma alanine aminotransferase and/or aspartate aminotransferase $>3 \times$ the upper limit of normal (ULN) at Study Visit 1 or 2 (Screening);
 21. Has total bilirubin $>2 \times$ ULN at Study Visit 1 or 2 (Screening); or
 22. Has international normalized ratio >1.2 at Study Visit 1 or 2 (Screening) (criterion not applicable for patients on anticoagulant therapy).
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STUDY DESIGN AND DURATION:

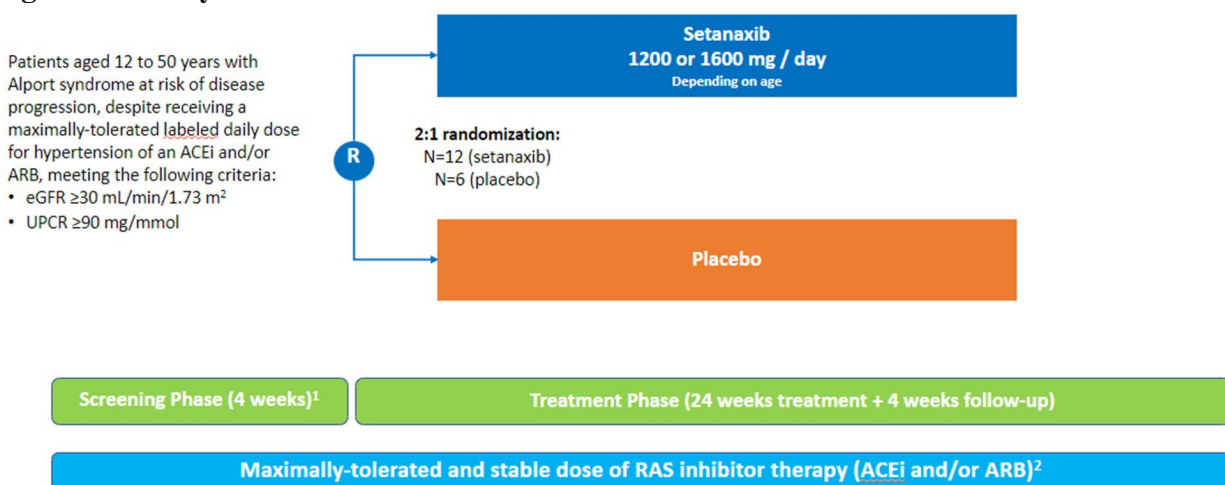
Study design

This is a randomized, double-blind, placebo-controlled Phase 2a study assessing oral setanaxib in patients with Alport syndrome. The safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of setanaxib will be assessed over 24 weeks of treatment. The study design is outlined in [Figure S1](#). The inclusion and exclusion criteria are designed to enroll a population of patients with Alport syndrome at risk of disease progression. In the EU, only adult patients (aged 18 to 50 years, inclusive) will be enrolled. Patients are required to have persistent proteinuria (UPCR ≥ 90 mg/mmol [0.8 g/g]) despite treatment with a stable dose of RAS inhibitor therapy (ACEis and/or ARBs) at the maximum allowed dose or maximum-tolerated daily dose for at least 8 weeks prior to consent/assent. A stable dose is defined as a dose within 25% of the dose at randomization. Patients should remain on their regimens of RAS inhibitors for the whole duration of the study. Patients with proven intolerance to ACEi and ARB are allowed in the study. This study aims to assess the safety of setanaxib as an add-on treatment to current RAS inhibitor treatment, in patients with Alport syndrome at risk of disease progression and with limited treatment options available. The double-blind, placebo-controlled design is chosen to provide safety data and preliminary efficacy for setanaxib in addition to the standard of care treatment in this patient population with a standard of care (with placebo) arm as reference. This will help to guide the design of further Phase 2/3 studies of setanaxib in Alport syndrome.

Patients must have UPCR ≥ 90 mg/mmol [0.8 g/g] at 2 consecutive measurements during Screening, separated by at least 2 weeks and calculated by the central laboratory. The baseline measurement will be the geometric mean of these 2 measurements. Patient must also have eGFR ≥ 30 mL/min/1.73 m² at Study Visit 1 or 2, calculated at the central laboratory using the CKD-EPI for patients ≥ 18 years of age and the revised bedside Schwartz formula for patients 12 to 17 years of age.

Eligible patients will be randomized in a 2:1 ratio to receive either setanaxib or placebo for 24 weeks, in addition to their stable dose of RAS inhibitor therapy, with setanaxib dosing based on age. In the EU, the setanaxib dose will be 1600 mg/day, as only adult patients will be enrolled.

Figure S1. Study Schematic



In the EU, only adult patients (18 to 50 years, inclusive) will be enrolled and the setanaxib dose will be 1600 mg/day.

1. Genetic test results are to be available prior to initiating other Screening procedures. In cases where genetic testing results are not available but the patient is likely to fulfill the other inclusion and exclusion criteria and has provided consent/assent, a sample for genetic testing should be processed locally and the Screening Period duration can be prolonged with the time it takes to receive the genetic test results. All other Screening assessments must be completed within 4 weeks (± 7 days) prior to randomization.
2. Patients with proven intolerance to ACEi and ARB are allowed in the study.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II type I receptor blocker; eGFR = estimated glomerular filtration rate; EU = European Union; R = randomization; RAS = renin-angiotensin system; UPCR = urine protein to creatinine ratio.

Independent Data Monitoring Committee

Safety and tolerability data will be regularly reviewed by an unblinded Independent Data Monitoring Committee (IDMC), with the first assessment after 2 patients have had the opportunity to complete at least 12 weeks of study treatment, followed by periodic assessments at a frequency defined in the IDMC Charter. Ad-hoc IDMC meetings may be scheduled as requested by the Sponsor or the IDMC. If there is a case of suspected drug-induced liver injury, study enrollment will be paused awaiting IDMC review and recommendation. The IDMC may recommend change(s) to the study conduct based on the safety data reviews, as defined in the IDMC Charter.

Study duration

The start of the study will be the date on which the first patient provides informed consent/assent, and the end of the study will be the last patient's last assessment.

The estimated study duration for an individual patient is approximately 32 weeks. Following a 4-week Screening Period (Note: the Screening Period may be longer than 4 weeks, as needed, to complete genetic testing), patients will receive setanaxib or placebo for a 24-week Treatment Period, followed by a 4-week Follow-up Period.

Planned number of patients

The study is planned to enroll and treat approximately 18 patients. Up to 6 patients should be in the age group of 12 to 17 years old at the time of consent/assent, and a minimum of 12 patients should be ≥ 18 years of age. In the EU, only adult patients (18 to 50 years, inclusive) will be enrolled. To ensure balance among treatment groups, randomization will be stratified by age group (12 to 17 years of age and ≥ 18 years of age) at the time of consent/assent.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Setanaxib

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

Patients will receive the following setanaxib doses according to age at the time of consent/assent:

- For patients aged 12 to 17 years: 1200 mg/day (800 mg morning + 400 mg evening) for 24 weeks; and
- For patients aged ≥ 18 years: 1600 mg/day (800 mg twice daily) for 24 weeks.

Administration

When study drug is dispensed, the patient will be instructed on study drug administration.

Patients must take the first dose of study drug in the presence of site staff during Study Visit 3. Similarly, the morning dose at the Week 2, Week 12, and Week 24 visits should be taken at the study site, to allow for proper PK sampling. Fasting prior to PK sampling will not be required.

Patients will self-administer (with caregiver supervision, as needed, if the patient is 12 to 17 years of age) 2 tablets of blinded study drug (setanaxib or placebo) in the morning and either 1 or 2 tablets of blinded study drug in the evening (according to age) with food or up to 30 minutes after eating a meal. Tablets may be divided (preferably using a pill cutter) if needed for easier administration. If divided, care must be taken to make sure that the whole dose is ingested, and tablets should be divided immediately prior to dosing, without any storage after being cut.

Placebo

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

Background therapy

Throughout the study, all patients will remain on their maximum allowed dose or maximum-tolerated daily dose of RAS blockade using ACEi and/or ARB. Patients with proven intolerance to ACEi and ARB are allowed in the study.

STATISTICAL METHODS:

The following analysis sets will be defined in the study:

- The Full Analysis Set (FAS) will be defined as all randomized patients;
- The Safety Analysis Set (SAS) will be defined as all randomized patients who take at least 1 dose of the study drug; and
- The PK Analysis Set will be defined as all randomized patients who take at least 1 dose of the study drug and have sufficient setanaxib plasma concentration data to calculate at least 1 PK parameter.

Other analysis sets may be defined as appropriate and, if applicable, will be described in the Statistical Analysis Plan (SAP).

Details of the statistical analyses, including supportive and sensitivity analysis if needed, will be provided in the SAP, which will be finalized prior to database lock and unblinding.

All endpoints will be summarized descriptively, and no formal hypothesis testing will be conducted. Descriptive statistics for continuous variables will include number of patients (n), mean, standard deviation, median, minimum, and maximum values. Analysis of categorical variables will include counts and percentages. Any statistical modeling or comparison, along with any associated p-values, will be considered nominal.

Analysis of safety

The analysis of the primary endpoint will be performed using the SAS. The number and percentages of patients with serious AEs and treatment-emergent AEs of special interest will be presented by treatment group, system organ class, and preferred term. Additional summaries of AEs, treatment-emergent AEs, AEs leading to discontinuation of study treatment, and AEs by severity, seriousness, and relationship to study drug(s) will be presented.

Clinical laboratory parameters, vital signs, electrocardiograms, thyroid, hearing and physical examinations will be summarized by treatment group by visit. Change from baseline values by visit will be presented for the continuous parameters. The count (and percentage) of patients with clinically significant changes will be tabulated by treatment group.

Analysis of efficacy

The analysis of secondary and exploratory endpoints will be performed using the FAS.

The UPCR data will be log-transformed prior to analysis. The analysis of the ratio of UPCR at 24 weeks compared to baseline will be analyzed using a mixed model repeated measurement approach. The analysis will include fixed effects for treatment, visit, and treatment by visit interaction, along with the log-transformed baseline value as a covariate. Model assumptions will be checked and, if not met, appropriate data transformations may be applied, or non-parametric approaches will be considered.

The proportions of patients achieving a 25% reduction in UPCR at 24 weeks from baseline in the setanaxib group will be compared to placebo group using a chi-square test.

The eGFR data will be log-transformed prior to analysis. eGFR data are such that it is possible there will be a small number of patients with extreme outlying data. Therefore, the analysis of the ratio of eGFR at 24 weeks compared to baseline will be based on a Robust Regression. In order to handle missing data, the analysis will be performed over 3 phases: an imputation, analysis, and pooling phase. Further details will be provided in the SAP. Results of the ratio at 24 weeks compared to baseline will be back-transformed to obtain estimated mean changes from baseline.

Baseline UPCR and eGFR will be defined as the geometric mean of 2 assessments prior to randomization. Similarly, the 24-week UPCR and eGFR will be calculated as for baseline. More details will be provided in the SAP.

PK parameters will be estimated for each individual patient using non-linear mixed effect methodology and prior PK knowledge of the compound. Further details will be provided in the SAP. The following PK parameters will be determined:

- $AUC_{0-24-ss}$: Area under the concentration-time curve over 24 hours at steady state;
- C_{min-ss} : Minimum plasma concentration at steady state; and
- C_{max-ss} : Maximum plasma concentration at steady state.

Plasma concentration time data and plasma PK parameter data for setanaxib and GKT138184 will be presented using descriptive summaries.

The exploratory endpoints will be summarized descriptively by treatment group.

SAMPLE SIZE DETERMINATION:

The sample size of approximately 18 patients is considered sufficient to provide an initial assessment of setanaxib versus placebo in Alport syndrome. Withdrawn patients may be replaced, unless withdrawn for a reason related to safety, as per the judgment of the Investigator. A maximum of 20 patients will be randomized for the study. The study sample size was chosen empirically, and no formal statistical hypothesis will be tested.

SITES: Approximately 15 investigational centers in the United Kingdom and at least 2 other countries in Europe.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
21 CFR	Title 21 of the Code of Federal Regulations
ACEi	Angiotensin-converting enzyme inhibitor
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARB	Angiotensin II type I receptor blocker
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BCRP	Breast cancer resistance protein
BID	Twice daily
BUN	Blood urea nitrogen
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C _{max}	Maximum plasma concentration
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CTA	Clinical trial authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
EU	European Union
FAS	Full Analysis Set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	Glomerular filtration rate
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation

Abbreviation	Definition
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IMP	Investigational medicinal product
INR	International normalized ratio
IRT	Interactive Response Technology
KO	Knock-out
NADPH	Nicotinamide adenine dinucleotide phosphate
NOAEL	No-observed-adverse-effect level
NOX	Nicotinamide adenine dinucleotide phosphate oxidase
NOX1/4	Nicotinamide adenine dinucleotide phosphate oxidase isoforms 1 and 4
OAT	Organic anion transporter
PBC	Primary biliary cholangitis
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PTA	Pure tone audiometry
QTc	Heart rate-corrected QT interval
QTcF	Heart rate-corrected QT interval using Fridericia's formula
RAS	Renin-angiotensin system
ROS	Reactive oxygen species
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SCCHN	Squamous cell carcinoma of the head and neck
SGLT2	Sodium/glucose co-transporter 2
SUSAR	Suspected Unexpected Serious Adverse Reaction
T4	Thyroxine
TEAE	Treatment-emergent adverse event
T _{max}	Time to maximum concentration
TSH	Thyroid-stimulating hormone
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
UPCR	Urine protein to creatinine ratio
WOCBP	Women of childbearing potential

1 INTRODUCTION AND BACKGROUND INFORMATION

Calliditas is developing setanaxib, a first-in-class inhibitor of the human protein nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) isoforms 1 and 4, (NOX1/4) for the treatment of Alport syndrome. This is a Phase 2a study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of setanaxib in patients with a high risk for disease progression, despite treatment with renin-angiotensin system (RAS) blockade.

1.1 Alport Syndrome

Alport syndrome is a hereditary kidney disease characterized by structural abnormalities and dysfunction of the glomerular basement membrane, as well as basement membranes of other tissues including the eye and ear.¹ It is the most commonly inherited kidney disease after autosomal dominant polycystic kidney disease.² It is widely acknowledged that the true prevalence of Alport syndrome in the general population is unknown. Nevertheless, the most conservative prevalence estimates of Alport syndrome based on epidemiological data from diagnosed cases remains 1 in 5000 estimated from a population of 1.5 million in Utah and Idaho, United States.³ Disease severity and prognosis are driven in large part by genetics.^{1,2,4,5} Three different patterns of inheritance – autosomal dominant, autosomal recessive, and X-linked – lead to a wide range of disease from isolated microhematuria with minimal and slow kidney function decline to rapid disease progression to end-stage renal disease (ESRD) in adolescence or early adulthood.²

Alport nephropathy progresses through a consistent set of milestones, beginning with isolated hematuria, followed by moderate albuminuria, severe proteinuria, and subsequent decline in renal function (glomerular filtration rate [GFR]). The interval and rate of progression between milestones varies from patient to patient, but is influenced primarily by sex and COL4A genotype.⁵ Age at ESRD is strongly correlated with the COL4A5 genotype (X-linked inheritance) in males, for whom the risk of ESRD by age 30 is 90% for deletions and nonsense mutations of COL4A5, 70% for splicing mutations, and 50% for missense mutations. In contrast, the effects of the COL4A5 genotype on age at ESRD are not observed in females with X-linked Alport syndrome. Homozygous or compound heterozygous mutations in COL4A3 or COL4A4 are the cause of autosomal recessive Alport syndrome, while a single mutation in either of these genes causes autosomal dominant Alport syndrome. The clinical presentation of these patients is highly variable, including many patients with heterozygous mutations in COL4A3 or COL4A4 who will never develop ESRD.²

At present, there is no curative treatment for Alport syndrome, and no treatments have been approved for the management of Alport syndrome, so all males with X-linked disease and all males and females with autosomal recessive Alport syndrome, as well as a certain percentage of patients with autosomal dominant Alport syndrome, will ultimately progress to ESRD.²

As for other chronic kidney diseases and in accordance with established Kidney Disease: Improving Global Outcomes guidelines, the current standard of care first-line treatment for the management of Alport syndrome in adolescents and adults is based on the lowering of proteinuria by maximally-tolerated inhibition of the RAS.^{6,7,8} Experimental and human studies have shown that angiotensin-converting enzyme inhibitor (ACEi) treatment safely and effectively reduces proteinuria in Alport syndrome,^{6,9,10} with optimal results achieved when initiated before GFR begins to decline.^{4,5}

Clinical practice recommendations suggest add-on therapy to ACEi should be considered in Alport syndrome patients with progressive proteinuria, despite treatment with ACEi.¹¹ Beyond RAS inhibition, aldosterone blockade has been shown to be safe and efficacious in Alport syndrome.² There is growing evidence relating to the benefit of sodium/glucose co-transporter 2 (SGLT2) inhibitors to slow the progression of chronic kidney disease (CKD) of diabetic and non-diabetic origin. However, there is to date only limited evidence of dapagliflozin in pediatric patients with Alport syndrome showing good tolerance and a reduction in proteinuria levels.^{12,13,14} These drugs are becoming more widely used in clinical practice. Although a number of other new therapies are under investigation for potential use in Alport syndrome, none have proven effective so far.

Thus, there remains a high unmet medical need for new treatment options in Alport syndrome, with the goal of safely lengthening the intervals between the milestones of kidney disease progression to the greatest extent possible. As treatment of the most severe cases is likely to be administered for many years in young adults and adolescents, therapeutic benefits must also be accompanied by an acceptable safety profile.

1.2 Setanaxib

Setanaxib (formerly GKT137831) is a first-in-class inhibitor of the human protein NADPH NOX1/4. It is a low molecular weight organic molecule and a member of the pyrazolopyridine dione chemical class.

The NOX family is a set of transmembrane proteins.¹⁵ 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.^{16,17,18,19} In the kidney, NOX-derived ROS have been shown to play an important role in many important functional processes; in particular, they are important mediators of the activation, migration, and trans-differentiation of mesenchymal fibroblasts to profibrotic myofibroblasts. As a consequence, through both direct and indirect mechanisms, excessive NOX-mediated ROS production can lead to the development of fibrosis that is fundamental to many kidney diseases.²⁰

Setanaxib is being investigated in several fibrotic and inflammatory disorders, and has been shown to have an acceptable safety profile for potential use in Alport syndrome.

1.3 Nonclinical Studies

1.3.1 In Vitro and In Vivo Pharmacology

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

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 transforming growth factor beta 1, platelet-derived growth factor, toll-like receptor 4, hedgehog ligand Shh, and angiotensin II.²¹ As a result, setanaxib markedly reduced the induction of markers of myofibroblast activation, including smooth muscle actin alpha, fibronectin, and procollagen I.^{22,23}

In a collagen COL4A3 knock-out (KO) mouse model of Alport syndrome, 40 homozygous COL4A3 KO/KO mice were allocated to 4 groups of 10 mice each and treated daily for 4 weeks with the following treatments, starting at an age of 4 weeks:

- Vehicle control;
- Setanaxib 60 mg/kg;
- Ramipril 10 mg/kg; and
- Setanaxib 60 mg/kg + ramipril 10 mg/kg.

Urine samples were collected at baseline and 6 and 8 weeks of age. As had previously been shown by Gross et al 2003,⁹ ramipril (an ACEi) was shown to be effective as a positive control by significantly reducing the albumin/creatinine ratio in urine samples ($p < 0.05$), as well as blood urea nitrogen (BUN) ($p < 0.001$) and Cystatin C levels in plasma ($p < 0.05$) compared with the vehicle control group. Body weight loss and histological readouts of tubular thickness and fibrosis deposition were also significantly reduced after 4 weeks of ramipril treatment. Other than BUN in plasma, which was significantly reduced in all treated groups compared with vehicle control, setanaxib alone had modest effects after 4 weeks of treatment. However, the combination of setanaxib + ramipril exhibited superior anti-fibrotic effects in the kidney including a significant reduction in glomerulosclerosis ($p < 0.01$), and a strong trend towards a further reduction in the albumin/creatinine ratio ($p < 0.001$). A significant improvement in survival was also observed in the ramipril and combination groups compared with vehicle control ($p = 0.0025$ and $p = 0.0002$, respectively).

1.3.2 Nonclinical Safety

Safety pharmacology studies revealed no effects related to central nervous system or respiratory function. In dogs, transient QTc prolongation was observed at 100 mg/kg/day and above, whereas no other findings related to cardiac function were reported.

A comprehensive repeated dose toxicology program has been conducted in rats and dogs. In rats dosed up to the limit dose of 1 g/kg/day, no relevant setanaxib-related toxicities were identified in any of the studies, whereas the no-observed-adverse-effect-level (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 findings in the dog included electrocardiogram (ECG) (QT-prolongation) and effects on the erythrocyte and reticulocyte counts indicative of effects on bone marrow. Reductions in red blood cell parameters were observed in dogs exposed to high dose levels of setanaxib (≥ 500 mg/kg/day) after a few weeks of treatment. The affected dogs showed minimal (10% to 20%) red blood cell reductions, occasionally with a concomitant increase in hematopoiesis in the spleen and/or bone marrow, followed by a marked increase in circulating reticulocytes, and subsequent recovery towards normal levels. One female developed non-regenerative anemia and was euthanized. Apart from this female, dogs that were affected at high exposures generally tended

to recover following a dose reduction or upon cessation of dosing. Slight to moderate follicular cell hypertrophy of the thyroid was observed in some dogs of the 28-day and 13-week study, but no such change was observed in the 26- and 39-week studies despite comparable exposures. Hormone analysis of thyroid-stimulating hormone (TSH) and thyroxine (T4) revealed indications of low total T4 and high TSH levels in individual high dose animals sometimes correlating with the hypertrophy. Setanaxib has been investigated in a standard battery of mutagenicity tests and was found not genotoxic.

Rat and rabbit studies addressing fertility, early embryonic- and embryo-fetal development have been conducted. There was no evidence of any embryo-fetal toxicity, except for a lower mean fetal weight at the dose level of 1000 mg/kg/day in rats. No treatment-related malformations have been observed. In addition, sperm parameters have been found unaffected by setanaxib treatment. For further details, refer to the IB.

No dedicated studies in juvenile animals have been performed to date. However, the animals in the 28-day and 26-week rat studies were approximately 6 weeks old at study start, corresponding to adolescence in humans. The dogs in the 28-day and 39-week studies were 6 to 7 months old at study start, thus plausibly at the age of puberty. The animals in the 13- and 26-week studies in dogs were older, 12 and 9 months, respectively, at study start. There were no findings in either rat or dog general toxicology studies indicating toxicity to organ systems potentially sensitive to disruptive effects during late childhood or throughout adolescence, such as skeletal bone and joints, the central nervous system, or reproductive organs. Also, based on available and extensive information on the pharmacology of NOX1/4 inhibition in animals and phenotypic data from NOX1 and NOX4 KO animals,^{24,25} there are no indications of effects that could be considered detrimental to growth or maturation.

1.4 Clinical Studies

To date, six Phase 1 studies in healthy volunteers (GSN000108, GSN000109, GSN000198, GSN000199, GSN000299, and GSN000310) and two Phase 2 studies (one in patients with primary biliary cholangitis [PBC] [GSN000300], and one in patients with Type 2 diabetes mellitus and albuminuria [GSN000200]) have been completed. A Phase 2 study of setanaxib in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) (GSN000400) and a Phase 2b/3 study of setanaxib in patients with PBC and elevated liver stiffness are ongoing [GSN000350, TRANSFORM]. Ongoing Investigator-initiated studies are evaluating setanaxib in patients with Type 1 diabetes mellitus and micro-albuminuria (GSN000241), and in patients with idiopathic pulmonary fibrosis (GSN000341/Protocol No. IRB-300003198).

The Phase 1 studies have characterized the clinical PK, safety, and tolerability profile of single and multiple ascending doses of setanaxib and the main active metabolite GKT138184 in healthy subjects. Potential food and drug interactions have been evaluated, including the effect of repeated setanaxib administration on the PK of selected cytochrome P450 (CYP) isoenzymes CYP2C9, CYP2C19, and CYP3A4 and transporter substrates, including for organic anion transporters (OAT), OAT1 and OAT3.

In Phase 1 studies, 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.

1.4.1 Pharmacokinetics

Both setanaxib and its main active metabolite GKT138184 exhibit approximate dose proportional PK up to the 800 mg BID level. Following both single and multiple dose administration of setanaxib across all doses studied, the main active metabolite exposure is consistently <10% of the total exposure.

Setanaxib is rapidly absorbed after oral administration (time to maximum concentration [T_{max}] is between 0.5 and 3 hours post-dosing), with a tendency for later T_{max} when setanaxib is administered under fed conditions. Following single-dose administration of setanaxib tablets, estimates of elimination half-life ranged from approximately 8 to 14 hours for setanaxib, and 9 to 12 hours 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 metabolism of setanaxib appear to be via uridine 5'-diphospho-glucuronosyltransferase (UGT)1A9 to the pharmacologically inactive metabolite GKT289993 (N-glucuronide) and via CYP3A4, to the active metabolite GKT138184. 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, 2C19, and 3A4 in healthy subjects. Setanaxib is also a weak inhibitor of OAT3.

1.4.2 Clinical Safety

Setanaxib has been safe and well tolerated in completed clinical Phase 1 and Phase 2 studies in patients with PBC, and in patients with type 2 diabetes mellitus and albuminuria. The frequency of treatment-emergent adverse events (TEAEs) is low and most TEAEs were graded as mild or moderate in intensity. No signals of setanaxib-related events or drug allergy have been noted. Specifically, no safety signals relating to hematopoietic, thyroid, or cardiovascular toxicity have been noted across the completed setanaxib studies. In the ongoing, blinded Phase 2b/3 study in PBC patients (GSN000350), 4 cases of increased hepatic enzymes (ie, suspected drug-induced liver injury [DILI]) have been observed to date in these patients with chronic liver disease. The patients were asymptomatic at the time of the suspected DILI. As the GSN000350 study is ongoing, treatment assignment data are still blinded. Two of these cases were considered suspected DILIs by the blinded study Adjudication Committee. To date, no suspected DILI events have been reported in any of the other completed or ongoing clinical studies. For further details, refer to the IB.

1.5 Study Rationale

Alport syndrome is a chronic, hereditary kidney disease that leads to early progression to ESRD in certain patient groups, primarily defined by their genetics. At present, there is no curative treatment for Alport syndrome and no treatments approved for the management of the condition.

Due to the relationship between type IV collagen abnormalities and kidney inflammation and fibrosis, there is growing relevance for targeted anti-inflammatory therapies in Alport syndrome and other forms of progressive CKD.¹ Cortical interstitial volumes become abnormal in many Alport syndrome males during the second decade of life, and are inversely correlated with GFR,

suggesting that, as in other chronic glomerulopathies, interstitial fibrosis is a significant contributor to loss of renal function, and prevention of interstitial fibrosis in Alport syndrome patients may require intervention during childhood.⁴

Given the role of NOX1 and NOX4 in fibrotic and inflammatory disorders, setanaxib is an attractive candidate to target the relationship between type IV collagen abnormalities and kidney inflammation and fibrosis in Alport syndrome. In a collagen COL4A3 KO mouse model of Alport syndrome, the combination of ramipril (an ACEi) + setanaxib exhibited anti-fibrotic effects in the kidney including a reduction in glomerulosclerosis.

Further supporting the hypothesis of an anti-fibrotic mechanism of action, treatment with setanaxib has been shown to reduce liver stiffness and alkaline phosphatase (ALP) levels in patients with severe fibrosis and cirrhosis in a Phase 2 study of patients with PBC (GSN000300). In a post-hoc analysis of patients with elevated liver stiffness ≥ 9.6 kPa (measured by FibroScan[®]), 24 weeks treatment with setanaxib 400 mg BID resulted in a 24% reduction from baseline in serum ALP compared with 3% on placebo ($p=0.02$). These patients with elevated liver stiffness ≥ 9.6 kPa also experienced greater absolute reductions from baseline in median liver stiffness following 24 weeks of setanaxib 400 mg BID (-3.0 kPa) compared with modest reductions following 24 weeks of setanaxib 400 mg once daily (-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). These results were supported by changes in collagen fragment levels, which showed treatment with setanaxib 400 mg BID resulted in a numerical reduction in collagen III formation and an increase in collagen III degradation, compared with no change in these biomarkers in the placebo group.

It is recognized that the classification of Alport syndrome patients into rapid and non-rapid progressors for recruitment into clinical studies is particularly important for those patients in whom their genotype leads to a variable clinical presentation and disease course. Therefore, patients enrolled will be required to have high levels of proteinuria (urine protein to creatinine ratio [UPCR] ≥ 90 mg/mmol [0.8 g/g]), indicative of a high risk for disease progression, despite treatment with RAS blockade.

Clinical manifestations of Alport syndrome often appear in childhood, as do the initial pathologic processes that lead to irreversible kidney injury. Early and efficient treatment is important to slow the progression of the disease, with the goal to prevent renal fibrosis. For this reason, adolescents from 12 years and adults up to 50 years of age will be included in this study. The rationale for including this age category is based on the extensive nonclinical and clinical safety data available for setanaxib to date, and the intent to start treatment early in order to interfere with the pathological process before irreversible kidney injury. In the European Union (EU), only adult patients (18 to 50 years, inclusive) will be enrolled. The study's preliminary efficacy endpoint is reduction in proteinuria levels in adults and adolescents. Proteinuria precedes the development of overt renal fibrosis and estimated glomerular filtration rate (eGFR) decline in both animals and humans with Alport syndrome and is currently the earliest step in the progression of the disease that can be clinically measured. eGFR will be monitored to evaluate treatment effect and to ensure that the study drug does not cause kidney injury or accelerate kidney function loss. Biomarkers for fibrosis is included to look for evidence that a target pathway relevant to eGFR preservation is modulated in study patients. This is in line with recent clinical trial recommendations for potential Alport syndrome therapies.²⁶

Since setanaxib is cleared to a large extent by the liver, and given the 4 cases of suspected DILIs (2 of which were considered suspected DILI by the study Adjudication Committee) observed to date in an ongoing blinded study with a population of patients with pre-existing liver disease (see [Section 1.4.2](#)), patients with abnormal liver function and pre-existing liver disease are excluded from study participation. Investigator guidance on liver function monitoring in case of suspected DILI during the study is further described in [Section 8.8.2](#).

As an additional safety measure, emerging safety and tolerability data will be regularly reviewed by an unblinded Independent Data Monitoring Committee (IDMC) with the first assessment after 2 patients have had the opportunity to complete at least 12 weeks of study treatment. Ad-hoc IDMC meetings may be scheduled as requested by the Sponsor or the IDMC. If there is a case of suspected DILI, study enrollment will be paused awaiting IDMC review and recommendation.

The results of this first study in Alport syndrome will be used to assess the safety of setanaxib in this patient population, including adolescents, and to aid the design of further Phase 2/3 studies of setanaxib in Alport syndrome.

1.6 Benefit/Risk Assessment

1.6.1 Potential Benefits

Patients included in this study will have Alport syndrome at high risk of progression to ESRD, despite treatment with RAS blockade. There are no approved treatments for Alport syndrome. While NOX1/4 inhibition represents a potential therapeutic strategy for patients with Alport syndrome, therapeutic benefits in patients with Alport syndrome have yet to be demonstrated. This is the first study to evaluate the safety and potential for efficacy of setanaxib in this population.

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

1.6.2 Potential Risks

Setanaxib has been extensively investigated in nonclinical ([Section 1.3](#)) and clinical ([Section 1.4](#)) studies. Setanaxib has not previously been studied in adolescents. However, there have been no findings from toxicology studies indicating toxicity to organ systems potentially sensitive to disruptive effects during late childhood or throughout adolescence. Based on available and extensive information on the pharmacology of NOX1/4 inhibition in animals and phenotypic data from NOX1 and NOX4 KO animals, there are no indications of effects that could be considered detrimental to growth or maturation.

In the completed Phase 1 and Phase 2 studies, the safety profile of setanaxib has been shown to be acceptable, with no relevant clinical safety signals identified.

Patients included in this study will undergo regular safety assessments. In addition, given the findings from the toxicology studies and ongoing clinical studies, appropriate exclusion criteria and safety endpoints for regular monitoring have been built into this study as precautions.

- **Thyroid disorders (hypothyroidism):** Patients with uncontrolled hypothyroidism will be excluded from this clinical study. Patients with subclinical hypothyroidism may be included. Subclinical hypothyroidism is defined biochemically as a normal serum free T4 concentration

in the presence of an elevated serum TSH concentration. The levels of TSH and free T4 will be regularly monitored during the study.

- **Anemia:** Patients with a history of aplastic anemia, or any current marked anemia defined as hemoglobin <10.0 g/dL, AND absolute reticulocyte counts of <50% of the baseline value (Screening Study Visit 2), which is confirmed by repeat testing, will be discontinued from the study treatment. Reticulocyte counts will be regularly monitored during the study. In case of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 2 anemia, investigational medicinal product (IMP) administration will be interrupted while the patient undergoes further evaluation. See [Section 8.8.1](#) for more information regarding the detection and management of potential bone marrow toxicity.
- **Cardiac disorders:** Patients with certain cardiac conduction abnormalities 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 severe cardiac condition per the Investigator's judgment, prolongation (mean QTcF >500 milliseconds AND increase by >60 milliseconds over the mean baseline QTcF), or conduction abnormality, IMP will be discontinued.
- **Suspected DILI:** Patients with a history of chronic liver disease or abnormal liver enzymes at Screening will be excluded from this clinical study. The levels of liver enzymes will be regularly monitored during the study (see [Section 8.8.2](#) for more information). If there is a case of suspected DILI, study enrollment will be paused awaiting IDMC review and recommendation.

Anemia with CTCAE Grade ≥ 2 , defined as hemoglobin <10 g/dL, AND absolute reticulocyte counts of <50% of the baseline value (Screening Study Visit 2), which are confirmed by repeat testing, will be considered an adverse event (AE) of special interest (AESI) in this study and will be reported within 24 hours of the Investigator becoming aware of the event.

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, to the 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, 2C19, 3A4, and OAT3. In vitro, setanaxib inhibited breast cancer resistance protein (BCRP) and multidrug resistance protein 1, and in vitro data also suggest 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 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.

One third of patients included in this study will be randomized to receive placebo. Although the study duration is relatively short, and patients will continue with their optimized RAS inhibitor therapy, there is a risk of disease progression during the study without the possibility of trying any other new potential treatments for Alport syndrome.

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 Alport syndrome.

2 STUDY OBJECTIVES AND ENDPOINTS

The objectives and endpoints of this study are provided in Table 1.

Table 1. Objectives and Endpoints

Primary Objective	Primary Endpoints
To evaluate the safety and tolerability of setanaxib compared to placebo in patients with Alport syndrome.	<ul style="list-style-type: none"> Percentage of patients with SAEs; and Percentage of patients with treatment-emergent AESIs, ie, anemia.
Safety Objectives	Safety Endpoints
To assess the effect of setanaxib on vital signs compared to placebo.	Percentage of patients with clinically significant changes in heart rate and blood pressure.
To evaluate the effect of setanaxib on 12-lead ECGs compared to placebo.	Percentage of patients with clinically significant changes in 12-lead ECG.
To evaluate the effect of setanaxib on physical examinations compared to placebo.	Percentage of patients with clinically significant changes in physical examination.
To evaluate the effect of setanaxib on clinical laboratory parameters compared to placebo.	Percentage of patients with clinically significant changes in hematology, serum chemistry, urinalysis, and thyroid function.
To evaluate the effect of setanaxib on hearing compared to placebo.	Percentage of patients with clinically significant changes in hearing audiometric testing (bone- and air-conduction).
Secondary Objectives	Secondary Endpoints
To assess the effect of setanaxib on UPCR compared to placebo.	<ul style="list-style-type: none"> The ratio of UPCR at 24 weeks compared to baseline; and Percentage of patients with a 25% reduction in UPCR at 24 weeks, compared to baseline.
To assess the effect of setanaxib on eGFR compared to placebo.	The ratio of eGFR at 24 weeks compared to baseline.
To assess the plasma exposure of setanaxib and its active metabolite GKT138184.	<p>Pre-dose and post-dose plasma concentrations of setanaxib and GKT138184 at steady state. The following PK properties will be calculated:</p> <ul style="list-style-type: none"> Area under the concentration-time curve over 24 hours at steady state ($AUC_{0-24-ss}$); Minimum plasma concentration at steady state (C_{min-ss}); and Maximum plasma concentration at steady state (C_{max-ss}).
Exploratory Objectives	Exploratory Endpoints
To assess the effect of setanaxib on biomarkers of inflammatory pathways, fibrosis, or disease progression compared to placebo.	<p>Change from baseline at 24 weeks in the following parameters:</p> <p>Urine-based biomarkers: MCP-1/Cr, EGF, Cystatin-C, TGF-β1, NGAL, KIM-1, B2-M, and osteopontin;</p> <p>Serum-based biomarkers: MCP-1, BUN, Cystatin-C, B2-M, TGF-β1, CCL3, IL1B, TIMP1, TNFα, VEGF, and YKL-40; and</p> <p>Plasma-based biomarkers: NGAL, MMP9, SPP1, and CCN2.</p>
Potential optional future analysis to assess the effect of setanaxib on additional biomarkers of inflammatory pathways, fibrosis, or disease progression compared to placebo.	Where allowed per local regulations, IEC approval and patient consent (and assent, where applicable), optional exploratory blood and urine samples will be collected. The samples will be used to assess additional biomarkers of Alport syndrome, inflammatory pathways, fibrosis, or disease progression compared to placebo. This may include, but will not be limited to, ADMA, TIMP-2, IGFBP7, and COL1A1.
<p>AESI = adverse event of special interest; BUN = blood urea nitrogen; C_{max} = maximum plasma concentration; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; IEC = Independent Ethics Committee; PK = pharmacokinetic(s); SAE = serious adverse event; UPCR = urine protein to creatinine ratio.</p>	

3 STUDY DESCRIPTION

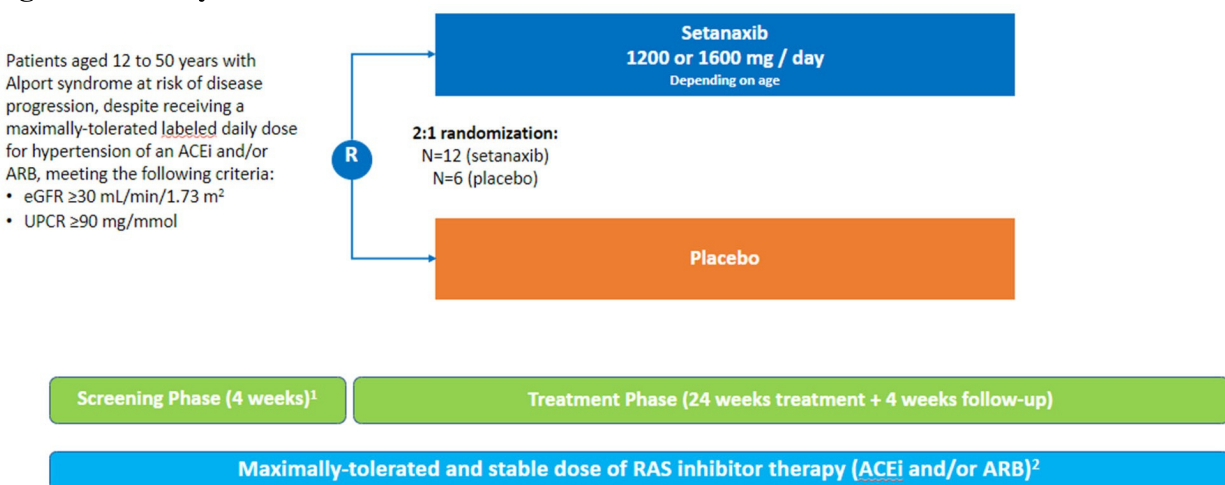
3.1 Summary of Study Design

This is a randomized, double-blind, placebo-controlled Phase 2a study assessing oral setanaxib in patients with Alport syndrome. The safety, tolerability, PK, PD, and preliminary efficacy of setanaxib will be assessed over 24 weeks of treatment. The study design is outlined in [Figure 1](#). The inclusion and exclusion criteria are designed to enroll a population of patients with Alport syndrome at risk of disease progression. In the EU, only adult patients (aged 18 to 50 years, inclusive) will be enrolled. Patients are required to have persistent proteinuria (UPCR ≥ 90 mg/mmol [0.8 g/g]) despite treatment with a stable dose of RAS inhibitor therapy (ACEis and/or angiotensin II type I receptor blocker [ARBs]) at the maximum allowed dose or maximum-tolerated daily dose for at least 8 weeks prior to consent/assent. A stable dose is defined as a dose within 25% of the dose at randomization. Patients should remain on their regimens of RAS inhibitors for the whole duration of the study. Patients with proven intolerance to ACEi and ARB are allowed in the study. This study aims to assess the safety of setanaxib as an add-on treatment to current RAS inhibitor treatment, in patients with Alport syndrome at risk of disease progression and with limited treatment options available. The double-blind, placebo-controlled design is chosen to provide safety data and preliminary efficacy for setanaxib in addition to the standard of care treatment in this patient population with a standard of care (with placebo) arm as reference. This will help to guide the design of further Phase 2/3 studies of setanaxib in Alport syndrome.

Patients must have UPCR ≥ 90 mg/mmol [0.8 g/g] at 2 consecutive measurements during Screening, separated by at least 2 weeks and calculated by the central laboratory. The baseline measurement will be the geometric mean of these 2 measurements. Patient must also have eGFR ≥ 30 mL/min/1.73 m² at Study Visit 1 or 2, calculated at the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI) for patients ≥ 18 years of age and the revised bedside Schwartz formula for patients 12 to 17 years of age.

Eligible patients will be randomized in a 2:1 ratio to receive either setanaxib or placebo for 24 weeks, in addition to their stable dose of RAS inhibitor therapy, with setanaxib dosing based on age. In the EU, the setanaxib dose will be 1600 mg/day, as only adult patients will be enrolled.

Figure 1. Study Schematic



In the EU, only adult patients (18 to 50 years, inclusive) will be enrolled and the setanaxib dose will be 1600 mg/day.

1. Genetic test results are to be available prior to initiating other Screening procedures. In cases where genetic testing results are not available but the patient is likely to fulfill the other inclusion and exclusion criteria and has provided consent/assent, a sample for genetic testing should be processed locally and the Screening Period duration can be prolonged with the time it takes to receive the genetic test results. All other Screening assessments must be completed within 4 weeks (± 7 days) prior to randomization.
2. Patients with proven intolerance to ACEi and ARB are allowed in the study.
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II type I receptor blocker; eGFR = estimated glomerular filtration rate; EU = European Union; R = randomization; RAS = renin-angiotensin system; UPCR = urine protein to creatinine ratio.

3.1.1 Independent Data Monitoring Committee

Safety and tolerability data will be regularly reviewed by an unblinded IDMC, with the first assessment after 2 patients have had the opportunity to complete at least 12 weeks of study treatment, followed by periodic assessments at a frequency defined in the IDMC Charter. Ad-hoc IDMC meetings may be scheduled as requested by the Sponsor or the IDMC. If there is a case of suspected DILI, study enrollment will be paused awaiting IDMC review and recommendation. The IDMC may recommend change(s) to the study conduct based on the safety data reviews, as defined in the IDMC Charter.

3.1.2 Study Duration

The start of the study will be the date on which the first patient provides informed consent/assent, and the end of the study will be the last patient's last assessment.

The estimated study duration for an individual patient is approximately 32 weeks. Following a 4-week Screening Period (Note: the Screening Period may be longer than 4 weeks, as needed, to complete genetic testing), patients will receive setanaxib or placebo for a 24-week Treatment Period, followed by a 4-week Follow-up Period.

3.1.3 Planned Number of Patients

The study is planned to enroll and treat approximately 18 patients. Up to 6 patients should be in the age group of 12 to 17 years old at the time of consent/assent, and a minimum of 12 patients should be ≥ 18 years of age. In the EU, only adult patients (18 to 50 years, inclusive) will be

enrolled. To ensure balance among treatment groups, randomization will be stratified by age group (12 to 17 years of age and ≥ 18 years of age) at the time of consent/assent.

3.2 Study Population

The target population for this study is male and female patients aged 12 to 50 years, inclusive, with Alport syndrome at risk of disease progression despite receiving maximum-tolerated RAS inhibitor therapy. For sites in the EU, patients aged 18 to 50 years, inclusive, will be enrolled.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Male or female patients aged 12 to 50 years, inclusive, at the time of informed consent/assent;
For sites in the EU: Male or female patients aged 18 to 50 years, inclusive, at the time of informed consent;
2. Diagnosis of Alport syndrome by genetic testing (documented mutation in a gene associated with Alport syndrome [ie, COL4A3, COL4A4, or COL4A5]). Patients with a variant of uncertain significance should not be included in the study;

Note: Genetic test results are to be available prior to initiating other Screening procedures. In cases where genetic testing results are not available but the patient is likely to fulfill the other inclusion and exclusion criteria and has provided consent/assent, a sample for genetic testing should be processed locally and the Screening Period duration can be prolonged with the time it takes to receive the genetic test results. All other Screening assessments must be completed within 4 weeks (± 7 days) prior to randomization.

3. Weight ≥ 40 kg;
4. Willing and able to give informed consent (and assent, where applicable), in accordance with local age requirements, and to comply with the requirements of the study;
5. 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 (as specified in 5c) up to 90 days after the last dose of IMP;
 - a. For the purposes of this study, women of childbearing potential (WOCBP) 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 level in the postmenopausal range will be required at Screening to confirm a postmenopausal state; and
 - 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 include the following:
 - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal);
 - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable);
 - Intrauterine device;
 - Intrauterine hormone-releasing system;

- Bilateral tubal occlusion;
 - Vasectomized partner; and
 - Sexual abstinence (refraining from heterosexual intercourse during the entire period of risk associated with the study treatments, ie, up to 90 days after the last dose of IMP). 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, or post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.
6. Female patients of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Visit 3 (after randomization and before dosing);
 7. 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 [inclusion criterion 5c](#)). Female condom and male condom should not be used together. This requirement begins at the time of informed consent/assent and ends 90 days after receiving the last dose of IMP;
 8. 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;
 9. $\text{eGFR} \geq 30 \text{ mL/min/1.73 m}^2$ at Study Visit 1 or 2, calculated at the central laboratory using the CKD-EPI formula for patients ≥ 18 years of age and the revised bedside Schwartz formula for patients 12 to 17 years of age;
 10. Proteinuria ($\text{UPCR} \geq 90 \text{ mg/mmol [0.8 g/g]}$) at 2 consecutive measurements (24-hour urine sampling), separated by at least 2 weeks and calculated by the central laboratory;
 11. Receiving maximum allowed dose or maximum-tolerated daily dose of an ACEi and/or ARB that has been stable for at least 8 weeks prior to consent/assent; and
- Note: A stable dose is defined as a dose within 25% of the dose at randomization.
- Note: Patients with proven intolerance to ACEi and ARB are allowed in the study.
- Note: SGLT2 inhibitors are allowed provided they have been given at the same dose for at least 8 weeks prior to Screening and are given at the same dose during the study.
12. Systolic and diastolic blood pressure ≤ 95 th percentile, based on the patient's age and weight for patients 12 to 17 years of age or with $\leq 130 \text{ mmHg}$ systolic blood pressure and $\leq 80 \text{ mmHg}$ diastolic blood pressure for patients ≥ 18 years of age.

Note: At least 1 blood pressure measurement during Screening (Study Visit 1 or 2) should be within these limits. Blood pressure will be measured after resting in the supine position for at least 5 minutes and will be measured 3 times with each measurement separated by at least 1 minute (the lowest value will be recorded on the electronic case report form [eCRF]).

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Has ongoing chronic hemodialysis or peritoneal dialysis;
2. Has a history of kidney transplant;
3. Has other causes of CKD (even if not yet on hemodialysis), including but not limited to other heritable disorders leading to CKD, diabetic nephropathy, hypertensive nephropathy, lupus nephritis, and immunoglobulin A nephropathy;
4. Has been treated with any investigational agent within 12 weeks of signing informed consent/assent or 5 half-lives of the investigational agent (if known), whichever is longer, or current enrollment in an interventional clinical study;
5. Has had prior treatment with setanaxib;
6. Has known malignancy that is progressing or requires active treatment, with the exception of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer that has undergone potentially curative therapy, or malignancy treated with curative intent and with no known active disease ≥ 2 years before the first dose of study drug and of low potential risk for recurrence;
7. Positive urine drug screen (if not due to prescription 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 exclusionary and may be allowed if the prescription and diagnosis are reviewed and approved by the Investigator;
8. Has an active HIV infection or acute or chronic hepatitis B or C infection, confirmed at Screening;
9. Has had a surgery (eg, gastric bypass) or medical condition that might significantly affect absorption of medicines (as judged by the Investigator);
10. Has a positive pregnancy test at Study Visit 2 (Screening) and/or Study Visit 3 (Day 1) (WOCBP only) or is breastfeeding;

Note: If a randomized patient has a positive pregnancy test at Study Visit 3 (Day 1), they will be considered a patient withdrawn for non-safety reasons.

11. Has evidence of any of the following cardiac conduction abnormalities at Screening or Day 1 (pre-dose): a QTcF interval >450 milliseconds for male patients or >470 milliseconds for female patients, or a PR interval ≥ 220 milliseconds;

Note: Patients with a second or third degree atrioventricular block are to be excluded.

12. Has a history of aplastic anemia, or any current marked anemia, defined as hemoglobin <10.0 g/dL;
13. Has uncontrolled hypothyroidism. Patients with subclinical hypothyroidism may be included. Subclinical hypothyroidism is defined biochemically as a normal serum free T4 concentration in the presence of an elevated serum TSH concentration;

14. Has 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;
15. Has any other condition that, 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;
16. Uses medications known to be potent CYP3A4 inhibitors (itraconazole, lopinavir/ritonavir, telaprevir, clarithromycin, ritonavir, ketoconazole, indinavir/ritonavir, conivaptan, and voriconazole), potent CYP3A4 inducers (avasimibe, carbamazepine, enzalutamide, mitotane, nevirapine, phenobarbital, phenytoin, rifabutin, rifampicin, rifapentine, and St John's wort), or potent UGT1A9 inhibitors and inducers (mefenamic acid and rifampicin) within 21 days prior to study drug administration;
17. Has known psychiatric illness/social situations that would limit compliance with study requirements, substantially increase risk of incurring AEs, or compromise the ability of the patient to give written informed consent/assent;
18. Has known hypersensitivity or intolerance to setanaxib or to any of its excipients;
19. Has a history of chronic liver disease (eg, PBC, alcoholic liver disease, chronic viral hepatitis including hepatitis B and C, non-alcoholic fatty liver disease, and hemochromatosis);
20. Has plasma alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $>3 \times$ the upper limit of normal (ULN) at Study Visit 1 or 2 (Screening);
21. Has total bilirubin $>2 \times$ ULN at Study Visit 1 or 2 (Screening); or
22. Has international normalized ratio >1.2 at Study Visit 1 or 2 (Screening) (criterion not applicable for patients on anticoagulant therapy).

4.3 Withdrawal Criteria

A patient may prematurely discontinue study drug and/or withdraw from the study at any time. A distinction must be made between premature discontinuation of study drug and withdrawal from the study. A patient may prematurely discontinue study drug and still continue his/her participation in the study.

The reasons for premature discontinuation of study drug and for withdrawal from the study must be documented in the eCRF. Reasons for premature discontinuation of study drug include, but are not limited to, the following:

- Withdrawal of consent/assent;
- Any event, laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient;
- Pregnancy;
- Patient failure to comply with Protocol requirements or study-related procedures;
- Termination of the study by the Sponsor or regulatory authority;

- Initiation of medications known to be potent CYP3A4 inhibitors (itraconazole, lopinavir/ritonavir, telaprevir, clarithromycin, ritonavir, ketoconazole, indinavir/ritonavir, conivaptan, and voriconazole), potent CYP3A4 inducers (avasimibe, carbamazepine, enzalutamide, mitotane, nevirapine, phenobarbital, phenytoin, rifabutin, rifampicin, rifapentine, and St John's wort), or potent UGT1A9 inhibitors and inducers (mefenamic acid and rifampicin);
- The patient experiences mean QT prolongation (mean QTcF interval >500 milliseconds AND increase by >60 milliseconds over the mean baseline QTcF);
- Severe allergic reactions to the study drug;
- The patient has CTCAE Grade ≥ 2 anemia AND the retest absolute reticulocyte count is below 50% of the baseline value. In this case, study drug will not be resumed and will be permanently discontinued; or
- The patient has suspected DILI meeting [Criterion 3](#) in [Appendix C](#).

Unless a patient withdraws his/her consent/assent to participate in the study, all patients should be encouraged to complete the remaining study visits, regardless of whether they are still receiving study drug.

For patients who are withdrawn from the study prior to completion of Study Visit 8, the Early Termination Visit procedures will be completed, if possible, at the time the decision is made to withdraw the patient. The Early Termination Visit will consist of all of the Study Visit 8 procedures. The reason for patient withdrawal must be documented in the eCRF.

In the case of a patient lost to follow-up, at least 3 attempts to contact the patient must be made and documented in the patient's records.

Withdrawn patients may be replaced, unless a patient is withdrawn for a reason related to safety, as per the judgment of the Investigator. A maximum of 20 patients will be randomized for the study.

4.4 Screen Failures and Patient Re-Screening Procedures

Patients who sign consent/assent but do not meet all of the eligibility requirements defined in [Sections 4.1](#) and [4.2](#) and therefore are not randomized will be considered a screen failure. Screen failure patients may be re-screened for the study if approval is given by the Medical Monitor. All re-screened patients must be re-consented and sign a new Informed Consent Form (ICF)/assent prior to completion of any re-screening study procedures.

Re-screened patients will be assigned a new patient number at the time of re-screening. The re-screened patient's new eCRF casebook will contain a reference to the patient's previous identification number.

5 STUDY TREATMENTS

5.1 Treatment Groups

5.1.1 Setanaxib

Patients will receive the following setanaxib doses according to age at the time of consent/assent:

- For patients aged 12 to 17 years: 1200 mg/day (800 mg morning + 400 mg evening) for 24 weeks; and
- For patients aged ≥ 18 years: 1600 mg/day (800 mg BID) for 24 weeks.

5.1.2 Placebo

Matching film-coated placebo tablets, containing only excipients, will also be provided.

5.2 Background Therapy

Throughout the study, all patients will remain on their maximum allowed dose or maximum-tolerated daily dose of RAS blockade using ACEi and/or ARB. Patients with proven intolerance to ACEi and ARB are allowed in the study. No clinically significant PK drug-drug interactions are expected to arise from combining setanaxib with ACE inhibitors.²⁷ Similarly, setanaxib is not expected to affect the PK of ARBs, with the possible exception for products that are substrates of CYP2C9 (losartan, irbesartan, azilsartan); setanaxib increased the losartan maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) by 70% and 45%, respectively; this effect may not be clinically significant. No clinically significant interactions are expected with valsartan, telmisartan, olmesartan, candesartan, or eprosartan.²⁸

5.3 Dose Justification

The adult dosing regimen for this study is the highest dose level of setanaxib previously investigated and considered safe and well tolerated, ie, 800 mg BID (1600 mg/day). At the adult dose level of 800 mg BID, the expected exposures are similar to the defined NOAEL in the preclinical setting for both the parent drug (setanaxib) and its active metabolite (GKT138184). The NOAEL-defining toxicology signals have been monitored in the clinical setting and no safety signals related to those findings have been observed in either healthy subjects at 800 mg BID for 10 days or in adult patients at up to 800 mg BID for up to 76 weeks.

In the completed clinical study GSN000300, 111 patients with PBC were randomized 1:1:1 to receive placebo, setanaxib 400 mg once daily, or setanaxib 400 mg BID for 24 weeks. This dosing regimen was considered safe and well tolerated, and the treatment was pharmacologically active (based on observed dose-related improvements in liver enzymes); however, the observed clinical efficacy in the target patient population was considered insufficient. As a result, doses of up to 800 mg BID are being used in the ongoing Phase 2b/3 study in patients with PBC and elevated liver stiffness (GSN000350) and in the Phase 2 study in patients with recurrent or metastatic SCCHN (GSN000400). The safety data from the ongoing clinical studies are regularly reviewed by the Sponsor Safety Management Team (blinded safety information) and by the respective study IDMCs (unblinded review). To date, there have not been any safety or tolerability concerns and both studies have continued without interruption. In the ongoing, blinded Phase 2b/3 study in PBC patients (GSN000350), 4 cases of increased hepatic enzymes (ie, suspected DILI) have been

observed to date in these patients with chronic liver disease. The patients were asymptomatic at the time of the suspected DILI. All cases have resolved. To date, no suspected DILI events have been reported in any of the other completed or ongoing clinical studies. The same 800 mg BID adult dose level is selected for the current study in Alport syndrome with the intent to be both safe and tolerable, and to provide an assessment of preliminary clinical efficacy.

The relationship between dose and inhibition of NOX1 and NOX4 pathways in humans is not clearly established, but estimates based on preclinical in vitro experiments and human PK suggest that at a dose of setanaxib of 800 mg BID, the average target inhibition over the dosing interval is about 80%. This is superior to the 400 mg BID dose level (about 68% inhibition). These estimates suggest that the 800 mg BID dosing regimen may provide sufficient target inhibition to evaluate the mechanism of action and clinical effects of setanaxib.

The dose selection for the adolescent patients is based on results from completed and ongoing studies, indicating that a dose of setanaxib of 800 mg BID in adults is safe, well tolerated, and may provide clinical benefit in adult patients. Since there is no suggestion that the pharmacology^{29,30,31,32} or safety and tolerability of setanaxib will be different in adolescent patients with Alport syndrome, the dose selection for adolescent patients aims to achieve the same systemic exposure levels as those seen in adults following dosing at the 800 mg BID dose level.

Available data for setanaxib suggest a drug disposition profile where renal clearance of unchanged parent drug represents a negligible portion of the elimination and where metabolism via UGT1A9-mediated glucuronidation and CYP3A4 are the dominant elimination pathways, with only minor contributions from other elimination pathways.

Following allometric principles, a dose level of 1200 mg/day (800 mg morning + 400 mg evening) for the 12 to 17 years of age range (restricted to a body weight of at least 40 kg) has been selected. On average, a 40 kg patient at 1200 mg/day is expected to have approximately 14% higher exposure (AUC) than a 70 kg patient at 1600 mg/day.

5.4 Randomization and Blinding

This is a randomized, double-blind study. Patients meeting eligibility criteria will be randomized in a 2:1 ratio to receive either setanaxib or placebo and the randomization of patients will be managed by an Interactive Response Technology (IRT) system. To ensure balance among treatment groups, randomization will be stratified by age group (12 to 17 years of age and ≥18 years of age) at the time of consent/assent.

After confirming all eligibility criteria (including laboratory values from Study Visits 1 and 2, UPCR, and eGFR), randomization will be performed through IRT, which will trigger the first shipment of study drug to the site for the patient. The patient does not need to be on site at the time of randomization. Study Visit 3 should occur within 10 days (+3 days) after randomization. Following the initial shipment, there will be an automatic resupply of study drug to the site for dispensing to the patient at Study Visits 5, 6, and 7.

Patients will be assigned a treatment assignment as determined by the IRT system. The IRT system will manage all aspects of treatment and logistical aspects of study product supply.

Randomized patients who prematurely discontinue the study for non-safety reasons may be replaced. Data should be continuously collected until Week 24, if possible.

5.5 Breaking the Blind

Individual treatment assignments may be unblinded when immediate knowledge of the treatment assignment is needed to optimize the clinical management of the patient. In case of medical emergency, the Investigator will have direct access to unblinding of treatment. In such emergency situations, the responsibility to break the treatment code resides solely with the Investigator. The Investigator should contact the Medical Monitor as soon as possible to discuss the event. The IRT system allows for immediate emergency unblinding of a patient by the site when determined necessary. Site personnel will be trained by the Clinical Research Associate (CRA) on the unblinding procedures.

A sealed code break envelope will be prepared and provided to the study site to enable emergency code break for an individual patient.

Documentation of the blind break, including the patient's identification, reason for breaking the blind, and the date and time of breaking the blind, must be retained in the patient's source notes at the site in such a way as to avoid unblinding the treatment assignment to other site or Sponsor blinded personnel.

5.6 Drug Supplies

5.6.1 Formulation and Packaging

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

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

5.6.2 Study Drug Preparation and Dispensing

Study drug will be dispensed at visits specified in [Appendix A](#), following IRT procedures and study drug assignment.

5.6.3 Study Drug Administration

When study drug is dispensed, the patient will be instructed on study drug administration.

Patients must take the first dose of study drug in the presence of site staff during Study Visit 3. Similarly, the morning dose at the Week 2, Week 12, and Week 24 visits should be taken at the study site, to allow for proper PK sampling. Fasting prior to PK sampling will not be required.

Patients will self-administer (with caregiver supervision, as needed, if the patient is 12 to 17 years of age) 2 tablets of blinded study drug (setanaxib or placebo) in the morning and either 1 or 2 tablets of blinded study drug in the evening (according to age) with food or up to 30 minutes after eating a meal. Tablets may be divided (preferably using a pill cutter) if needed for easier administration. If divided, care must be taken to make sure that the whole dose is ingested, and tablets should be divided immediately prior to dosing, without any storage after being cut.

5.6.4 Treatment Compliance

Patients will be instructed to return all empty bottles and unused study drug to the site at the study visits indicated in [Appendix A](#). Patients will return all remaining unused study drug at Study

Visit 8. Treatment compliance will be assessed at each study visit after baseline (Day 1) through Week 24.

Accountability of the used and unused study drug will be recorded. Compliance with the study drug regimen will be evaluated by counting unused tablets. During the Treatment Period, if compliance is not between 80% and 120%, inclusive, the patient will be counseled about the importance of compliance with the study drug regimen.

5.6.5 Storage and Accountability

Setanaxib formulations should be stored at room temperature (15°C to 25°C [59°F to 77°F]) and should not be frozen.

The Investigator or designee will maintain accurate records of receipt and condition of study drug. Any reasons for departure from the Protocol-specified dispensing regimen must also be recorded. All unused study drug for all patients should be maintained until review by a study monitor during site visits and at the time of database lock. The site will maintain accountability records to document receipt and dispensing of setanaxib and placebo throughout the study.

All unused setanaxib and placebo tablets remaining at the completion of the study will either be returned to the Sponsor or destroyed at the study site, per Sponsor instruction. It is the responsibility of the Investigator to ensure that the Sponsor has provided written authorization prior to return or destruction of study drug. Study drug return/destruction will be documented in the site files. No unused study drug may be disposed of until fully accounted for by the study monitor.

Refer to the Pharmacy Manual for additional details.

5.7 Prior and Concomitant Medications and/or Procedures

5.7.1 Excluded Medications and/or Procedures

The following medications and/or procedures will exclude patients from participation in this study:

- Medications known to be potent CYP3A4 inhibitors (itraconazole, lopinavir/ritonavir, telaprevir, clarithromycin, ritonavir, ketoconazole, indinavir/ritonavir, conivaptan, and voriconazole), potent CYP3A4 inducers (avasimibe, carbamazepine, enzalutamide, mitotane, nevirapine, phenobarbital, phenytoin, rifabutin, rifampicin, rifapentine, and St John's wort), or potent UGT1A9 inhibitors and inducers (mefenamic acid and rifampicin) within 21 days prior to study drug administration;
- Systemic steroids given for a period of greater than 2 weeks are not permitted;
- Investigational agents within 12 weeks of signing informed consent/assent or 5 half-lives of the investigational agent (if known), whichever is longer;
- Prior treatment with setanaxib; and
- Any surgery (eg, gastric bypass) that might significantly affect absorption of medicines (as judged by the Investigator).

5.7.2 Medications to be Used With Caution

Setanaxib has been shown to be a weak inhibitor of OAT3, CYP2C9, and CYP2C19 in a clinical pharmacology 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 the following:

- 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); and
- Sensitive substrates of BCRP and P-glycoprotein, such as digoxin.

In vitro data suggest 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 the following:

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

5.7.3 Allowed Medications

All patients must be receiving the maximum allowed dose or maximum-tolerated daily dose of an ACEi and/or ARB that has been stable for at least 8 weeks prior to consent/assent. A stable dose is defined as a dose within 25% of the dose at randomization. Patients with proven intolerance to ACEi and ARB are allowed in the study.

SGLT2 inhibitors are allowed provided they have been given at the same dose for at least 8 weeks prior to Screening and are given at the same dose during the study.

Local and topical steroids are permitted.

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 exclusionary and may be allowed if the prescription and diagnosis are reviewed and approved by the Investigator.

5.7.4 Documentation of Prior and Concomitant Medication Use

Medications taken within 3 months prior to the date of consent/assent and concomitant medications and therapies administered throughout the course of the study until the last patient visit will be recorded in the eCRFs.

6 STUDY PROCEDURES

Study procedures will follow the Schedule of Procedures ([Appendix A](#)).

7 EFFICACY ASSESSMENTS

7.1 Pharmacokinetic Sampling

PK samples will be collected at timepoints specified in [Appendix A](#).

PK samples will be collected at Week 2 (pre-dose and 1, 2, 3, 4, and 6 hours post-dose), at Week 12 (pre-dose), and at Week 24 (pre-dose).

The PK sampling windows are as follows:

- Pre-dose: within 90 minutes prior to dose;
- 1, 2, 3, and 4 hours post-dose: ± 5 minutes; and
- 6 hours post-dose: ± 15 minutes.

7.2 24-Hour Urine Testing

Urine testing will be performed at visits specified in Appendix A. Urine testing results will include creatinine clearance, total albumin, total cortisol, total creatinine, total protein, and UPCR, based on a 24-hour sample collection at each specified timepoint.

The screening urine collection consists of 2 separate 24-hour collections. Patients will be provided with containers for collection and will collect urine at home on 2 occasions at least 2 weeks apart prior to returning to Visit 2. The urine collection is to be kept in the fridge and must be provided to the site within 48 hours of completing each 24-hour collection. UPCR will be determined for 24-hour urine collections during the Screening Period to confirm eligibility. The geometric mean values will be used for baseline.

During the study visits prior to Weeks 6, 12, 24 (or Early Termination), and the Follow-up Visit, the patient will be provided with containers for urine collection. One 24-hour urine collection is to be done by the patient at home within 5 days prior to Visit 5 (Week 6), Visit 6 (Week 12), and the Follow-up Visit, respectively. Prior to the End of Study Visit at Week 24 (or Early Termination), urine will be collected on 2 occasions at least 1 week apart and not more than 2 weeks apart, with the last one completed within 5 days prior to the study visit. UPCR geometric mean values will be used for the final analysis. The urine collection must be kept in the fridge and is to be provided to the site within 48 hours of completing each 24-hour collection.

A urine collection may need to be repeated if it is deemed potentially inadequate, as per the evaluation of the testing parameters by the Medical Monitoring team. For rare occasions where a 24-hour collection is not feasible for an adolescent study patient, an alternative method for urine collection may be accepted (such as a 12-hour sample), if discussed and pre-approved by the Medical Monitoring team.

UPCR history up to 12 months prior to signing informed consent/assent, including local laboratory results, will be collected.

7.3 Estimated Glomerular Filtration Rate

Plasma samples for eGFR will be collected at timepoints specified in Appendix A.

The central laboratory will calculate the eGFR using the CKD-EPI formula for patients ≥ 18 years of age and the revised bedside Schwartz formula for patients 12 to 17 years of age.

Note: Two eGFR samples will be collected at Week 24, at least 1 week apart but no more than 2 weeks apart, with the last sample collected during the Week 24 study visit.

eGFR history up to 12 months prior to signing informed consent/assent, including local laboratory results, will be collected.

7.4 Exploratory Biomarker Sampling

Blood (up to 48 mL) and urine (up to 20 mL) samples will be collected for exploratory biomarker analyses at timepoints specified in [Appendix A](#).

8 SAFETY ASSESSMENTS

Safety assessments will include AEs, clinical laboratory evaluations (including serum chemistry, hematology, endocrinology, and urinalysis), vital signs, physical examination, and 12-lead ECG.

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF. The Investigator should update the appropriate eCRF if additional follow-up information becomes available (eg, the AE has subsided, stabilizes, or the condition becomes chronic in nature).

AEs, which include clinical laboratory test results, will be monitored and documented from the time of informed consent/assent until the end of the Follow-up Period (Study Visit 9). Patients should be instructed to report any event that they experience to the Investigator, whether or not they think the event is due to study drug. From the time of informed consent/assent, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at informed consent/assent should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline change in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at informed consent/assent and significantly worsen during the study should be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Thus, abnormal test results that are determined to be an error should not be reported as an AE, while laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should usually be reported as an AE if any of the following are applicable:

- An intervention is required as a result of the abnormality;
- Action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

8.1.1 Adverse Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Reaction

An unexpected adverse reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information/reference safety information.

For setanaxib, the reference safety information is included in Section 5.3.7 of the IB currently in force. The reference safety information will be reviewed annually by the Sponsor and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report, where possible.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE and will also categorize each AE as to its potential relationship to the investigational study drug.

8.1.3.1 Assessment of severity

The severity of all AEs should be graded according to the CTCAE version 5.0. For those AE terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated; or
- CTCAE Grade 5: Death related to the AE.

8.1.3.2 Causality assessment

The relationship of an AE to the administration of study drug is to be assessed according to the following definitions:

- **No (not related or unlikely related):** The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and/or another cause (concomitant drugs, therapies, complications, etc) is suspected; or
- **Yes (possibly, probably, or definitely related):** The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

Note: The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- **The temporal sequence from study drug administration:** The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event;
- **Underlying, concomitant, intercurrent diseases:** Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have;
- **Concomitant drug:** The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question;
- **Known response pattern for this class of study drug:** Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect;
- **Exposure to physical and/or mental stresses:** The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event; and
- **The pharmacology and PK of the study drug:** The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.1.4 Adverse Events of Special Interest

The Investigator will monitor each patient for clinical and laboratory evidence of predefined AESIs throughout the patient's participation in this study.

The Investigator will assess and record any additional information on the AESI in detail on an AE eCRF, which must be completed within 24 hours of awareness of the event, following the same procedure as for serious AEs (SAEs) (see [Section 8.3](#)).

For this study, CTCAE Grade ≥ 2 anemia, defined as hemoglobin < 10 g/dL, AND absolute reticulocyte counts of $< 50\%$ of the baseline value (Screening Study Visit 2), which are confirmed by repeat testing, will be considered an AESI.

During the course of the study, additional AESIs may be identified by the Sponsor. AESIs must be recorded in the eCRF.

8.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalization;

Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent/assent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

Note: Important medical events that do not meet any of the above criteria may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting – Procedures for Investigators

8.3.1 Initial Reports

All SAEs occurring from the time of informed consent/assent until 30 days after the last study drug dose must be recorded in the electronic data capture (EDC) and be reported to the Calliditas Patient Safety Mailbox at Patient.Safety@Calliditas.com within 24 hours of the knowledge of the occurrence. Following 30 days after the last study drug dose, any SAE that the Investigator considers related to study drug must be reported to the Calliditas Patient Safety Mailbox.

To report the SAE, complete the Safety Report Form along with supporting documents if applicable (eg, laboratory reports, hospital discharge summaries, etc) and report to the Calliditas Patient Safety Mailbox at Patient.Safety@Calliditas.com or call the Calliditas SAE reporting line, and email the completed paper Safety Report Form to Calliditas (contact information listed below) within 24 hours of awareness.

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.

Calliditas SAE reporting line:
Telephone (Germany): +49 (621) 5705971
Email: Patient.Safety@Calliditas.com

8.3.2 Follow-Up Reports

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, or until the patient is lost to follow-up.

At the time the patient 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 and procedure as noted above for initial reports after receipt of the information.

8.4 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 the following:

- Packaging that is damaged or broken;
- Missing or illegible labelling;
- Inability of customer to administer the product; and
- 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 product.complaints@Calliditas.com.

Any AEs that are associated with a product complaint, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF, per instructions for AE Reporting in [Section 8.3](#).

8.5 Pregnancy Reporting

If a patient becomes pregnant during the study, the Investigator is to stop dosing with study drug(s) immediately and the patient should be withdrawn from the study.

A pregnancy is not considered to be an AE or SAE; however, any pregnancy occurring during the study and up to 30 days after the last dose of study drug must be reported to the Calliditas Patient Safety Mailbox within 24 hours of knowledge of the event. The Calliditas Patient Safety Mailbox will then provide the Investigator/site the Pregnancy Form for completion. The Investigator/site must complete the Pregnancy Form and email it back to the Calliditas Patient Safety Mailbox at Patient.Safety@Calliditas.com.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug, the Investigator should notify the Calliditas Patient Safety Mailbox as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the Pregnancy Form should be completed and emailed to the Calliditas Patient Safety Mailbox. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.6 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to EudraVigilance for applicable European competent authorities, other regulatory authorities, as applicable, and to applicable Ethics Committee(s), and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported, as applicable, to EudraVigilance for applicable European competent authorities, other regulatory authorities, as applicable, and to applicable Ethics Committee(s) as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also submit any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to IMPs.

8.7 Special Situation Reports

Special Situation Reports include reports of IMP overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the Protocol. 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. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s), or the Investigator has reason to suspect that the patient has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the Protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer. The administration or consumption of the unassigned treatment and administration of an expired product are

always reportable as medication errors; cases of patients missing doses of investigational product are not considered reportable as medication errors.

All special situation events as described above must be reported on the Special Situation Report form and emailed to the Calliditas Patient Safety Mailbox (contact information listed in [Section 8.3.1](#)) within 24 hours of knowledge of the event. All AEs associated with these Special Situation Reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and reported to the Calliditas Patient Safety Mailbox by completing the Safety Report Form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

8.8 Clinical Laboratory Evaluations

Clinical laboratory evaluations (including serum chemistry, hematology, endocrinology, and urinalysis) will be collected at timepoints specified in [Appendix A](#).

Baseline values for liver tests (ALT, AST, and total bilirubin) are determined by averaging the values obtained at Screening Visits 1 and 2 to obtain the arithmetic mean.

For WOCBP only: a serum pregnancy test will be performed at Study Visit 2. A pregnancy test via a local urine assessment will be performed at all other applicable study visits prior to study drug dosing.

The total number of venipunctures and the total volume of blood collected during the study will be limited to that needed for PK, PD, and safety assessments. The total whole blood volume collected during the study will not exceed those allowed per European Medicines Agency guidance (Ethical considerations for clinical trials on medicinal products conducted with minors).

See [Appendix B](#) for the complete list of analytes.

8.8.1 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 site within 7 days so that the absolute reticulocyte count can be retested. If the retest value is below 50% of the baseline value (Screening Study Visit 2), IMP will not be resumed and will be permanently discontinued. IMP administration will be resumed only if the retest value of the absolute reticulocyte count is $\geq 50\%$ 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 8.1.4](#), following the same procedure as for SAEs ([Section 8.3](#)).

8.8.2 Suspected Drug-Induced Liver Injury

During the study, the Investigator will remain vigilant for increases in liver enzymes and other measures of liver function. In the event that the patient has any of the following laboratory results, the Investigator should refer to [Appendix C](#) for details regarding the detection and management of suspected DILI, including instructions for retesting, close monitoring, and action to take regarding the IMP:

- AST or ALT $\geq 3 \times$ ULN;
- AST or ALT $>2 \times$ Baseline; or
- Total bilirubin $>2 \times$ ULN.

If there is a reported case of suspected DILI, an ad-hoc IDMC meeting will be scheduled for an unblinded review of safety data. The study enrollment will be paused awaiting IDMC review and recommendation. IMP treatment of already enrolled study patients may continue pending IDMC recommendation.

8.9 Vital Signs

Vital signs will be collected at timepoints specified in [Appendix A](#), including at Screening, Day 1 (pre-dose and 3 and 6 hours post-dose), Weeks 2, 6, 12, and 18 (pre-dose), Week 24 (pre-dose and 3 and 6 hours post-dose), and at the Follow-up Visit. Timing windows for vital signs measurements are ± 10 minutes for 3 hours post-dose and ± 20 minutes for 6 hours post-dose.

Vital sign measurements will include systolic and diastolic blood pressure and heart rate. Blood pressure and heart rate will be measured after resting in the supine position for at least 5 minutes and will be measured 3 times with each measurement separated by at least 1 minute (the lowest value will be recorded on the eCRF).

8.10 Electrocardiograms

12-lead ECGs will be collected at timepoints specified in [Appendix A](#), including at Screening, Day 1 (pre-dose and 3 and 6 hours post-dose), Weeks 2, 6, 12, and 18 (pre-dose), Week 24 (pre-dose and 3 and 6 hours post-dose), and at the Follow-up Visit. Timing windows for ECGs are ± 10 minutes for 3 hours post-dose and ± 20 minutes for 6 hours post-dose.

ECGs should be collected in triplicate, 1 to 3 minutes apart, and read locally. Investigators and site staff are encouraged to consult with a local cardiologist, if needed, to interpret suspected QT prolongation or other clinically significant abnormalities.

If collected at the same time point as PK blood draws, ECGs should be recorded before blood draws to avoid effects of blood draw on autonomic tone.

8.11 Physical Examinations

Physical examinations will be performed at timepoints specified in [Appendix A](#).

Physical examinations will include the following body systems: general appearance, skin, head, ears, eyes, nose, throat, neck, lungs, heart, abdomen, musculoskeletal, extremities, and neurological systems.

8.12 Weight and Height

Height and weight will be collected at all timepoints specified in [Appendix A](#).

Height will be collected at the beginning (Study Visit 3/Day 1) and at the end of the study (Study Visit 8/Week 24) and, for patients between 12 and 17 years of age, at all other visits where eGFR is calculated. Weight will be collected for all patients at all timepoints.

8.13 Hearing Examinations

Hearing examinations will be completed at timepoints specified in Appendix A.

Pure tone audiometry (PTA) air conduction thresholds will be conducted at frequencies 250, 500, 1000, 2000, 4000, and 8000 Hz.

PTA bone conduction thresholds will be conducted at frequencies 500, 1000, 2000, and 4000 Hz.

9 STATISTICS

9.1 Analysis Sets

The following analysis sets will be defined in the study:

- The Full Analysis Set (FAS) will be defined as all randomized patients;
- The Safety Analysis Set (SAS) will be defined as all randomized patients who take at least 1 dose of the study drug; and
- The PK Analysis Set will be defined as all randomized patients who take at least 1 dose of the study drug and have sufficient setanaxib plasma concentration data to calculate at least 1 PK parameter.

Other analysis sets may be defined as appropriate and, if applicable, will be described in the Statistical Analysis Plan (SAP).

9.2 Statistical Methods

Details of the statistical analyses, including supportive and sensitivity analysis if needed, will be provided in the SAP, which will be finalized prior to database lock and unblinding.

All endpoints will be summarized descriptively, and no formal hypothesis testing will be conducted. Descriptive statistics for continuous variables will include number of patients (n), mean, standard deviation, median, minimum, and maximum values. Analysis of categorical variables will include counts and percentages. Any statistical modeling or comparison, along with any associated p-values, will be considered nominal.

9.2.1 Analysis of Safety

To assess the primary objective, the primary safety estimand for SAE is defined by the following key attributes, according to the framework provided in International Council for Harmonisation (ICH) E9 (R1):

Treatment: Setanaxib treated patients compared to placebo.

Population: The SAS comprised of all randomized patients who took at least 1 dose of the study drug.

Variable of interest: SAEs.

Intercurrent event handling: All events will be counted regardless of early discontinuation of treatment, up to 30 days post-last dose of study drug.

Summary measure: Count and percentage of patients experiencing SAEs during the Treatment Period up to 30 days post-final dose.

The analysis of the primary endpoint will be performed using the SAS. The number and percentages of patients with SAEs and treatment-emergent AESIs will be presented by treatment group, system organ class, and preferred term. Additional summaries of AEs, TEAEs, AEs leading to discontinuation of study treatment, and AEs by severity, seriousness, and relationship to study drug(s) will be presented.

Clinical laboratory parameters, vital signs, ECGs, thyroid, hearing and physical examinations will be summarized by treatment group by visit. Change from baseline values by visit will be presented for the continuous parameters. The count (and percentage) of patients with clinically significant changes will be tabulated by treatment group.

9.2.2 Analysis of Efficacy

The analysis of secondary and exploratory endpoints will be performed using the FAS.

The UPCR data will be log-transformed prior to analysis. The analysis of the ratio of UPCR at 24 weeks compared to baseline will be analyzed using a mixed model repeated measurement approach. The analysis will include fixed effects for treatment, visit, and treatment by visit interaction, along with the log-transformed baseline value as a covariate. Model assumptions will be checked and, if not met, appropriate data transformations may be applied, or non-parametric approaches will be considered.

The proportions of patients achieving a 25% reduction in UPCR at 24 weeks from baseline in the setanaxib group will be compared to placebo group using a chi-square test.

The eGFR data will be log-transformed prior to analysis. eGFR data are such that it is possible there will be a small number of patients with extreme outlying data. Therefore, the analysis of the ratio of eGFR at 24 weeks compared to baseline will be based on a Robust Regression. In order to handle missing data, the analysis will be performed over 3 phases: an imputation, analysis, and pooling phase. Further details will be provided in the SAP. Results of the ratio at 24 weeks compared to baseline will be back-transformed to obtain estimated mean changes from baseline.

Baseline UPCR and eGFR will be defined as the geometric mean of 2 assessments prior to randomization. Similarly, the 24-week UPCR and eGFR will be calculated as for baseline. More details will be provided in the SAP.

PK parameters will be estimated for each individual patient using non-linear mixed effect methodology and prior PK knowledge of the compound. Further details will be provided in the SAP. The following PK parameters will be determined:

- $AUC_{0-24-ss}$: Area under the concentration-time curve over 24 hours at steady state;
- C_{min-ss} : Minimum plasma concentration at steady state; and
- C_{max-ss} : Maximum plasma concentration at steady state.

Plasma concentration time data and plasma PK parameter data for setanaxib and GKT138184 will be presented using descriptive summaries.

The exploratory endpoints will be summarized descriptively by treatment group.

9.2.3 Sample Size Determination

The sample size of approximately 18 patients is considered sufficient to provide an initial assessment of setanaxib versus placebo in Alport syndrome. Withdrawn patients may be replaced, unless withdrawn for a reason related to safety, as per the judgment of the Investigator. A maximum of 20 patients will be randomized for the study. The study sample size was chosen empirically, and no formal statistical hypothesis will be tested.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be entered into eCRFs in the EDC system by personnel allocated to this task, as documented on the site delegation log, and will be reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data will be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data will be recorded using the EDC system as the study is in progress. All delegated site personnel will log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR) Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

The following dictionaries will be used for coding medical information:

- Medical Dictionary for Regulatory Activities Version 26.0 or later for AEs, medical history, and concomitant procedures; and
- World Health Organization drug dictionary Version March 2023 or later for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the data, will be applied to ensure accurate, consistent, and reliable data. Data identified as erroneous or missing will be referred to the investigative site for resolution through data queries.

The eCRFs will be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained

in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study (study completion) is defined as the date of the last Protocol-specified visit/assessment (including telephone contact) for the last patient in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible. This study will be conducted in compliance with the Protocol and with the ethical principles that have their origin in the Declaration of Helsinki, the ICH guidelines for GCP, the EU Clinical Trials Regulation No 536/2014, and applicable regional regulations.

11.2 Institutional Review Board/Independent Ethics Committee

It is the responsibility of the Sponsor or their designee (ie, Medpace) to ensure the Independent Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where written IEC approval has been obtained. The Protocol, IB, ICF/assent, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IEC by the Investigator.

Federal regulations and ICH guidelines require that approval be obtained from an IEC prior to participation of patients in research studies. Prior to study onset, the Protocol, any Protocol Amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IEC.

No drug will be released to the site for dosing until written IEC authorization has been received by the Sponsor.

11.3 Informed Consent Procedures

The ICF/assent and any changes to the ICF/assent made during the course of the study must be agreed to by the Sponsor/designee and the IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation, and that patients have sufficient opportunity to have all questions answered in a suitable facility. The Investigator must ensure that the patient has been informed of his/her rights to privacy and his/her rights and guarantees regarding his/her protection, in particular the right to refuse to participate and the right to withdraw from the clinical study at any time without any resulting detriment and without having to provide any justification. The Investigator will obtain written informed consent and/or assent from each patient and/or legally authorized representative or parent/guardian, after they have had sufficient time to consider participation, and before any study-specific activity is performed, unless the activity is part of standard-of-care for the patient and/or indication, and should document in the source that consent/assent was obtained prior to Screening in the study. All site staff obtaining informed consent/assent must be properly trained and delegated informed consent/assent responsibilities.

Patients will participate as much as possible in the informed consent/assent procedure; however, as permitted by local law and institutional Standard Operating Procedures, in case of a lack of decision-making capacity, informed consent/assent on behalf of the patient may be provided by a legally authorized representative, independent physician, or consortium of independent physicians and/or qualified individuals. These patients will, if possible, upon return of their capacity, be consented and allowed to make their own informed medical decisions.

The original signed copy of the ICF/assent must be maintained by the Investigator and is subject to inspection by the Sponsor, their representatives, auditors, the IEC, and/or regulatory agencies.

A copy of the signed ICF/assent will be given to the patient.

All rescreened patients must be reconsented and sign a new ICF/assent prior to completion of any rescreening study procedures.

11.4 Future Use of Biological Samples

In order to be able to address future scientific questions, patients will be asked to voluntarily donate optional biospecimens for banking. If the patient agrees, banked samples may be used for future biomarker (including, but not limited to, ADMA, TIMP-2, IGFBP7, and COL1A1) research and drug development projects, eg, to identify patients who are more likely to benefit from a treatment or experience an AE, or to gain a mechanistic or genetic understanding of drug effects.

Participation in biobanking is voluntary and not a prerequisite for participation in the study. Biobanking will only occur after informed consent/assent has been given in accordance with local ethical and regulatory requirements.

Blood and urine samples for future research studies may be stored for patients who have consented. It is the responsibility of the Investigator or designee (if acceptable under local regulations), to obtain written informed consent from each individual who has consented to have his/her samples stored for future research in a contract laboratory facility under the responsibility of the Sponsor and its potential partners after adequate explanation of the aims, methods, objectives, and potential hazards. Patients must receive an explanation that they are completely free to refuse long-term storage of their samples for future research and may withdraw consent/assent at any time and for any reason during the storage period of the specimen(s), and that refusal of long-term storage does not preclude participation in the study.

Patient samples and information will be stored in a secure storage area and will be identified only by a coded patient identification number. Patient samples will be kept for a maximum of 5 years, after which the samples will be destroyed according to the standard procedures of the laboratory.

At any time, if informed consent/assent is withdrawn, no new data will be added to the study database. Data already obtained from the samples will continue to be kept and used. Patients have the right to request their identifiable samples be destroyed at any time and to be informed of any plans for new analyses on the retained samples.

All samples will be stored at an external biobanking facility contracted by Calliditas. Measures are in place to comply with the applicable rules for the collection, biobanking, and future use of biological samples and clinical data, including the following:

- Sample and data usage must be in accordance with the ICF/assent;
- The facilities storing biological samples from clinical study patients are qualified for the storage of biological samples collected in clinical studies;
- An appropriate sample and data management system is in place, including audit trails for clinical data and/or samples, and the ability to identify and destroy such samples according to ICF/assent; and
- Data and/or samples may be transferred to third parties and other countries as specified in the ICF/assent.

11.5 Patient Card

Upon screening in the study, the patient will receive a patient card to be carried at all times. The patient card will state that the patient is participating in a clinical research study, and will specify the type of treatment, number of treatment packs received, and contact details in case of an SAE.

11.6 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the Protocol, ICH GCP, the EU Clinical Trials Regulation No 536/2014, applicable regulatory requirements, and the Declaration of Helsinki, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor, in the maintenance of complete, legible, well-organized, and easily retrievable data. Before the screening of any patient in this study, the Sponsor/designee will review with the Investigator and site personnel the following documents: Protocol, IB, eCRFs and procedures for their completion, informed consent/assent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor/designee to monitor the study as frequently as deemed necessary to determine that data recording and Protocol adherence are satisfactory. Study monitoring may include onsite, remote, or a combination of both onsite and remote monitoring. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site designee, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the CRA and provide any missing information, whenever possible.

All monitoring activities will be reported and archived.

11.7 Disclosure of Data

Data generated by this study must be available for inspection by the Sponsor/designee, regulatory authorities, and the IEC, as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.8 Data Protection

The conduct of this study and the processing of any personal data collected from each patient (or from a patient's healthcare professional or other relevant third-party sources) by the Sponsor or its designee, the site, or the Investigator for use in the study will fully adhere to the requirements set out in applicable data protection and medical privacy laws or regulations, including, without limitation, the General Data Protection Regulation (GDPR) EU 2016/679 and EU Directive 95/46/EEC. The Sponsor or its designee shall ensure that, at all times, it has an appropriate legal basis for processing personal data under applicable data protection laws. Site-based organizational and technical arrangements to avoid unauthorized access vary by site but all include access-controlled/access-limited document control and technical solutions, including passwords and security control measures to protect study-specific data, both in paper and electronic format.

The Investigators shall provide coded data to the Sponsor or its designee, which do not reveal the patient's name, full date of birth, or any other information that can identify the patient. All personal information shall be replaced with a Subject Identification Code before any information leaves the investigative sites.

The Investigator shall report any data breaches that occur to the Sponsor or its designee, without undue delay. The Sponsor has implemented a Business Practice to address data breaches that complies with the requirements of applicable laws and regulations, including the GDPR. The data breach procedures in the Business Practice provide specific responses to actual or potential threats and involve investigation, containment, and mitigation. If applicable, the authorities and the data patients shall be notified of a data breach within the required timeframes of the applicable laws and regulations, including those of the GDPR.

11.9 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, such as eCRFs and hospital records), all original signed ICFs/assents, copies of all eCRFs, Safety Report Forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator or institution, or to the Sponsor.

11.10 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.11 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.12 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor will provide patient liability insurance for all patients who have given their consent/assent to the clinical study. This coverage is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

11.13 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve clinical trial authorisation (CTA).

The study will commence with the initiation of investigative sites when the CTA and favorable ethics committee opinions have been received.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any Amendments to the study Protocol will be communicated to the Investigators by Medpace or the Sponsor. All Protocol Amendments will undergo the same review and approval process as the original Protocol. A Protocol Amendment may be implemented after it has been approved by the IEC and applicable competent authorities unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IEC and applicable competent authorities without undue delay and at the latest within 7 calendar days of the Sponsor becoming aware.

12.2 Reporting Study Results

A summary of the results of the study will be available within 6 months of the completion of the study.

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APPENDIX A: SCHEDULE OF PROCEDURES

Table 2. Schedule of Procedures

Study Period	Screening (4 Weeks)			Treatment Period (24 Weeks)								Follow-Up (4 Weeks) ^a
			2	N/A ^b								8 EOS/ ET ^d
Study Visit	1				3 ^c					7		9
Study Day or Week	See footnote ^e				Day 1	2w	6w	12w	18w	24w		28w
Visit Window (Days)		±7			+3	±3	±7	±7	±7	±7		±7
Study Procedures												
Genetic testing to confirm Alport syndrome diagnosis ^f	X											
Informed consent/assent ^g	X											
Demographics and medical/surgical history	X											
UPCR/eGFR history ^h	X											
Update medical/surgical history			X		X							
Eligibility criteria assessment	X		X	X								
Contact IRT to trigger study drug shipment and randomization				X								
Prior and concomitant medications and procedures ⁱ	X		X		X	X	X	X	X	X	X	X
AE assessment ^j	X		X		X	X	X	X	X	X	X	X
Physical examination ^k	X											
Hearing examination ^l		X										
Vital signs ^m	X		X		X	X	X	X	X	X	X	X
Body weight and height ⁿ	X		X		X	X	X	X	X	X	X	X
12-lead ECG ^o	X		X		X	X	X	X	X	X	X	X
Hematology ^p	X		X			X	X	X	X	X	X	X
Serum chemistry ^p	X		X			X	X	X	X	X	X	X
INR ^q		X										
FSH ^r			X									
TSH and free T4	X					X	X	X	X	X	X	X

Table 2. Schedule of Procedures (Continued)

Study Period	Screening (4 Weeks)			Treatment Period (24 Weeks)							Follow-Up (4 Weeks) ^a
	1	2	N/A ^b	3 ^c	4	5	6	7	8 EOS/ ET ^d		
Study Visit											
Study Day or Week	See footnote ^e			Day 1	2w	6w	12w	18w	24w		9
Visit Window (Days)	±7			+3	±3	±7	±7	±7	±7		±7
Study Procedures											
HIV, HBV, and HCV ^s	X										
Drug screen (urine)	X										
Supply 24-hour urine containers	2X				X	X		2X	X		
24-hour urine collection ^f		2X				X	X		2X	X	
UPCR		2X				X	X		2X	X	
eGFR ^u	X	X			X	X	X	X	2X	X	
Urinalysis ^v	X	X			X	X	X		X	X	
Biomarker sampling ^w		X					X		X		
Future analysis sampling		X					X		X		
PK sampling ^x					X		X		X		
Pregnancy test ^y		X		X	X	X	X	X	X	X	
Dispensing of study drug				X		X	X	X			
Start of study drug ^z				X							
Return of unused study drug					X	X	X	X	X ^{aa}		
Study drug accountability and compliance assessment ^{bb}					X	X	X	X	X		

Note: Prior to conducting any study-related activities, written informed consent/assent must be signed and dated by the patient and/or legally authorized representative or parent/guardian.

- Following completion of the Treatment Period, patients will enter a 4-week Follow-up Period.
- After confirming all eligibility criteria (including laboratory values from Study Visits 1 and 2, UPCR, and eGFR), randomization will be performed through IRT, which will trigger the first shipment of study drug to the site for the patient. The patient does not need to be on site at the time of randomization. Following the initial shipment, there will be an automatic resupply of study drug to the site for dispensing to the patient at Study Visits 5, 6, and 7. When study drug is dispensed, the patient will also be instructed on study drug administration.
- Study Visit 3 should occur within 10 days after randomization.
- For patients who are withdrawn from the study prior to completion of Study Visit 8, the ET Visit procedures will be completed, if possible, at the time the decision is made to withdraw the patient. The ET Visit will consist of all of the Study Visit 8 procedures.

- e. Patients will have a Screening Period of 4 weeks (± 7 days) (prior to randomization) unless genetic testing is required. Patients will be provided with containers for 24-hour urine collection and will collect urine at home on 2 occasions at least 2 weeks apart prior to returning to Visit 2. UPCR eligibility criteria is to be determined based on the 2 separate 24-hour urine collections. All other Screening assessments must be completed within 4 weeks (± 7 days) prior to randomization.
- f. Genetic test results are to be available prior to initiating other Screening procedures. In cases where genetic testing results are not available but the patient is likely to fulfill the other inclusion and exclusion criteria and has provided consent/assent, a sample for genetic testing should be processed locally and the Screening Period duration can be prolonged with the time it takes to receive the genetic test results. The analysis is to be locally arranged but will be reimbursed by the Sponsor as part of the study. A blood (6 mL) sample must be collected for genetic analysis if Alport syndrome has not already been confirmed with a genetic test.
- g. The estimated duration of individual patient participation will be approximately 32 weeks (excluding time needed for genetic testing, if applicable). As part of the informed consent/assent process, only patients who fully understand and agree to full participation and follow-up should be consented to participate.
- h. eGFR and UPCR history up to 12 months prior to signing informed consent/assent, including local laboratory results, will be collected.
- i. Medications taken within 3 months prior to the date of consent/assent and concomitant medications and therapies administered throughout the course of the study until the last patient visit will be recorded in the eCRFs.
- j. AEs, AESIs, and SAEs will be monitored and reported from the time of signing informed consent/assent.
- k. Physical examinations will include the following body systems: general appearance, skin, head, ears, eyes, nose, throat, neck, lungs, heart, abdomen, musculoskeletal, extremities, and neurological systems.
- l. PTA air conduction thresholds will be conducted at frequencies 250, 500, 1000, 2000, 4000, and 8000 Hz. PTA bone conduction thresholds will be conducted at frequencies 500, 1000, 2000, and 4000 Hz.
- m. Vital sign measurements will include systolic and diastolic blood pressure and heart rate. Blood pressure and heart rate will be measured after resting in the supine position for at least 5 minutes and will be measured 3 times with each measurement separated by at least 1 minute (the lowest value will be recorded on the eCRF). Vital signs will be collected at Screening, Day 1 (pre-dose and 3 and 6 hours post-dose), Weeks 2, 6, 12, and 18 (pre-dose and 3 and 6 hours post-dose), Week 24 (pre-dose and 3 and 6 hours post-dose), and at the Follow-up Visit. Timing windows for vital signs measurements are ± 10 minutes for 3 hours post-dose and ± 20 minutes for 6 hours post-dose.
- n. Height will be collected at the beginning (Study Visit 3/Day 1) and at the end of the study (Study Visit 8/Week 24) and, for patients between 12 and 17 years of age, at all other visits where eGFR is calculated. Weight will be collected for all patients at all timepoints.
- o. ECGs should be collected in triplicate, 1 to 3 minutes apart, and read locally. If collected at the same time point as PK blood draws, ECGs should be recorded before blood draws to avoid effects of blood draw on autonomic tone. ECGs will be collected at Screening, Day 1 (pre-dose and 3 and 6 hours post-dose), Weeks 2, 6, 12, and 18 (pre-dose), Week 24 (pre-dose and 3 and 6 hours post-dose), and at the Follow-up Visit. Timing windows for ECGs are ± 10 minutes for 3 hours post-dose and ± 20 minutes for 6 hours post-dose.
- p. See [Appendix B](#) for the complete list of analytes. Baseline values for liver tests (ALT, AST, and total bilirubin) are determined by averaging the values obtained at Screening Visits 1 and 2 to obtain the arithmetic mean.
- q. INR testing is to be completed as part of Screening assessments only (Visit 1 or Visit 2). Thereafter, INR will be tested as part of follow-up assessments for a suspected case of DILI. See [Appendix C](#) for details regarding additional follow-up assessments to be completed for suspected cases of DILI.
- r. 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 FSH level in the postmenopausal range will be required at Screening to confirm a postmenopausal state.
- s. If the patient is re-screened, HBV, HCV, and HIV screenings should not be repeated if done as part of the study within the last 12 months.
- t. The screening urine collection consists of 2 separate 24-hour collections. Patients will be provided with containers for collection and will collect urine at home on 2 occasions at least 2 weeks apart prior to returning to Visit 2. The urine collection is to be kept in the fridge and must be provided to the site within 48 hours of completing each 24-hour collection. UPCR will be determined for 24-hour urine collections during the Screening Period to confirm eligibility. The geometric mean values will be used for baseline. During the study visits prior to Weeks 6, 12, 24 (or ET), and the Follow-up Visit, the patient will be provided with containers for urine collection. One 24-hour urine collection is to be done by the patient at home within 5 days prior to Visit 5 (Week 6), Visit 6 (Week 12), and the Follow-up Visit, respectively. Prior to the EOS Visit at Week 24 (or ET), urine will be collected on 2 occasions at least 1 week apart and not more than 2 weeks apart, with the last one completed within 5 days prior to the study visit. The urine collection must be kept in the fridge and is to be provided to the site within 48 hours of completing each 24-hour collection.
- u. The central laboratory will calculate the eGFR using the CKD-EPI formula for patients ≥ 18 years of age and the revised bedside Schwartz formula for patients 12 to 17 years of age. Two eGFR samples will be collected at Week 24, at least 1 week apart but no more than 2 weeks apart, with the last sample collected during the Week 24 study visit.
- v. A fresh urine sample will be collected for the urinalysis, and in addition, urine will be assessed by dipstick. See [Appendix B](#) for the complete list of analytes.
- w. Blood (up to 48 mL) and urine (up to 20 mL) samples will be collected for exploratory biomarker analyses.

- x. PK samples will be collected at Week 2 (pre-dose and 1, 2, 3, 4, and 6 hours post-dose), at Week 12 (pre-dose), and at Week 24 (pre-dose). PK sampling windows are provided in [Section 7.1](#).
 - y. For WOCBP only: A serum pregnancy test will be performed at Study Visit 2. A pregnancy test via a local urine assessment will be performed at all other applicable study visits prior to study drug dosing.
 - z. Patients must take the first dose of study drug in the presence of site staff during Study Visit 3. Similarly, the morning dose at the Week 2, Week 12, and Week 24 visits should be taken at the study site, to allow for proper PK sampling. Fasting prior to PK sampling will not be required. Patients will self-administer (with caregiver supervision, as needed, if the patient is 12 to 17 years of age) 2 tablets of blinded study drug (setanaxib or placebo) in the morning and either 1 or 2 tablets of blinded study drug in the evening (according to age) with food or up to 30 minutes after eating a meal. Tablets may be divided (preferably using a pill cutter) if needed for easier administration. If divided, care must be taken to make sure that the whole dose is ingested, and tablets should be divided immediately prior to dosing, without any storage after being cut.
 - aa. Patients will return all remaining unused study drug at Study Visit 8.
 - bb. Treatment compliance will be assessed at each study visit after baseline (Day 1) through Week 24.
- AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; DILI = drug-induced liver injury; ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EOS = End of Study; ET = Early Termination; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; IRT = Interactive Response Technology; N/A = not applicable; PK = pharmacokinetic(s); PTA = pure tone audiometry; SAE = serious adverse event; T4 = thyroxine; TSH = thyroid-stimulating hormone; UPCr = urine protein to creatinine ratio; w = week(s); WOCBP = women of childbearing potential.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
	Estimated glomerular filtration rate (eGFR)
Creatinine	[1]
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	Uric acid

1. Calculated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for patients ≥ 18 years of age and the revised bedside Schwartz formula for patients 12 to 17 years of age:

$$eGFR = 141 \times \min(SCr/K, 1)^{\alpha} \times \max(SCr/K, 1)^{-1.209} \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if black}]$$
where SCr is standardized serum creatinine in mg/dL, K is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/K or 1, and max indicates the maximum of SCr/K or 1).
Reference: Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612.
Bedside Schwartz formula = $([0.413 \times \text{height (cm)}] / \text{Scr [mg/dL]})$.

Serology

Hepatitis B virus	Hepatitis C virus
Human immunodeficiency virus	

Coagulation

International normalized ratio (INR) [1]

1. INR testing is to be completed as part of Screening assessments only (Visit 1 or Visit 2). Thereafter, INR will be tested as part of follow-up assessments for a suspected case of drug-induced liver injury (DILI). See [Appendix C](#) for details regarding additional follow-up assessments to be completed for suspected cases of DILI.

Endocrinology

Follicle-stimulating hormone (FSH) [1]	Human chorionic gonadotropin [2]
Thyroid-stimulating hormone	Thyroxine (T4)

1. 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 FSH level in the postmenopausal range will be required at Screening to confirm a postmenopausal state.
2. For women of childbearing potential only. A serum pregnancy test will be performed at Study Visit 2. A pregnancy test via a local urine assessment will be performed at all other applicable study visits prior to study drug dosing.

Hematology

Hematocrit

Platelets

Reticulocyte count

Hemoglobin

Red blood cell count

White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis (Freshly Voided Urine)

Assessed by Dipstick

Bilirubin

Glucose

Leukocyte esterase

pH

Specific gravity

Blood

Ketones

Nitrite

Protein

Urobilinogen

Assessed by Chemical Assay

Albumin

Creatinine

Sodium

Cortisol

Protein

Urine Drug Screen (Freshly Voided Urine)

Alcohol

Cannabinoids

Ecstasy

Opiates

Amphetamines

Cocaine

Methamphetamine

Oxycodone

24-Hour Urine Analysis

Creatinine clearance

Total cortisol

Total protein

Total albumin

Total creatinine

Urine protein to creatinine ratio (UPCR)

Exploratory Biomarkers

Urine-Based Biomarkers

B2-M

EGF

MCP-1/Cr

Osteopontin

Cystatin-C

KIM-1

NGAL

TGF- β 1

Serum-Based Biomarkers

B2-M	BUN
CCL3	Cystatin-C
IL1B	MCP-1
TGF-β1	TIMP1
TNFα	VEGF
YKL-40	

Plasma-Based Biomarkers

CCN2	MMP9
NGAL	SPP1

APPENDIX C: 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 drug-induced liver injury (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 48 hours of receipt of the laboratory test results to undergo a retest:

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq 3 \times$ the upper limit of normal (ULN);
- AST or ALT $> 2 \times$ Baseline;
- Total bilirubin $> 2 \times$ ULN; or
- 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. Retesting of eosinophilia ($> 5\%$) will only be required in case this is observed in combination with at least 1 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 Visits 1 and 2 to obtain the arithmetic mean.

The results of the test and retest will be reviewed to determine if they meet Criteria 1, 2, or 3, as outlined below.

Criteria for Close Monitoring of Liver Biochemistry and IMP Action

Criteria for close monitoring of liver biochemistry and investigational medicinal product (IMP) action include the following:

1. For patients with **Baseline ALT and/or AST $< \text{ULN}$** , unless an alternative cause for the laboratory abnormalities is immediately apparent in the opinion of the Investigator and documented at the time of the laboratory test elevations, close monitoring for suspected DILI will be performed in patients with any of the following criteria confirmed by repeat testing:
 - a. ALT or AST $> 3 \times$ ULN;
 - b. Total bilirubin $> 2 \times$ ULN;
 - c. International normalized ratio (INR) > 1.5 (except for patients on anticoagulant therapy); or
 - 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 Criterion 1).
2. For patients with **Baseline ALT and/or AST between $\geq \text{ULN}$ and $< 3 \times \text{ULN}$** , unless an alternative cause for the laboratory abnormalities is immediately apparent in the opinion of the

Investigator and documented at the time of the laboratory test elevations, close observation for suspected DILI will be performed in patients with any of the following criteria confirmed by repeat testing:

- a. ALT or AST $>2 \times$ Baseline at any time;
- b. Total bilirubin $>2 \times$ ULN;
- c. INR >1.5 (except for patients on anticoagulant therapy); or
- 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 [Criterion 2](#)).

During the close monitoring period in [Criteria 1](#) or 2, IMP can be continued, unless any of the following occur:

- The patient is symptomatic in addition to having elevated laboratory parameters;
 - Close monitoring is not possible;
 - Criterion 3 (see below) are met and no other cause for laboratory abnormalities is clinically apparent and documented by the Investigator in the study documents; or
 - At the discretion of the Investigator.
3. **For patients meeting any of the following events**, IMP will be discontinued when no other cause for the laboratory abnormalities is immediately apparent:
- a. ALT or AST $>5 \times$ Baseline;
 - b. ALT or AST $>10 \times$ ULN;
 - c. ALT or AST $>3 \times$ Baseline with 1 or more of the following; or
 - Total bilirubin $>2 \times$ ULN;
 - Total bilirubin $>1.5 \times$ Baseline and $>ULN$;
 - INR >1.5 (except for patients on anticoagulant therapy); or
 - 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:
 - Total bilirubin $>2 \times$ ULN or $1.5 \times$ Baseline;
 - INR >1.5 (except for patients on anticoagulant therapy); or
 - Clinical signs or symptoms that are, in the opinion of the Investigator, consistent with drug-induced hepatotoxicity.

If the above criteria in Criterion 3 are met, the Investigator will instruct the patient to discontinue IMP administration and return to the study center within 48 hours of receipt of the laboratory test results to undergo a retest and additional investigations (ie, close monitoring) to assess for suspected DILI. IMP cannot be reintroduced.

Any suspected or confirmed DILI event, defined as events meeting [Criteria 1, 2, or 3](#) above, will be closely monitored by the Investigator and the Independent Data Monitoring Committee.

Close Monitoring Activities

Close monitoring for all patients who meet suspected DILI evaluation Criteria 1, 2, or 3 (laboratory analytes are performed at the central laboratory) includes the following:

- Monitor patient 2 or 3 times weekly until liver biochemistries (ALT, AST, alkaline phosphatase, 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; and
- 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.

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.

Follow-Up Procedures

Recommended follow-up procedures (per Investigator decision) to exclude alternative causes for suspected DILI (laboratory analyses, as applicable, performed at the local laboratory) include the following:

- 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%);

Note: 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.

- Obtain a more detailed history of prior or concomitant diseases;
- Obtain a history for concomitant medications, acetaminophen, dietary supplements, herbal remedies, other over the counter medications, recreational drug use, and special diets;
- If possible, quantify the alcohol consumption to assess for alcoholic hepatitis;
- Obtain a history of exposure to environmental chemical agents;
- If INR is also elevated, a trial of intravenous vitamin K administration may be considered, especially in cholestatic patients;
- Viral hepatitis serology, including:
 - Hepatitis A immunoglobulin M (IgM) antibody;
 - Hepatitis B surface antigen and Hepatitis B core antibody (IgM);
 - Hepatitis C RNA;
 - Hepatitis E IgM antibody;

- Cytomegalovirus IgM antibody; and
- 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 on signs and symptoms consistent with potential immune-mediated injury and, if relevant, monitor until the abnormalities resolve and to the End of Study Visit, including the following:
 - Fever, malaise, pruritus, etc;
 - Rash;
 - Edema;
 - Lymphadenopathy;
 - Hematological changes (leukopenia, anemia, thrombocytopenia, etc), urinalysis, electrocardiogram, etc; and
 - Other organ involvement, in addition to liver (kidney, heart, lungs, etc).
- Other laboratory tests and assessments including:
 - Serum creatine phosphokinase and lactate dehydrogenase;
 - Fractionate bilirubin, if total bilirubin $>2 \times$ ULN;
 - A liver biopsy, at the discretion of the Investigator;
 - Assess for peripheral eosinophilia. Investigators are also encouraged to obtain a skin biopsy in patients who have liver enzyme elevation together with eosinophilia; and
 - Assess for hypoxic/ischemic hepatopathy, and biliary tract disease.

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

- Antinuclear antibody, antismooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (or gamma globulins);
- If required, evaluation of competing undiagnosed liver disease (hemochromatosis, Wilson's disease, alpha-1 anti-trypsin deficiency);
- 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); and
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease at the discretion of the Investigator.