ASSURE: An Open Label Long-Term Study to Evaluate the Safety and Tolerability of Seladelpar in Subjects with Primary Biliary Cholangitis (PBC)

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This study has been transitioned to CTIS with ID 2024-511753-22-00 check the CTIS register for the current data. Primary:• To evaluate the long-term safety and tolerability of seladelparSecondary:• To evaluate the long-term efficacy of seladelpar•...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON51913

Source
ToetsingOnline

Brief title
ASSURE

Condition

- Hepatic and hepatobiliary disorders
- Autoimmune disorders

Synonym
Primary biliary cirrhosis; Disease of the liver

Research involving
Human

Sponsors and support

Primary sponsor: CymaBay Therapeutics Inc
Source(s) of monetary or material Support: Farmaceutisch bedrijf

Intervention

Keyword: Long-Term Study, Open-label, Primary Biliairy Cholangitis (PBC), Seladelpar

Outcome measures

Primary outcome

Treatment-emergent adverse events (TEAEs) (National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0), biochemistry and hematology results

Secondary outcome

Secondary:

1. Occurrence of the following adjudicated PBC clinical outcomes:

o Overall death

o Liver transplantation

o Model for End-Stage Liver Disease (MELD) score >= 15 for at least 2 consecutive visits

o Ascites requiring treatment

o Hospitalization for new onset, or recurrence, of any:

* Variceal bleeding

* Hepatic encephalopathy (as defined by a West Haven score >= 2)

* Spontaneous bacterial peritonitis (confirmed by culture from diagnostic paracentesis)

2. Biochemical markers:

o Response on composite endpoint of alkaline phosphatase (ALP) and total bilirubin

o Proportion of subjects with normalization of ALP

o Relative and absolute changes of ALP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase, bilirubin (total, direct, indirect)

3. Change from Baseline in pruritus numerical rating scale (NRS)

Exploratory

1. Liver histology changes as based on biopsy analysis assessment

2. Plasma concentrations of seladelpar and its metabolites (M1, M2, M3)

3. Change from Baseline in QoL questionnaires (PBC-40, 5-D Itch)

4. Change from Baseline in United Kingdom-Primary Biliary Cirrhosis (UKPBC) and Global PBC Study Group risk scores by visit.

5. Absolute and relative changes in lipids and bile acids, and biomarkers of bile acid synthesis 7α-hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF-19).

6. PBC response criteria results (Barcelona, Paris I and II, Toronto I and II, Rotterdam)

7. Absolute and relative chance in markers of enhanced liver fibrosis as measured by liver stiffness using FibroScan®.

Study description

Background summary

Primary biliary cholangitis (PBC, formerly known as primary biliary cirrhosis) is a serious, rare, slowly progressive and potentially life-limiting autoimmune liver disease characterized by impaired bile flow (cholestasis) and accumulation of toxic bile acids. The disease occurs more frequently in women and presents most often in middle age. The disease course is usually slow but frequently impactful; patients at greatest risk of future poor outcomes are identifiable based on patterns of presentation including biochemical markers of disease at baseline and ontreatment.
The hallmark of PBC is cholestasis secondary to hepato-biliary injury and bile acid accumulation, with an accompanying elevation in disease associated serum biomarkers including alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and, depending on the severity of the disease, bilirubin and liver transaminases. Serologically, PBC is characterized by the presence of anti-mitochondrial antibodies (AMA) in nearly all patients. Clinical symptoms of PBC include pruritus and fatigue, which can be disabling for many patients. PBC peak incidence occurs in the fifth decade of life and is uncommon in persons under 25 years of age. The liver histopathology of patients with PBC is characterized by portal inflammation and immunemediated destruction of intrahepatic bile ducts. These changes occur at different rates and with varying degrees of severity. The loss of bile ducts leads to decreased bile secretion and the retention hydrophobic bile acids within the liver, resulting in hepatocellular injury, fibrosis, cirrhosis, and eventually liver failure.
The first line therapy for PBC is ursodeoxycholic acid (UDCA), a non-cytotoxic bile acid that has been the mainstay of treatment for more than 20 years. However, up to 40% of patients have persistent elevation of ALP and/or bilirubin despite UDCA and are considered inadequate responders.
Obeticholic acid, a synthetic analogue of chenodeoxycholic acid, was conditionally approved by the Food and Drug Administration and the European Medicines Agency in 2016 based on significant decreases in ALP levels while maintaining normal total bilirubin levels in subjects with PBC who are inadequate responders to UDCA or as a monotherapy in subjects with PBC who are intolerant to UDCA (17).

In summary, despite the previously mentioned therapeutic interventions and recent approval of obeticholic acid, it is evident that many patients with PBC do not respond adequately to therapy and continue to have a progression of their disease and that additional treatments are needed.

Study objective

This study has been transitioned to CTIS with ID 2024-511753-22-00 check the CTIS register for the current data.

Primary:
• To evaluate the long-term safety and tolerability of seladelpar

Secondary:
• To evaluate the long-term efficacy of seladelpar
• To evaluate the effect of seladelpar on patient-reported outcomes (pruritus)
Exploratory
• To evaluate the effect of seladelpar on liver histology, additional measures of quality of life (QoL), biomarkers of cholestasis, lipids, and liver fibrosis
• To evaluate the plasma concentrations of seladelpar and its metabolites

Study design

Open label, uncontrolled, international multicenter long-term interventional study. The study will include subjects who participated in a previous PBC study with seladelpar (CB8025-21629, CB8025-31735, and CB8025-31731), current PBC studies (CB8025-32048 and CB8025-21838), or future PBC studies with seladelpar that allow rollover into CB8025-31731-RE, allowing their treatment to continue. Subjects who were previously on placebo in CB8025-31735 can choose to participate in this study as long as they meet eligibility criteria.
Qualified subjects will receive 10 mg seladelpar. Subjects with noted tolerability issues may receive seladelpar 5 mg if in the opinion of the Investigator, that would be the appropriate starting dose. Subjects on 5 mg may be up-titrated to 10 mg after a period of clinical stability if the Investigator deems it medically appropriate and after consultation with the Medical Monitor. Subjects can be down-titrated from 10 mg to 5 mg throughout the study for reasons of safety or tolerability. They can also be re-challenged with 10 mg if the reason for prior down-titration has resolved. Treatment can also be re-initiated after dose interruption if it is agreed to be medically appropriate by consultation between the Investigator and Medical Monitor. Potential adjustment of doses for safety or tolerability will be managed as outlined in Section 6.1.3. Subjects will continue ursodeoxycholic acid (UDCA) intake in accordance with their prescribed dose.
Subjects will be evaluated for pruritus and QoL throughout the duration of study participation.
Subjects will be regularly evaluated for PBC clinical outcomes. Subjects who meet any PBC clinical outcome per Section 7.2.7 will discontinue seladelpar. Subjects who discontinue seladelpar anytime during the treatment period will be asked to stay in the study to collect PBC clinical outcomes.
Pharmacokinetics Sample Collection
Subjects will be invited to participate in a pharmacokinetic (PK) sample collection to evaluate plasma concentrations of seladelpar and its metabolites. Subjects who consent to participate in this PK sample collection will provide 1 pre-dose (-30 minutes prior to dosing) and 2 post-dose samples at 1 hour ± 30 min and at 3 hours ± 30 min at Month 3, Month 12, every 12 Months thereafter, and End of Treatment (EOT) or Early Termination (ET) Visit. A single PK sample collection may be collected at an unscheduled visit for safety.
A Critical Event Review Committee (CERC) will be established to analyze and adjudicate clinical events that occur during the study.
A Pathology Review Committee (PRC) will be established to evaluate the biopsies

in accordance with a defined histopathology plan.

Intervention

Subjects will receive seladelpar 10 mg upon entry to the study. Subjects with noted tolerability issues in the previous study may receive 5 mg if in the opinion of the Investigator that would be the appropriate starting dose. The 5 mg dose may be up-titrated to 10 mg after a period of clinical stability if the Investigator deems it medically appropriate and after consultation with the Medical Monitor

Study burden and risks

For the study, the subject needs to visit hospital 17 times in 60 months. A visit lasts approximately 60-120 minutes depending on the assessments and procedures to complete. Some study visits will take longer, up to 4 hours (240 minutes).
The following procedures will be carried out:
- Review of adverse events
- Review of medications
- Vital signs and weight.
- Complete or symptom-directed (brief) physical examination.
- PBC and cirrhosis status will be evaluated
- a 12-Lead electrocardiogram (ECG)
- Questionnaires.
- Blood test.
- PK Sub-Study (optional
- COVID-19 testing if deemed necessary.
- Serum pregnancy testing will be conducted for women of child-bearing potential
- FibroScan® (at selected sites only)
- Abdominal ultrasound
- Optional Liver Biopsy.

To date, 315 PBC patients have received seladelpar in clinical studies. In these studies, 106 received seladelpar treatment for >= 1 year, and 51 patients for >= 2 years.
The following side effects were commonly reported in >= 10% of PBC patients (33 - 51 of 315 patients):
- Itching (Pruritus)
- Feeling sickness with the urge to vomit (nausea)
- Urinary tract infection
- Diarrhea
- Upper abdominal pain

The following side effects were occasionally reported in >= 5% and < 10% of PBC patients (16 - 32 of 315 patients):

- Abdominal pain
- Fatigue
- Joint pain
- Headache
- Infection of nose and throat (Nasopharyngitis)
- Upper respiratory tract infection
- Dizziness
- Cough
- Constipation
- Indigestion (Dyspepsia)
- Back pain
- Vomiting
- Dry mouth
- Generalized itching
- Muscle pain (Myalgia)
- Gastroesophageal (acid) reflux disease

Unforeseeable unknown risks
All drugs may cause adverse effects or affect other drugs the subject is are taking. Consequently, the administration of seladelpar may include risks that are currently unknown or unforeseeable.

Blood draw risks
Collecting blood samples may cause fainting and some pain and/or bruising at the site on the arm where the blood was taken. In rare occasions, an infection may occur.

Fasting risks
Fasting for 8 hours in preparation for certain blood draws and the abdominal ultrasound or at least 4 hours in preparation for the FibroScan could cause dizziness, headache, stomach discomfort or fainting.

FibroScan risks
During the procedure, the patient will feel a slight vibration on the skin at the tip of the probe. Other than that, there are no risks associated with a FibroScan. It is a painless, quick and easy procedure.

Abdominal ultrasound risks
There are virtually no risks for this procedure. The lubricating jelly may feel slightly cool when initially applied.

Liver biopsy risks (the liver biopsy is optional)
• Pain and discomfort located at or near the puncture site and radiating upwards toward the right shoulder region
• Bleeding at the biopsy site
• Possible internal bleeding for up to a few hours after the procedure
• Infections at the biopsy site or internal organs

• Puncture of internal organs (gall bladder, lung, intestine, or kidney)
• Allergic reaction to the anesthetic
• 1 in 10,000 risk of death from a complication resulting from a liver biopsy

Other risks
The adhesive pads for the ECG may cause skin reactions such as redness or itching. The subject may also feel localized skin discomfort and/or bruising, or have hair pulled out locally due to the placement of the ECG leads.

There may be risks or side effects related to seladelpar or other study procedures that are unknown at this time.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Must have given written informed consent (signed and dated)
2. Participated in a prior PBC study with seladelpar (including CB8025-21629, CB8025-31735, or CB8025-31731), current PBC studies (CB8025-32048 or CB8025-21838), or completed a future PBC study with seladelpar that allows rollover into CB8025-31731-RE, and meet eligibility criteria for the current study.
3. Females of reproductive potential must use at least one barrier contraceptive and a second effective birth control method during the study and for at least 90 days after the last dose. Male subjects who are sexually active with female partners of reproductive potential must use barrier contraception and their female partners must use a second effective birth control method during the study and for at least 90 days after the last dose

Exclusion criteria

Exclusion criteria are only applicable for subjects with a study drug interruption greater than 4 weeks prior to Day 1 of this study and for subjects who participated in CB8025-21838 irrespective of seladelpar interruption.
1. Treatment-related adverse event (AE) leading to study drug discontinuation in a previous PBC study with seladelpar
2. A medical condition, other than PBC, that in the Investigator*s opinion would preclude full participation in the study or confound its results (e.g., cancer, any active infection)
3. AST or ALT above 3 × the upper limit of normal (ULN)
4. Total bilirubin above 2 × ULN
5. MELD score >= 12. For subjects on anticoagulation medication, evaluation of the baseline INR, in concert with any current dose adjustments in anti-coagulant medications, will be taken into account when calculating this score. This will be done in consultation with the medical monitor.
6. Evidence of advanced PBC as defined by the Rotterdam criteria: albumin below 1× the lower limit of normal AND total bilirubin above 1 × ULN)
7. Estimated glomerular filtration rate <= 45 mL/min/1.73 m2 (calculated by Modification of Diet in Renal Disease formula)
8. Auto-immune hepatitis
9. Primary sclerosing cholangitis
10. Known history of alpha-1-antitrypsin deficiency
11. Known history of chronic viral hepatitis
12. For females, pregnancy or breast-feeding
13. Use of colchicine, methotrexate, azathioprine, or long-term use of systemic steroids (e.g. prednisone, prednisolone, budesonide) (>2 weeks) within 2 months prior to Screening. See the concomitant medication section for additional medications that may be excluded.

14. Current use of fibrates or use of fibrates within 3 months prior to Screening
15. Current use of obeticholic acid or use of obeticholic acid within 3 months prior to Screening
16. Use of an experimental or unapproved treatment for PBC within 3 months prior to Screening
17. History of malignancy diagnosed or treated, actively or within 2 years, or active evaluation for malignancy; localized treatment of squamous or non-invasive basal cell skin cancers and cervical carcinoma in-situ is allowed if appropriately treated prior to Screening
18. Treatment with any other investigational therapy or medical device within 30 days or within 5 half-lives, whatever is longer, prior to Screening
19. Any other condition(s) that would compromise the safety of the subject or compromise the quality of the clinical study, as judged by the Investigator
20. Immunosuppressant therapies (e.g., cyclosporine, tacrolimus, anti TNF or other immunosuppressive biologics)
21. Other medications that effect liver or GI functions such as absorption of medications or roux-en-y gastric bypass procedure may be prohibited and should be discussed with the medical monitor on a case-by-case basis
22. Positive for:
a. Hepatitis B, defined as the presence of hepatitis B surface antigen
b. Hepatitis C, defined as the presence of hepatitis C virus ribonucleic acid
c. Human immunodeficiency virus (HIV) antibody
23. Active COVID-19 infection during Screening.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-11-2021
Enrollment:	15

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	seladelpar
Generic name:	seladelpar

Ethics review

Approved WMO Date:	31-03-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-06-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-12-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-01-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-511753-22-00
EudraCT	EUCTR2020-005198-29-NL
ClinicalTrials.gov	NCT03301506
CCMO	NL75533.091.20