A Multicenter, Open-Label, Single- and Multiple-Dose, Dose-Finding Study, with an Optional Open-Label Extension to Assess the Safety, Tolerability, and Pharmacokinetics of Obeticholic Acid in Pediatric Subjects with Biliary Atresia.;Trial Acronym: ObetiCholic Acid in Pediatric Subjects with BiliaRy AtrEsia (CARE)

Published: 04-08-2015
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Primary Objectives• Safety and tolerability• PK of OCA and its conjugates o SD PK Phase: To assess the PK of OCA and its conjugates after a single low dose of OCA on Day 1 and determine subject eligibility for the MD Phase o MD Phase: To assess the...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Hepatobiliary disorders congenital
Study type	Interventional

Summary

ID

NL-OMON53035

Source
ToetsingOnline

Brief title
ObetiCholic Acid in Pediatric Subjects with BiliaRy AtrEsia (CARE)

Condition

- Hepatobiliary disorders congenital
- Bile duct disorders

Synonym
Biliary atresia

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: Biliary atresia, Dose-finding, Obeticholic Acid, Pediatric

Outcome measures

Primary outcome

- Safety and tolerability: Treatment-emergent AEs (TEAEs) including serious AEs

(SAEs), electrocardiogram (ECG), physical exam, clinical laboratory results,

vital signs.

- PK: Plasma concentrations of unconjugated OCA, its conjugates (glycine

conjugate of OCA [glyco-OCA] and taurine conjugate of OCA [tauro-OCA]), and

total OCA in the SD and MD Phases

Secondary outcome

Secondary Endpoints

-PD: Markers of FXR activation: Fibroblast growth factor-19 (FGF-19),

7-hydroxy-4-cholesten-3-one (C4), and endogenous bile acids.

- PD: Biomarkers of hepatobiliary function: Alkaline phosphatase (ALP), AST, ALT, GGT, total and direct (conjugated) bilirubin, prothrombin time, INR, albumin, platelet count.

Exploratory Endpoints

-Acceptability and swallowability: Subject*s ability to swallow the dose regimen and overall acceptability of the dose regimen will be evaluated via a five-point criteria evaluation (refer to the protocol).

- Palatability (Day 28): On the first day of the MD Phase, palatability of OCA will be assessed using a five-point facial hedonic scale with a correlated 100-point visual analog scale (FHS/VAS-5) in children >=4 years of age. Children <4 years will evaluate palatability using a four-point criteria evaluation (refer to protocol).

- Additional efficacy measures during OLE: Vitamin A and D levels Noninvasive assessment of liver stiffness (e.g., FibroScan TE, or other ultrasound elastography of the liver) based on site availability.

Study description

Background summary

Biliary atresia is a disease of early infancy manifest by biliary obstruction due to maldevelopment of the biliary tree, which is fatal without hepatoportoenterostomy (HPE, also known as Kasai procedure). Following HPE, the children progress along 2 paths: around half of the infants fail to get

adequate biliary drainage from their HPE procedure and they either receive a liver transplant by 2 years of age or they die. In the other patients, those who exhibit a good
response to the surgical HPE procedure, develop a progressive fibrotic disease over the ensuing years. Nearly all of these patients develop cirrhosis by the time they are 18 years old.
An essential regulator of bile acid homeostasis is the farnesoid X receptor (FXR) which is a nuclear receptor expressed in multiple tissues, including the liver and intestine. FXR is activated by endogenous bile acids and regulates key response elements in both synthesis and release of bile acids by the liver. Cholestatic conditions which impair delivery of bile acids to the intestine greatly diminish the activation of intestinal FXR and, consequently, bile acid synthesis is no longer properly regulated leading to sustained elevations in hepatic bile acids.
Aside from HPE, there are no approved medicinal treatments for BA. OCA has exhibited anti-cholestatic and hepatoprotective properties in in vitro and in vivi studies. Based on the pathologic mechanisms leading to cholestasis and fibrosis in chronic liver diseases, it is hypothesized that treatment with OCA will improve liver function.

Study objective

Primary Objectives
• Safety and tolerability
• PK of OCA and its conjugates
o SD PK Phase: To assess the PK of OCA and its conjugates after a single low dose of OCA on Day 1 and determine subject eligibility for the MD Phase
o MD Phase: To assess the steady-state PK of OCA and its conjugates for a range of OCA doses

Secondary Objectives
• Pharmacodynamics (PD) of OCA as measured by markers of farnesoid X receptor (FXR) activation and the biomarkers of hepatobiliary function

Exploratory Objectives
• Acceptability and swallowability
• Palatability (MD Phase only)

OLE Phase Objectives
• Long-term safety and tolerability
• Durability of the PD of OCA as measured by markers of FXR activation and the biomarkers of hepatobiliary function
• Levels of vitamins A and D
• Noninvasive assessment of liver stiffness (e.g., FibroScan® transient elastography [TE] or other ultrasound elastography of the liver) based on site

availability

Study design

This is a multicenter, open-label, SD and MD, dose-finding study followed by an optional OLE to evaluate the safety, tolerability, PK, and PD of a range of OCA doses in eligible pediatric subjects with biliary atresia with successful hepatoportoenterostomy (HPE, also known as a Kasai portoenterosomy). The OLE will continue to evaluate safety, tolerability, PD, and efficacy of OCA. In addition, a change in vitamin A and D levels, and where possible the degree of change in liver stiffness, will be assessed during the OLE.

Intervention

Single- Dose (SD) Phase: All participants will receive an OCA dose equivalent to 1.5- mg dose for an adult on Day 1, and on the basis of blood test results taken after that single OCA dose, the dose for the MD-phase for the patient will be determined.

Multi- Dose (MD) Phase: The patient will be assigned to 1 of three dose groups: low (1.5 mg adult-equivalent), medium (5 mg adult-equivalent) or high (10 mg adult-equivalent). The study doctor will explain to you which group you will be assigned to. Patient will take that assigned dose every day for 28 days.

Phase Group assignments (adult equivalent dose)
Category 1
A 1.5 mg, once daily
B 5 mg, once daily
C 10 mg, once daily
Category 2
D 1.5 mg, once daily
E 5 mg, once daily
Category 3
F 1.5 mg, once daily
Category 4
G 0.75 mg, once daily
Category 5
H 0.75 mg, twice a week

Study burden and risks

Following HPE (hepatoportoenterostomy, also known as Kasai procedure), children progress along 2 paths: around half of the infants fail to get adequate biliary drainage from their HPE procedure and they either receive a liver transplant by 2 years of age or they die. In the other patients, those who exhibit a good

response to the surgical HPE procedure, develop a progressive fibrotic disease over the ensuing years. Nearly all of these patients develop cirrhosis by the time they are 18 years old.

Biliary tract occlusion with Biliary Atresia causes a rise in endogenous bile acids to cytotoxic levels, causing inflammatory damage, an increase in hepatocellular enzymes and apoptosis which over time results in hepatic fibrosis and cirrhosis.
Obeticholicacid being a modified bile acid, and FXR agonist protects the liver by:
- Regulation of bile synthesis and flow resulting in less cholestasis
- Inhibition of inflammation (in the liver and the rest of the body)
- Prevention of and/or reversal of scarring (i.e., fibrosis and/or cirrhosis)
- Prevention of and/or reduction in portal hypertension (i.e., high blood pressure in the liver that causes numerous complications)

Based on the pathologic mechanisms in Biliary Atresia post-HPE, it is hypothesized that treatment with OCA may improve survival with subject*s native liver, prevent the onset of cirrhosis and subsequently delay/prevent liver transplant.

Aside from HPE, there are no approved medicinal treatments for Biliary Atresia. Moreover, as this is a rare disease (in The Netherlands, approximately 10 new patients per year), relatively little is known on this disease.

There are up to 15 scheduled visit (including screening visit) expected in this trial. There is a 3-day visit and three 2-day visits where the subject will have to stay overnight at the UMCG or stay nearby and return early next morning. the second day for the 3 day visit and the first day for the other 3 overnight stays will be a PK day where the patient will have to stay at the clinic about 8 hours before being released for the day. The following day the patient will have to return the next day for a 24 hour blood sample. If the patient is local, the burden of missing school and parents missing full day*s work may be minimized. If the subject is not local this burden may increase. The overnight stay at the clinic are not mandatory, but preferred, depending on patients proximity to the site.

Due to the burden of number of visits on a family and their wages, reasonable travel costs will be reimbursed.
Other possible monetary hardships may be considered if the investigative site finds it necessary.

Blood samples will be collected during the study and collection of these samples can irritate or be painful to the
arms, but will likely clear up. Children are able to have a cream placed on those areas to numb the skin prior to the
blood draw.

Screening Phase: All subjects will be given the choice to receive placebo during the Screening Phase.
Placebo tablets and placebo mini-tablets will be used at the Screening and Day 0 Visits to evaluate acceptability
and swallowability of a subject*s assigned dose regimen. Placebo may also be dispensed at the Screening Visit
to take home and practice dosing administration techniques (at home) prior to randomization on Day 0.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Male or female pediatric subjects >=2 to <18 years old.

2. Diagnosis of biliary atresia.
3. Demonstrated successful HPE (also known as a Kasai portoenterostomy) as defined by total bilirubin <2 mg/dL (34.2 µmol/L) at least 3 months post-HPE procedure.
4. Able to swallow tablets (i.e., tablet or mini-tablet formulations)

Exclusion criteria

1. Prior liver transplant or active status on transplant list.
2. Conjugated (direct) bilirubin >=ULN of site specific reference range.
3. If conjugated bilirubin is not availble: total bilirubin >=2 mg/dL (34.2 µmol/L).
4. Platelets <150,000/µL.
5. INR >=1.5.
6. Current or history of complications of decompensated chronic liver disease including:
a. high-risk gastroesophageal varices and/or varcieal bleeding
b. clinically evident ascites related to portal hypertension
c. hepatic encephalopathy
d. prior placement of portosystemic shunt
e. hepatopulmonary syndrome or portopulmonary hypertension
f. hepatorenal syndrome
7. Current intractable pruritus or requires systemic treatment for pruritus within 3 months of Screening (e.g., with bile acid sequestrants or rifampicin)
8. Height and weight Z-score <-2 per site specific reference ranges
9. Acholic (pale) stools
10. AST >4x ULN
11. ALT >4x ULN
12. Gamma-glutamyl transferase (GGT) >500 U/L
13. Anticoagulation therapy
14. Albumin <3.5 g/dL

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ocaliva
Generic name:	Obeticholic Acid
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-08-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-11-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-01-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-06-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	08-08-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-06-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-07-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-11-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-07-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-07-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-12-2021
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2014-004693-42-NL
CCMO	NL53004.000.15

Study results

Results posted: 11-09-2023

Summary results
Trial never started

First publication
31-08-2023