52-week, placebo-controlled, randomized, Phase 3 study to evaluate the safety and efficacy of seladelpar in subjects with primary biliary cholangitis (PBC) and an inadequate response to or an intolerance to ursodeoxycholic acid (UDCA)

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Primary: • To evaluate the safety and effect on cholestasis of two seladelpar regimens (5 mg/day titrated to 10 mg/day and 10 mg/day) over 52 weeks of treatment compared to placeboKey Secondary: • To evaluate the effect of seladelpar on...

Ethical review	Approved WMO
Status	Pending
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON48405

Source
ToetsingOnline

Brief title
CymaBay ENHANCE

Condition

- Autoimmune disorders

Synonym
Primary biliary cholangitis; Disease of the liver

Research involving
Human

Sponsors and support

Primary sponsor: CymaBay Therapeutics, Inc.
Source(s) of monetary or material Support: CymaBay Therapeutics;Inc.

Intervention

Keyword: Phase 3, Primary Biliary Cholangitis (PBC), Seladelpar, Ursodeoxycholic acid (UDCA)

Outcome measures

Primary outcome

• Response on the composite endpoint of AP and total bilirubin at 12 months:

o AP < 1.67 × upper limit of normal (ULN), and

o >= 15% decrease in AP, and

o Total bilirubin <= ULN

• Assessment of treatment-emergent AEs (TEAEs) (National Cancer Institute [NCI]

Common Terminology Criteria for Adverse Events [CTCAE] Version 4.0),

biochemistry and hematology

Secondary outcome

Key Secondary:

• Proportion of subjects with AP <= 1.0 × ULN at 12 months

• Change from baseline in pruritus numerical rating scale (NRS) at 6 months

Other Secondary:

• PBC-40 QoL at 6 and 12 months

• PBC-40 QoL itch domain, and 5-D itch questionnaire

• Response on the composite endpoint at 6 months

• Proportion of subjects with AP < 1.67 × ULN and AP < 1.5 × ULN at 6 and 12 months

• Proportion of subjects with AP <= 1.0 × ULN at 6 months and 12 months

• Change from baseline in pruritus NRS at 12 months

• Absolute and relative changes in AP

• Proportion of subjects with PBC response criteria (Barcelona, Paris I and II, Toronto I and II, Rotterdam)

• Change in UK-PBC and GLOBE risk scores

• Absolute and relative changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), bilirubin (total, direct, and indirect), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL- C), triglycerides, and total cholesterol

• The first occurrence of any of the following events:

o Overall Death

o Liver transplantation

o MELD score >=15

o Uncontrolled ascites (diuretic resistant)

o Hospitalization for new onset or recurrence of any of the following:

* variceal bleeding

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

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

o Hepatocellular carcinoma

o Advanced PBC as defined by the Rotterdam criteria (albumin below low limit of normal (LLN) AND total bilirubin above ULN)

Exploratory Measures:

• C4 (7α-hydroxy-4-cholesten-3-one), fibroblast growth factor 19 (FGF19), N-terminal type III collagen propeptide (Pro-C3)

• Haptoglobin, fibrinogen and high-sensitivity C-reactive protein (hs-CRP), homocysteine, immunoglobulin M (IgM)

• Autotaxin

• Enhanced liver fibrosis (ELF) score, fibrosis-4 (FIB-4) score, Lok-Index, non-alcoholic fatty liver disease (NAFLD) fibrosis score

• Liver elastography (at selected centers)

Study description

Background summary

Primary biliary cholangitis (PBC, formerly known as primary biliary cirrhosis) is a serious and potentially life threatening autoimmune disease of the liver characterized by impaired bile flow (cholestasis) and accumulation of toxic bile acids (BA).
The first line therapy for PBC is ursodeoxycholic acid (UDCA), a non-cytotoxic BA that has been the mainstay of treatment for more than twenty years. However, up to 40 percent of patients have persistent elevation of AP and/or bilirubin despite UDCA and are considered inadequate responders.
Seladelpar (MBX-8025) is an oral, once-daily administered, potent and selective peroxisome proliferator-activated receptors (PPAR) δ agonist. Seladelpar is being developed for the treatment of PBC in subjects with inadequate response to UDCA or intolerance to UDCA and in nonalcoholic steatohepatitis (NASH).Seladelpar demonstrated the potent and rapid decrease in biochemical markers of cholestasis (AP, GGT, and total bilirubin), decrease a marker of inflammation (hs-CRP) and decrease LDL-C in PBC subjects who had an inadequate response or intolerance to UDCA. In addition, the current data suggest that

seladelpar has a potential to improve PBC related pruritus. Lower doses of seladelpar (up to 10 mg) were generally safe and well tolerated. There was no evidence that seladelpar was associated with transaminase elevations at these doses. There was also no evidence that seladelpar induced or worsened pruritus. The clinical experience with seladelpar is nonetheless limited, and appropriate precautions are incorporated into this protocol, with careful monitoring of potential transaminase elevations

Study objective

Primary:
• To evaluate the safety and effect on cholestasis of two seladelpar regimens (5 mg/day titrated to 10 mg/day and 10 mg/day) over 52 weeks of treatment compared to placebo
Key Secondary:
• To evaluate the effect of seladelpar on normalization of alkaline phosphatase (AP) levels
• To evaluate the effect of seladelpar on pruritus
Other Secondary:
• To evaluate the effect of seladelpar on quality of life (QoL)
• To evaluate the effect of seladelpar on other measures of cholestasis, metabolic outcomes, and PBC prognosis criteria
• To evaluate the effect of seladelpar on PBC clinical outcomes
Exploratory:
• To evaluate the effect of seladelpar on markers of inflammation, bile acid synthesis, levels of autotaxin, and markers of liver fibrosis

Study design

Double-blind, randomized, placebo controlled, 52 weeks dose ranging (placebo, 5/10 mg/day, and 10 mg/day), parallel treatment groups
Subjects on 5/10 mg who are tolerating study drug but who are not responding to the therapy based on composite endpoint, will have dose adjustment performed after 6 months of treatment.

Intervention

Study subjects will be randomized 1:1:1 to one of following treatment arms:
• Seladelpar 5/10 mg
• Seladelpar 10 mg
• Placebo

Study burden and risks

Patients are asked to undergo procedures described on pages 26 - 27 of the study protocol. These procedures include physical examination, blood draw (i.e.

Hepatitis B and C testing, etc.) urine sampling (i.e. drug screen, etc.), vital signs, ECG, abdominal ultrasound, liver Elastography (at selected centers), Liver biopsy, completion of questionnaire, answer questions of investigator and study team and administration of study drug. Additionally, fertile subjects are asked to use contraceptives, and female subjects of childbearing potential will have pregnancy tests.
Subject*s participation in this study will last approximately 60 weeks (about 1 year and 2 months). This duration includes a screening period (up to 2 weeks), a run-in period (up to 2 weeks), a 12-month (52 weeks) treatment period, and a final follow-up visit (4 weeks).
The study medication is a nonregistered medication. Possible known side effects are described in the IB and patient information and can also occur during this study. Common adverse events that were reported with use of study drug (occur in 1 in 10 people or more): Skin itching, Nausea (feeling sickness with the urge to vomit), Abdominal distension (gas or fluid in the abdomen), Abdominal pain, Arthralgia (joint pain), Diarrhea, Fatigue, Headache, Nasopharyngitis (infection of nose and throat) and Urinary tract infection.
Other adverse event reported related to use of study drug (occur in less than 1 in 10 people): Asymptomatic hepatic enzyme (ALT and AST) increase, Peripheral swelling or edema, Cough, Dizziness, Dry mouth, Muscle spasms, Oropharyngeal pain (throat pain), Vomiting, Abdominal tenderness, Asthenia (weakness or loss of strength), Back pain, Blood creatine phosphokinase increased, Bronchitis, Chest discomfort, Constipation, Cystitis (urinary bladder inflammation), Dyspepsia (indigestion), Erythema (skin inflammation or reddening), Gastroesophageal reflux disease (GERD), Myalgia (muscle pain), Nasal congestion and Neck pain. Furthermore, there may be risks asscoaited with study procedures (i.e. blood draw, abdominal ultrasound, liver elastography, etc.)
Taking the study drug may result in an improvement in subject's PBC and PBC-associated itch, but an improvement is not guaranteed for all subjects. Some subjects may not improve at all.

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

Subjects must meet all of the following criteria to be eligible for study participation:
1. Must have given written informed consent (signed and dated) and any authorizations required by local law
2. 18 to 75 years old (inclusive)
3. Male or female with a diagnosis of PBC, by at least two of the following criteria:
• History of AP above ULN for at least six months
• Positive anti-mitochondrial antibody (AMA) titers (>1/40 on immunofluorescence or M2 positive by enzyme linked immunosorbent assay [ELISA]) or positive PBC-specific antinuclear antibodies
• Documented liver biopsy result consistent with PBC
4. On a stable and recommended dose of UDCA for the past twelve months OR intolerant to UDCA (last dose of UDCA > 3 months prior to Screening)
5. AP >= 1.67 × ULN
6. 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

Subjects must not meet any of the following criteria to be eligible for study participation:
1. Previous exposure to seladelpar (MBX-8025)
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)

3. AST above 3 × ULN
4. ALT above 3 × ULN
5. Total bilirubin above 2.0 × ULN
6. Advanced PBC as defined by the Rotterdam criteria (albumin below LLN AND total bilirubin above 1 × ULN)
7. Creatine kinase (CK) above 1.0 × ULN
8. eGFR below 60 mL/min/1.73 m2 (calculated by MDRD formula)
9. International normalized ratio (INR) above 1.0 × ULN
10. Platelet count below 100 × 103/µL
11. Presence of clinically significant hepatic decompensation, including:
- History of liver transplantation, current placement on liver transplantation list, or current MELD score >= 15
- Complications of portal hypertension, including known esophageal varices, history of variceal bleeds or related interventions (e.g., transjugular intrahepatic portosystemic shunt placement), relevant ascites, hepatic encephalopathy
- Cirrhosis with complications, including history or presence of spontaneous bacterial peritonitis
12. Other chronic liver diseases:
a. Current features of auto-immune hepatitis as determined by the investigator based on immunoserology, liver biochemistry and histology
b. Primary sclerosing cholangitis determined by presence of diagnostic cholangiographic findings
c. History or clinical evidence of alcoholic liver disease
d. History or clinical evidence of alpha-1-antitrypsin deficiency
e. Biopsy confirmed nonalcoholic steatohepatitis
f. History or evidence of Gilbert* Syndrome with elevated total bilirubin
g. History or evidence of hemochromatosis
h. Hepatitis B defined as presence of hepatitis B surface antigen (HBsAg)
i. Hepatitis C defined as presence of HCV RNA
13. Known history of HIV
14. Evidence of significant alcohol consumption
15. Evidence of drug abuse
16. Subjects with inadequate response to obeticholic acid (OCA) or intolerance to OCA: OCA must be discontinued 30 days prior to Screening
17. Use of colchicine, methotrexate, azathioprine, or long-term systemic corticosteroids (> 2 weeks) within two months prior to Screening
18. Use of fibrates within 30 days prior to Screening
19. Use of simvastatin within 7 days prior to Screening
20. Use of an experimental or unapproved treatment for PBC within 30 days prior to Screening
21. Use of experimental or unapproved immunosuppressant within 30 days prior to Screening
22. Treatment with any other investigational therapy or device within 30 days or within five half-lives, whatever is longer, prior to Screening
23. For females, pregnancy or breast-feeding
24. 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

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	20-02-2019
Enrollment:	15
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	16-11-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	18-04-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-06-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-06-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-12-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-12-2019
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
EudraCT	EUCTR2018-001171-20-NL
ClinicalTrials.gov	NCT03602560

Register	ID
CCMO	NL67407.091.18