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Obeticholic acid in patients with primary biliary cirrhosis

Submission date	Recruitment status	[_] Prospectively registered
10/02/2012	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
24/02/2012	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
24/04/2019	Digestive System	

Plain English summary of protocol

Background and study aims
Primary biliary cirrhosis (PBC) is a rare disease which mostly affects women. PBC is irritation and swelling (inflammation) of the bile ducts of the liver. This inflammation blocks the flow of bile. The blockage damages liver cells and leads to scarring called cirrhosis. Currently, ursodeoxycholic acid (UDCA) is the only drug available for the treatment of PBC. This study will investigate the effectiveness of a new drug, obeticholic acid (OCA).

Who can participate?
To take part in this study you must have been diagnosed with PBC and have elevated liver function blood tests.

What does the study involve?
The study involves taking study medication daily for up to 6 years. During the first year you will be randomly assigned to take one of two different doses of OCA or a placebo (dummy drug). After the first year of treatment you may receive OCA for up to 5 more years at doses prescribed by your doctor. You will be asked to have a liver biopsy performed at the beginning of the study and again after 3 years on the study drug. The liver biopsy procedure includes numbing the skin over the liver with a local anesthetic. You may be sedated for the liver biopsy and you may need someone to drive you home after the procedure. A small piece of your liver is removed using a needle. Liver biopsy gives your doctor the ability to look at the cells of your liver and determine the extent of liver damage if any. Throughout the entire course of the study blood samples will be taken from you to determine how well the study drug is working. You will need to return to your doctor’s office every three months during the study and you will be contacted by telephone between study visits.

What are the possible benefits and risks of participating?
You may have side effects from taking the study drug. You will be checked at each study visit for side effects and it is very important that you tell the study doctor or nurse of any side effects that you have. Itching is the most common side effect and the most common reason for patients to stop taking OCA. When blood samples are taken from a vein, there may be some minor pain and risk of bruising at the site. Sometimes a person may become dizzy or faint when blood is drawn and there is a rare possibility of infection. About 20% of patients having a liver biopsy

have some degree of pain over the liver that may last a few minutes to several hours. This rarely requires pain medication. A rare complication of a liver biopsy is severe bleeding such that a blood transfusion or even an open operation to sew up the hole in the liver is needed. These complications occur in less than 1 in 1,000 cases. Very rarely (less than 1 in 10,000 reported cases) death has occurred from bleeding after a liver biopsy.

Where is the study run from?
It is being conducted at up to 80 centres in the following countries: Austria, Belgium, Canada, France, Germany, Italy, The Netherlands, Poland, Spain, Sweden, UK and USA.

When is the study starting and how long is it expected to run for?
January 2012 to January 2018

Who is funding the study?
Intercept Pharmaceuticals, Inc. (USA)

Who is the main contact?
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General queries (public contact), medinfo@interceptpharma.com
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Additional identifiers

ClinicalTrials.gov (NCT)
NCT01473524

Protocol serial number
747-301

Study information

Scientific Title
A phase III, double-blind, placebo-controlled trial and long term safety extension of obeticholic acid in patients with primary biliary cirrhosis

Study objectives
INT-747 will cause a reduction in alkaline phosphatase (AP) levels in primary biliary cirrhosis (PBC) patients

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee North East - Newcastle & North Tyneside 1, 21/02/2012, ref: 12/NE/0004
All other centres will seek ethics approval before recruitment of the first participant.

Study design
Phase 3 double-blind placebo-controlled multicentre study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Primary Biliary Cirrhosis

Interventions
Year 1:
1. Experimental treatment: OCA 5 mg orally (po) once daily (QD)
2. Experimental treatment: OCA 10 mg po QD
3. Matched placebo comparator: placebo po QD

Years 2-6:
Open-label OCA 5mg up to 50 mg as prescribed by investigator

Screening can last up to 8 weeks. Treatment is 1 year blinded, 5 years open-label.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Obeticholic acid

Primary outcome(s)
1.Obeticholic acid (OCA) is safe and tolerated in patients with cirrhosis and portal hypertension
2. Obeticholic Acid (OCA) will reduce alkaline phosphatase (ALP) to less than 1.67 times the upper limit of normal and total bilirubin will be within normal limits, and ALP will have a total decrase of at least 15%.

Key secondary outcome(s))
1. Hepatocellular injury and liver function, including histology (inflammatory, structural [portal, parenchymal] and fibrotic assessments)
2. Disease specific symptoms
3. Biomarkers and noninvasive assessments of liver fibrosis
4. Bile acids (BA)
5. Other exploratory evaluations

Completion date
17/12/2018

Eligibility

Key inclusion criteria
1. Definite or probable PBC diagnosis (consistent with AASLD and EASL Practice Guidelines, as demonstrated by the presence of ≥ 2 of the following 3 diagnostic factors:
1.1. History of elevated Alkaline phosphatase (ALP) levels for at least 6 months prior to Day 0
1.2. Positive antimitochondrial antibodies (AMA) titer or if AMA negative or in low titer (<1:80) PBC specific antibodies (anti-GP210 and/or anti-SP100 and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)
1.3. Liver biopsy consistent with PBC
2. At least 1 of the following qualifying biochemistry values:
2.1. ALP ≥ 1.67x upper limit of normal (ULN)
2.2. Total bilirubin > ULN but < 2x ULN
3. Age ≥ 18 years
4. Taking ursodeoxycholic acid (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 must be postmenopausal, surgically sterile, or if premenopausal, be prepared to use ≥ 1 effective (≤ 1% failure rate) method of contraception during the trial and until the EOT visit. Effective methods of contraception are considered to be:
5.1. Hormonal (e.g., contraceptive pill, patch, intramuscular implant or injection); or
5.2. Double barrier method, i.e., (a) condom (male or female) or (b) diaphragm, with spermicide; or
5.3. Intrauterine device (IUD)

5.4. Vasectomy (partner)
6. Must provide written informed consent and agree to comply with the trial protocol

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
217

Key exclusion criteria
1. History or presence of other concomitant liver diseases including:
1.1. Hepatitis B or C virus (HCV, HBV) infection
1.2. Primary sclerosing cholangitis (PSC)
1.3. Alcoholic liver disease
1.4. Definite autoimmune liver disease or overlap hepatitis
1.5. Nonalcoholic steatohepatitis (NASH)
1.6. Gilberts Syndrome (due to interpretability of bilirubin levels)
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
2.1. History of liver transplantation, current placement on a liver transplant list or current Model for End-Stage Liver Disease (MELD) score ≥ 15
2.2. Portal hypertension and complications, including: known esophageal varices, poorly controlled or diuretic resistant ascites, history of variceal bleeds or related interventions (e.g., insertion of variceal bands or transjugular intrahepatic portosystemic shunts [TIPS]), hepatic encephalopathy
2.3. Cirrhosis with complications, including history or presence of: spontaneous bacterial peritonitis, hepatocellular carcinoma, bilirubin > 2x ULN
2.4. Hepatorenal syndrome (type I or II) or Screening serum creatinine > 2 mg/dL (178 µmol/L)
3. Patients with a history of severe pruritus requiring current or prior systemic treatment [e.g., with bile acid sequestrants (BAS) or rifampicin]
4. Administration of the following medications is prohibited as specified below:
4.1. Prohibited 6 months prior to Day 0 and throughout the trial (i.e., to last dose 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)
4.2. Prohibited 12 months prior to Day 0 and throughout the trial (i.e., to last dose 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, or prolongation of Screening (pretreatment) QT or QTc interval of > 500 msec
7. If female: known pregnancy, or has a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
8. Known history of human immunodeficiency virus (HIV) infection
9. History or presence of any other disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs including bile salt metabolism in the intestine (e. g., inflammatory bowel disease or gastric bypass procedures; [gastric lap band is acceptable])
10. Medical conditions that may cause nonhepatic increases in ALP (e.g., Paget's disease) or which may diminish life expectancy to < 2 years, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukemia)
11. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the trial
12. Anticipated changes to current concomitant medications during the course of the trial
13. History of alcohol abuse, defined as consumption of more than 210 mL of alcohol per week (i. e., the equivalent of 14 4-ounce (125 mL) glasses of wine or 14 12 ounce cans/bottles of beer), or other substance abuse within 1 year prior to Day 0
14. Participation in another investigational drug, biologic, or medical device trial within 30 days prior to Screening
15. History of noncompliance with medical regimens, or patients who are considered to be potentially unreliable
16. Blood or plasma donation within 30 days prior to Day 0
17. Mental instability or incompetence, such that the validity of informed consent or compliance with the trial is uncertain

Date of first enrolment
31/01/2012

Date of final enrolment
19/12/2012

Locations

Countries of recruitment
United Kingdom

Austria

Belgium

Canada

France

Italy

Netherlands

Poland

Spain

Sweden

United States of America

Study participating centre
Intercept Pharmaceuticals Inc.
San Diego
United States of America
92122

Sponsor information

Organisation
Intercept Pharmaceuticals Inc. (USA)

ROR
https://ror.org/01sx6jc36

Funder(s)

Funder type
Industry

Funder Name
Intercept Pharmaceuticals, Inc. (USA)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	18/08/2016		Yes	No

HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes