A Phase 2, Double-Blind, Randomized, Parallel-Group Study Evaluating the Efficacy, Safety, and Tolerability of Obeticholic Acid, Administered in Combination with Bezafibrate, in Subjects with Primary Biliary Cholangitis Who Had an Inadequate Response or Who Were Unable to Tolerate Ursodeoxycholic Acid

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON54633

Source
ToetsingOnline

Brief title
Evaluation of OCA and BZF on primary biliary cholangitis

Condition

- Gastrointestinal inflammatory conditions

Synonym
bile duct inflammation, Primary biliary cholangitis (PBC)

Research involving
Human

Sponsors and support

Primary sponsor: Intercept Pharmaceuticals, Inc.
Source(s) of monetary or material Support: industry

Intervention

Keyword: Bezafibrate (BZF), Obeticholic acid (OCA), Phase 2, Primary biliary cholangitis (PBC)

Outcome measures

Primary outcome

Absolute change in ALP from baseline to Week 12 in the DB treatment period.

Secondary outcome

The secondary endpoints include:

• The response rates of >=10%, >=20%, >=30%, and >=40% reduction from baseline and normalization rates of ALP at Week 12

• Normalization rates at Week 12 of GGT, ALT, AST, ALP total and conjugated bilirubin, and a lipid panel

• Change from baseline to Week 12 in GGT, ALT, AST, and total and conjugated bilirubin, and a lipid panel

• Change from baseline to Week 12 in 7α-hydroxy-4-cholesten-3-one (C4) and bile acids

Study description

Background summary

Primary biliary cholangitis is a chronic liver disease resulting from progressive destruction of the bile ducts in the liver called the intrahepatic bile ducts. When the ducts are destroyed, bile builds up in the liver contributing to inflammation and scarring (fibrosis).
The current first line treatment for PBC is Ursodeoxycholic Acid (UDCA). However, it has shown that PBC may progress despite using this treatment. In this study an alternative treatment will be investigated, namely OCA combined with Beza. OCA is a modified version of a natural compound made in the liver called bile acid, which helps with digestion and has effects on liver function. Beza helps the liver process triglycerides and may add additional benefit to OCA in the treatment of PBC to improve liver function.

Study objective

This study has been transitioned to CTIS with ID 2024-513762-18-00 check the CTIS register for the current data.

The primary objective is to assess the effects of the combination of OCA and BZF on alkaline phosphatase
(ALP) in comparison to BZF alone in subjects with primary biliary cholangitis (PBC)

To assess the effects of the combination of OCA and BZF in comparison to BZF alone in subjects with PBC on
the following:
• Biochemical disease markers, including ALP, GGT, ALT, AST, total and conjugated bilirubin, and a lipid panel.
• Disease-specific symptoms as assessed by health-related quality of life questionnaires (PBC-40, pruritus visual analog scale [VAS], EQ-5D-5L, and SF-36)
• Biomarkers of bile acid synthesis and homeostasis, including 7α-hydroxy-4-cholesten-3-one (C4) and bile acids
• Safety and tolerability

Study design

This Phase 2, proof-of-concept, randomized, double-blind, parallel-group study will evaluate the efficacy, safety, and tolerability of OCA (5 mg and 10 mg) administered in combination with 2 different BZF doses (200 mg and 400 mg) or BZF alone (at two doses, 200 mg and 400 mg) in up to 72 subjects with PBC over at least 12 weeks.

Protocol Version 2 and 3 overview of differences: Protocol version 2 had a 3-arm design (Group 1, OCA 5 mg to 10 mg; Group 2, OCA 5 mg to 10 mg + BZF 200 mgimmediate release [IR]; Group 3, OCA 5 mg to 10 mg + BZF 400 mg sustained release [SR], whereas Protocol Version 3 onwards has a 4-arm design: Group 1 (Treatment A: BZF 200 mg IR); Group 2
(Treatment B: BZF 400 mg SR); Group 3 (Treatment C: OCA 5 mg to 10 mg + BZF 200 mg IR); and Group 4 (Treatment D: OCA 5 mg to 10 mg + BZF 400 mg SR). Subjects enrolled under Protocol Version 2 will remain on the initial study arm/treatment regimen (one of 3 treatment arms) throughout the double-blind (DB), DB-follow-up and LTSE periods while completing the visits and assessments described under Protocol Version 4. Upon completion of visit 10 of the DB Follow-up period, subjects enrolled under the current protocol approved at the site, will transition to the LTSE period.

Screening Period (2 weeks and up to 8 weeks):
Subjects will be screened for a period of 2 to 8 weeks before being randomized into the study to allow for the collection of repeat serum chemistry samples (there will be 2 screening visits at least 2 weeks apart) for verification of inclusion/exclusion criteria and to establish baseline (including Day 1).

Double-Blind Treatment Period (12 weeks):
Subjects who meet the entry requirements will be randomized in a 1:1:1:1 ratio on Day 1 to receive either Treatment A (BZF 200 mg IR once daily [QD]), Treatment B (BZF 400 mg SR tablet QD), Treatment C (OCA 5 mg*10 mg QD + BZF 200 mg IR QD), or Treatment D (OCA
5 mg*10 mg QD + BZF 400 mg SR QD).

Subjects who are randomized to combination groups will receive OCA 5 mg QD from Day 1 to the day before the Week 4 Visit, followed by OCA 10 mg QD from the Week 4 Visit through the end of the study. To preserve the study blind, appearance-matched placebo tablets for OCA and/or BZF will be administered to subjects in each treatment group from Day 1 to Week 12 as shown in the study design diagrams for the double-blind (DB) and LTSE treatment periods. Subjects will be instructed to begin dosing on Day 1 and to take investigational product at approximately the same time each day (morning dosing for the entire study is preferred to align with all study visits). Subjects must be instructed to swallow the tablets whole; investigational product must not be chewed, divided, or crushed and must be taken with food and water (ad libitum) throughout the study. At study visits, all doses of investigational product (and of UDCA, for subjects on UDCA) will be administered at the clinic. Subjects are instructed to take investigational product with a meal onsite after all procedures have been completed, following a fast of at least 8 hours before dosing. A low-fat meal or meal replacement drink will be given with investigational product administration at visits with serial PK collections.
Subjects will be maintained on the DB dose and will transition to the DB Follow-Up Period on the same dose. All subjects will be held in the DB Follow-Up Period until the last subject completes Week 12 of the DB Period.

Please refer to Appendix A for a description of treatment arms and study design for subjects who were randomized under Protocol Version 2.

Intervention

Treatment A:
OCA 5 mg*10 mg QD:
- 1 OCA 5 mg tablet (Weeks 0 to 4)
- 1 OCA 10 mg tablet (Week 4 to end of DB treatment)
- 1 placebo BZF 200 mg IR tablet
- 1 placebo BZF 400 mg SR tablet

Treatment B:
OCA 5 mg*10 mg QD + BZF 200 mg IR QD:
- 1 OCA 5 mg tablet (Weeks 0 to 4)
- 1 OCA 10 mg tablet (Week 4 to end of DB treatment)
- 1 BZF 200 mg IR tablet
- 1 placebo BZF 400 mg SR tablet

Treatment C:
OCA 5 mg*10 mg QD + BZF 400 mg SR QD:
- 1 OCA 5 mg tablet (Weeks 0 to 4)
- 1 OCA 10 mg tablet (Week 4 to end of DB treatment)
- 1 placebo BZF 200 mg IR tablet
- 1 BZF 400 mg SR tablet

BZF = bezafibrate; DB = double-blind; IR = immediate release; OCA = obeticholic acid; QD = once daily; SR = sustained
release

Study burden and risks

Please refer to table 1 and 2 in section 7.1.2 of the protocol (schedule of assessments) for more information.

The patient participation in this study will take approximately 2 years. During this period, the patient will visit the hospital about 13 times and the patient will be called about 3 times by the study team. A visit will take approximately 4-8 hours, this is depending on the tests and procedures that take place during a study visit. For some visits, the patient must fast 8 hours prior to the study visit. During this period, the patient is only allowed to drink water.

The following tests and procedures will take place during these visits:
- Physical examination is performed and questions are asked about the medical history.
- ECG is done.

- Fibro Scan (TE).
- Weight, height, hips and waist circumference, blood pressure temperature and heart rate are measured.
- Blood and urine samples are taken.
- The research doctor will also perform a pregnancy test on female subjects of child-bearing age.
- The subject is asked to fill in a number of questionnaires regarding the quality of life: PBC-40, EQ-5D-5L, SF-36

Possible side effects that are already known are described in the Investigator's Brochure and the patient informed consent form.

Contacts

Public
Intercept Pharmaceuticals, Inc.

Madison Avenue 305
New Jersey 07960
US
Scientific
Intercept Pharmaceuticals, Inc.

Madison Avenue 305
New Jersey 07960
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- A definite or probable diagnosis of PBC (consistent with the European Association for the Study of the Liver [EASL] Practice Guidelines and the American Association for the Study of Liver Diseases; [Lindor 2009a, EASL 2017])
- Qualifying ALP and / or bilirubin liver biochemistry values
- Age >=18 years
- Taking UDCA for at least 12 months (stable dose for >=3 months) before Day 1 or no UDCA for 3 months before Day 1

Exclusion criteria

- History or presence of other concomitant liver diseases
- Clinical complications of PBC
- History or presence of decompensating events
- History of or current gallbladder diseases
- If female, known pregnancy, or has a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
- Treatment with commercially available OCA or participation in a previous study involving OCA

Note: Other protocol defined Inclusion/Exclusion criteria may apply

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	03-02-2022
Enrollment:	12
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Bezalip
Generic name:	Bezafibrate
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Ocaliva
Generic name:	Obeticholic acid
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-01-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-05-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-05-2021

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-06-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	17-10-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389

	mecamc@amsterdamumc.nl
Approved WMO Date:	07-02-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	22-04-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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	CTIS2024-513762-18-00
EudraCT	EUCTR2018-002575-17-NL
ClinicalTrials.gov	NCT04594694
CCMO	NL71595.018.19