A Phase 3, Double Blind, Placebo Controlled Trial and Long Term Safety Extension of Obeticholic Acid in Patients with Primary Biliary Cirrhosis

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Main Objective: To assess the effects of OCA in patients with PBC on: -Serum alkaline phosphatase (ALP) and total bilirubin, together as a composite endpoint -SafetySecondary Objectives:To assess the effects of OCA in patients with PBC on:-...

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

Summary

ID

NL-OMON46899

Source
ToetsingOnline

Brief title
A study of OCA in Patients with Primary Biliary Cirrhosis (747-301)

Condition

- Hepatic and hepatobiliary disorders

Synonym
autoimmune liver disease, Primary Biliary Cirrhosis

Research involving
Human

Sponsors and support

Primary sponsor: Intercept Pharmaceuticals Inc.

Source(s) of monetary or material Support: Sponsor of the study;Intercept Pharmaceuticals;Inc.

Intervention

Keyword: Double Blind, Obeticholic Acid, Placebo Controlled, Primary Biliary Cirrhosis

Outcome measures

Primary outcome

Primary Endpoint (evaluated as a responder analysis):

ALP < 1.67x ULN and total bilirubin within normal limits (WNL), and

ALP decrease of >= 15% (to exclude clinically insignificant ALP changes)

Secondary outcome

Analyses regarding secondary endpoints will be specified in the SAP and conducted for the following parameters. It is anticipated that additional disease prognostic algorithms will be published during the course of the trial. Where appropriate, secondary analyses will be conducted using such algorithms. At the blinded data review a determination will be made as to which algorithms will be evaluated statistically, as it is likely that there will be small numbers of patients for some algorithms and formal statistical analysis will not therefore be appropriate.

• ALP response rates of 10%, 20% and 40% change

• Disease Prognostic Risk (criteria in relevant patients):

-ALP <= 3x ULN and AST <= 2x ULN and normal bilirubin

- ALP <= 1.5x ULN and AST <= 1.5x ULN and bilirubin within normal limits

- ALP <= 1.67x ULN and normal bilirubin

- Normal bilirubin and normal albumin

• Clinical laboratory values:

- GGT, ALT, AST, total and conjugated bilirubin

- Albumin, prothrombin time and INR

• Liver biopsy/histology: Inflammatory, structural (portal, parenchymal)

and fibrotic assessments

• Disease Specific Symptoms:

- PBC-40

- 5-D Pruritus Questionnaire

- Pruritus VAS

• Biomarkers and non-invasive assessments of liver fibrosis

- Fibrosis biomarkers (ELF)

- TE (at selected trial sites)

- Other analytes: TNF-α, TGF-β, IL-6, CK-18 and lysophosphatidic acid

• Bile acids

- Plasma OCA, other bile acids and conjugate concentrations

- Bile and feces concentrations (at selected trial sites)

Study description

Background summary

Relevance/Medical Need:
The only approved drug therapy for PBC is the bile acid UDCA marketed under many names including, Ursodiol, URSO®, Actigall®, URSO 250® and URSO Forte*). There is a significant proportion of patients who experience an incomplete response to UDCA treatment with continued PBC disease progression. There is no alternative medical treatment currently available to slow disease progression in such non-responsive patients. With no other available treatment options, there is a need for additional effective and safe therapies for the treatment

of PBC. This study is designed to determine the safety and the efficacy of OCA as a potential treatment for PBC. OCA has orphan drug designation for the treatment of PBC.

Justification of Dose Selection:
The safety and tolerability of OCA has been established in healthy subjects, and in 2 different patient populations, including PBC patients, at doses up to 50 mg once daily. In patients with PBC it has been demonstrated that OCA can significantly reduce alkaline phosphatase (ALP) levels in patients at doses of 10, 25 and 50 mg, but with an increase in the incidence and severity of pruritus at the higher dose levels. This phase 3 trial has been designed to assess the efficacy, safety and tolerability of lower doses (5 mg and 10 mg) of OCA in patients with PBC so as to provide pivotal data to support a marketing authorization application for OCA in this indication.

Under Protocol Version 3 and prior versions all patients entering the LTSE will start at the 5 mg dose which may be increased (titrated) up to 25 mg daily (doses higher than 25 mg daily may be allowed up to 50 mg but will require sponsor approval). The 5 mg starting dose was chosen in order to maintain the blind of the DB phase and assess the continued response and tolerability of patients taking 10 mg during the DB phase. Data for the 25 mg dose from the 747-202 phase 2 trial has shown a benefit in patients who were able to tolerate this dose.

The DB phase of this Phase 3 PBC trial (747-301) evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability) and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and both doses were safe and generally well-tolerated. Starting patients on 5 mg OCA and titrating to 10 mg based on the clinical response appears to be an appropriate dosing strategy in patients with PBC and is the planned dose regimen for OCA in the treatment of PBC at the time of marketing approval. Hence, effective with Protocol Version 4, patients who are tolerating 5 mg OCA daily and whose bilirubin and/or ALP are > ULN should be titrated to a maximum of 10 mg daily. Patients who were titrated above 10 mg prior to Protocol Version 4 may remain on their current dose or the dose may be decreased as clinically indicated.

However, effective with Protocol Version 5, all patients will be titrated to a maximum of 10 mg daily. If a patient is receiving a dose that is greater than 10 mg daily OCA, they should be down-titrated to a maximum daily dose of 10 mg OCA. The exact dose and/or dosing frequency will depend on several factors including the patient*s Child-Pugh score, tolerability and clinical response.

Justification for Placebo:
The placebo arm is included to maintain the study blind and scientific validity of the study. However, patients will also continue their pre-study, standard-of-care dose of UDCA for PBC throughout the study with the exception

of patients who cannot tolerate UDCA(their standard of care does not include UDCA).

Justification for Duration of Treatment:
Patients will be dosed in the DB phase of this trial for 12 months. In the earlier phase 2 trials, the majority of the effects (reductions in ALP and liver enzymes) were seen after 1 month of treatment. A longer trial duration of 12 months, will allow an evaluation of both efficacy (effectiveness) and safety over a considerably longer period of time. Patients who complete the DB phase (including those who receive placebo) will be enrolled in a very long (5 year) open label, safety extension upon completing the DB phase, which will allow for a continued, thorough evaluation of the long-term safety and efficacy of the study medication at doses up to 25 mg daily.

The trial will be conducted in compliance with Good Clinical Practice (GCP) guidelines. Additionally, the protocol and the investigations are adapted for the PBC patient population and will be approved by responsible research ethics committee(s) in accordance with current International Committee of Harmonisation (ICH) guidelines.

*Obeticholic acid is also known as OCA and was previously called INT-747. OCA is also known as, 6α-ethylchenodeoxycholic acid; 6-ECDCA.

Study objective

Main Objective:
To assess the effects of OCA in patients with PBC on:
-Serum alkaline phosphatase (ALP) and total bilirubin, together as a composite endpoint
-Safety
Secondary Objectives:
To assess the effects of OCA in patients with PBC on:
-Hepatocellular injury and liver function, including histology (inflammatory, structural [portal, parenchymal] and fibrotic assessments)
-Disease specific symptoms
-Biomarkers and noninvasive assessments of liver fibrosis
-Bile acids
-Other exploratory evaluations

Study design

This is a phase 3, double blind (DB), placebo controlled, parallel group trial followed by a long term safety extension (LTSE) of OCA in patients with PBC. In the DB phase, approximately 180 patients (60 patients per arm) will be randomized in a 1:1:1 ratio to 1 of 3 treatment arms: (a) placebo, (b) 10 mg

OCA, or (c) 5 mg titrating to 10 mg OCA. Study medication will be administered orally, once daily for 12 months.
Under Protocol Version 3 and in prior versions, during the LTSE phase, patients could receive up to 25 mg of OCA for up to 5 years.
Effective with Protocol Version 4, patients should be titrated to a maximum of 10 mg daily. Patients who were titrated above 10 mg prior to Protocol Version 4 may remain on their current dose or the dose may be decreased as clinically indicated.

However, effective with Protocol Version 5, all patients will be titrated to a maximum of 10 mg daily. If a patient is receiving a dose that is greater than 10 mg daily OCA, they should be down-titrated to a maximum daily dose of 10 mg OCA. The exact dose and/or dosing frequency will depend on several factors including the patient*s Child-Pugh score tolerability and clinical response.
Patients will continue their standard treatment of ursodeoxycholic acid (UDCA) throughout trial participation. Those patients who do not tolerate UDCA will continue receiving the investigational drug only for the duration of the trial (initial DB phase and 5 years during the LTSE phase).

Intervention

In the DB phase, first of three group of patients will receive orally placebo once daily for 12 months, patients in the second group will receive orally 10 mg of OCA once daily for 12 months, and third group will receive orally 5 mg of OCA titrating to 10 mg once daily for 12 months.
Under Protocol Version 3 and in prior versions, during the LTSE phase, patients may receive up to 25 mg of OCA for up to 5 years.Effective with Protocol Version 4, patients should be titrated to a maximum of 10 mg daily. Patients who were titrated above 10 mg prior to Protocol Version 4 may remain on their current dose or the dose may be decreased as clinically indicated.

However, effective with Protocol Version 5, all patients will be titrated to a maximum of 10 mg
daily. If a patient is receiving a dose that is greater than 10 mg daily OCA, they should be down-titrated to a maximum daily dose of
10 mg OCA. The exact dose and/or dosing frequency will depend on several factors including the patient*s Child-Pugh score
tolerability and clinical response.

New Safety information:
• No patient should be dosing above 10 mg once daily
• All patients should be monitored during treatment for signs and symptoms related to progression of their PBC disease. Patients who progress to moderate or severe hepatic impairment (i.e., Child-Pugh A to Child-Pugh B or C) should have their dose adjusted to align with the approved label dosing. All subjects with moderate or severe hepatic impairment should be dosing at or below the

maximum allowed dose of 10 mg twice weekly.

Study burden and risks

Common and very common side effects depend on the type of liver disease you have and includes itching, irritated or chaffed skin or skin wounds (ie, due to itching), abdominal bloating and pain, constipation, diarrhea, feeling tired, headache nausea, rash, joint pain, bruising, difficulty sleeping, dizziness, dry eyes, sore throat, swelling of ankles, rapid or irregular heartbeat, fever and abnormal function of thyroid gland.
As of September 2017, more than 3000 patients have received the study drug [Ocaliva® (OCA)] in the *post-marketing* setting. Post-marketing means that in the United States, Canada and Europe, where OCA has been approved for the treatment of PBC, information on side effects in patients who are not participating in a clinical study, but who are taking OCA under the care of their doctor, are now being collected. Although information reported for these patients is often not as detailed compared to that collected in a clinical study, there have been recent safety findings reported for patients being treated with OCA that you should be aware of. Patients with PBC who received commercially available OCA have reported liver related events, which sometimes resulted in death. The Sponsor reviewed the data and found that these patients had moderate to severe liver disease and OCA was prescribed at a dose up to 7 times more than they were supposed to take. It is not known if these side effects were possibly related to OCA, or to their liver disease. If your disease gets worse, the dose of study drug may need to be reduced, stopped for a little while or stopped forever by your study doctor.
In clinical studies, the blood levels of OCA were found to be higher in some patients who had worse liver function or liver impairment. Liver impairment is often caused by outside factors, such as disease, or liver injury from other medical treatments. Patients with moderate or severe liver impairment have liver cells that do not function properly, which means, the liver may not be able to carry out normal activities that help the body function. This is important because in clinical studies of PBC, liver-related side effects have been shown to happen with higher levels of OCA in the blood. In addition, in ongoing NASH clinical studies there have been reports of serious liver illness, including one death in a patient with severe liver disease. The patients who experienced these events in the NASH clinical studies were taking other medications that are known to cause liver-related side effects. These patients also had other ongoing medical conditions and health issues, that may have contributed to these serious events. The following side effect may occur:
swelling of your stomach-area from a build-up of fluid
yellowing of your skin or the whites of your eyes
black, tarry, or bloody stools
coughing up or vomiting blood, or your vomit looks like *coffee grounds*
mental changes such as confusion, sleepier than usual or harder to wake up, slurred speech, mood swings, or changes in personality
There may also be worsening in the results of tests that monitor your body*s

ability to prevent bleeding.
Blood fat level changes (such as an increase in cholesterol) are typically associated with undesirable effects on the heart and blood vessels, such as narrowing of blood vessels. Use of OCA may lead to such changes in blood fat levels. However, it is not clear if these changes caused by OCA also lead to undesirable effects on the heart and blood vessels, such as heart attacks or strokes.

The course of disease in chronic progressive liver diseases is hard to predict, and it may be difficult to tell apart liver-related adverse events due to the worsening of your liver disease from potential liver injury due to other causes, including ongoing medical treatments. For all patients participating in clinical studies with OCA, it is important that you understand the signs and symptoms of possible worsening (progression) of your liver disease. These signs and symptoms may include the following:
abdominal (belly) pain worsening or new fatigue (tired)
nausea rash
vomiting diarrhea
weight loss fever and chills
weakness loss of appetite
confusion pale-colored stools
swelling of the legs or abdomen markedly reduced urination
yellowing of the skin or the whites of eyes dehydration
urine color change from pale to deep amber [dark]

Pregnancy:
The effects of OCA on pregnancy and the unborn child (fetus) in people are unknown. In experimental animal studies with OCA lasting up to 2 years, no effect on pregnancy or animal fetal development has been seen. Nevertheless, in the absence of data from humans, female patients who are able to become pregnant must use at least 1 effective method of birth control throughout the study period and for 30 days after taking the last dose of study drug.

Allergic Reactions
In addition to the risks listed above, there may be unknown, infrequent, and unforeseeable risks associated with the use of the study drug, including severe or life-threatening allergic reactions or unexpected interactions with another medication. Symptoms of an allergic reaction may include rash; flushing; itching; sneezing or runny nose; abdominal pain; diarrhea; swelling of face, tongue, or throat; dizziness, lightheadedness, or fainting; trouble breathing; irregular or racing heart rate; and seizures.
If you have any known allergies, please inform the study doctor or study staff.

Contacts

Public
Intercept Pharmaceuticals Inc.

Intercept Pharmaceuticals Inc. , Eastgate Mall 4760
San Diego CA 92121
US
Scientific
Intercept Pharmaceuticals Inc.

Intercept Pharmaceuticals Inc. , Eastgate Mall 4760
San Diego CA 92121
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Definite or probable PBC diagnosis (consistent with AASLD and EASL Practice Guidelines; [Lindor 2009; EASL 2009]), as demonstrated by the presence of >= 2 of the following 3 diagnostic factors:;-History of elevated ALP levels for at least 6 months ;-Positive AMA titer or PBC specific antibodies;-Liver biopsy consistent with PBC;2. At least 1 of the following qualifying biochemistry values:;- ALP>=1.67x ULN;-Total bilirubin > ULN but < 2x ULN;3. Age >=18 years;4. Taking UDCA for at least 12 months (stable dose for >= 3 months) prior to Day 0, or unable to tolerate UDCA (no UDCA for >= 3 months) prior to Day 0;5. Contraception: Female patients of childbearing potential must use >= 1 effective (<= 1% failure rate) method of contraception during the trial and for 30 days after the EOT visit.;6. Must provide written informed consent and agree to comply with the trial protocol.

Exclusion criteria

Patients will be excluded from the trial if they meet any of the following:;1. History or presence of other concomitant liver diseases including:;-Hepatitis C virus (HCV) infection; patients with active hepatitis B (HBV)
infection will be excluded, however, patients who have seroconverted
(HbsAg and Hbe Ag negative) may be included after consultation with
the medical monitor.;-Primary sclerosing cholangitis (PSC);-Alcoholic liver disease;-Definite autoimmune liver disease or overlap hepatitis;-Nonalcoholic steatohepatitis (NASH);-Gilbert*s Syndrome (exclusion due to interpretability of bilirubin levels);2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:;-History of liver transplantation, current placement on a liver transplant list or current MELD score >= 15;-Portal hypertention with complications, including: known gastric or large esophageal varices, poorly controlled or diuretic resistant ascites, history of variceal bleeds or related therapeutic or prophylactic interventions (e.g., beta blockers, insertion of variceal bands or transjugular intrahepatic portosystemic shunt [TIPS]), or hepatic encephalopathy;-Cirrhosis with complications, including history or presence of: spontaneous bacterial peritonitis, hepatocellular carcinoma, bilirubin > 2x ULN;-Hepatorenal syndrome (type I or II) or Screening serum creatinine > 2 mg/dL (178 µmol/L) ;3. Patients with severe pruritus or those requiring systemic treatment for pruritus (e.g., with bile acid sequestrants [BAS] or rifampicin) within 2 months of Day 0 will be excluded.;4. Administration of the following medications is prohibited as specified below:;-Prohibited 6 months prior to Day 0 and throughout the trial (i.e., to last dose and/or EOT): azathioprine, colchicine, cyclosporine, methotrexate,;mycophenolate mofetil, pentoxifylline; fenofibrate or other fibrates;;budesonide and other systemic corticosteroids; potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin);-Prohibited 12 months prior to Day 0 and throughout the trial (i.e., to last dose and/or EOT): antibodies or immunotherapy directed against interleukins or other cytokines or chemokines;5. Patients who have previously participated in a clinical trial of OCA will not be allowed to participate.;6. History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the trial, or prolongation of Screening (pretreatment) QT or QTc interval of > 500 milliseconds (msec).;7. If female: known pregnancy, or has a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating

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:	Recruitment stopped
Start date (anticipated):	18-07-2012
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ocaliva (Obeticholic acid)
Generic name:	6&alfa;-ethyl chenodeoxycholic acid (6-ECDCA)
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-02-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-06-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-06-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-06-2012
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2015
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2011-004728-36-NL
ClinicalTrials.gov	NCT01473524
CCMO	NL39066.018.12