A Double-Blind, Randomized, Placebo-Controlled, Phase 3 Study to Demonstrate Efficacy and Safety of A4250 in Children with Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC 1)

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To demonstrate the efficacy of repeated daily doses of 40 µg/kg/day and 120 µg/kg/day A4250 in children with progressive familial intrahepatic cholestasis (PFIC) Types 1 and 2, as determined by the following:* Proportion of patients experiencing at...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary disorders congenital
Study type	Interventional

Summary

ID

NL-OMON48541

Source
ToetsingOnline

Brief title
PEDFIC 1 (2191/0010)

Condition

- Hepatobiliary disorders congenital
- Hepatic and hepatobiliary disorders

Synonym
Progressive Familial Intrahepatic Cholestasis (PFIC)

Research involving
Human

Sponsors and support

Primary sponsor: Albireo AB
Source(s) of monetary or material Support: Albireo AB

Intervention

Keyword: A4250, Children, Progressive familial intrahepatic cholestasis, Type 1 & 2

Outcome measures

Primary outcome

The primary efficacy endpoints are:

* EU and rest of world (RoW): Proportion of patients experiencing at least a

70% reduction in fasting s-BA concentration from baseline to the end of

treatment or reaching a level *70 µmol/L compared to placebo after 24 weeks of

treatment.

* US: Proportion of positive pruritus assessments at the subject level over the

24-week Treatment Period

Secondary outcome

Secondary efficacy endpoints include the following:

* EU and RoW: Proportion of positive pruritus assessments at the subject level

over the 24-week Treatment Period.

* US: Proportion of patients experiencing at least a 70% reduction in fasting

s-BA concentration from baseline to the end of treatment or reaching a level

*70 µmol/L compared to placebo after 24 weeks of treatment.

All Regions:

All secondary endpoints will be compared to placebo.

* Change from baseline to Week 12 and to Week 24 in fasting s-BA

* Change from baseline to Week 12 and to Week 24 in serum ALT concentration

* Change in growth from baseline to Week 12 and to Week 24

* Proportion of responders for pruritus scores at Weeks 12 and 24 based on the Albireo PRO and ObsRO instruments

* Change in sleep parameters measured with the Albireo PRO and ObsRO instruments from baseline over the 24-week Treatment Period

* Proportion of individual assessments meeting the definition of a positive pruritus assessment at the subject level over the 24-week Treatment Period. A positive pruritus assessment includes an itch score *1, or at least a one-point drop from baseline based on the Albireo PRO instrument; only patients *8 years of age will complete the Albireo PRO instrument

* Proportion of individual assessments meeting the definition of a positive pruritus assessment at the subject level from Weeks 0-4, Weeks 0-8, Weeks 0-12, Weeks 0-18, Weeks 0-24, respectively, or the proportion of positive pruritus assessments at each 4-week interval.

* Proportion of individual AM assessments meeting the definition of a positive pruritus assessment at the subject level from Weeks 0-4, Weeks 0-8, Weeks 0-12, Weeks 0-18, Weeks 0-24, respectively, or the proportion of positive pruritus assessments at each 4-week interval.

* Proportion of individual PM assessments meeting the definition of a positive pruritus assessment at the subject level from Weeks 0-4, Weeks 0-8, Weeks 0-12, Weeks 0-18, Weeks 0-24, respectively, or the proportion of positive pruritus assessments at each 4-week interval.

* Number of patients undergoing biliary diversion surgery or liver

transplantation

Study description

Background summary

PFIC is a rare autosomal recessive cholestatic liver disease estimated to affect between 1 in every 50,000 to 100,000 children born worldwide. PFIC represents 10% to 15% of causes of cholestasis in children and 10% to 15% of liver transplantation indications in children. All types of PFIC exist worldwide and both sexes appear to be equally affected.
The common underlying pathogenesis of PFIC is disruption of bile formation and bile transport through the liver [Jacquemin 2000]. The classification of PFIC has evolved over the years. The most commonly used sub classifications are PFIC Types 1, 2, and 3, which are based on the associated affected gene and described in more detail below.
* PFIC, Type 1: also referred to as *Byler disease* or *familial intrahepatic cholestasis 1 (FIC1) protein deficiency.* FIC1 protein is located on the canalicular membrane of hepatocytes and facilitates movement of aminophospholipids from the outer to inner leaflet of the plasma membrane of the hepatocyte. The ATP8B1 gene encodes FIC1 protein. Biallelic pathologic variants in the ATP8B1 gene are associated with FIC1 dysfunction and classified clinically as PFIC Type 1 disease.
* PFIC, Type 2: also referred to as *Byler syndrome* or *bile salt export pump (BSEP) deficiency.* BSEP is a transporter protein that is expressed at the canalicular membrane of hepatocytes, and is the primary exporter of bile acids. The ABCB11 gene encodes the BSEP protein. Biallelic pathologic variations in the ABCB11 gene are associated with BSEP dysfunction and classified clinically as PFIC Type 2 disease.
* PFIC, Type 3: is caused by a deficiency of the multidrug resistance protein 3 (MDR3) due to mutations in the ABCB4 gene. MDR3 is a phospholipid translocase critical for phospholipid secretion.
Severe pruritus is common in children diagnosed with PFIC. Itching (and subsequent scratching) is a significant morbidity for these patients and their families [Suchy 2007]. A more severe degree of pruritus is experienced compared to patients with other forms of liver disease and to other pruritic conditions such as atopic dermatitis [Murray 2011]. In patients with PFIC, liver biopsy reveals canalicular cholestasis and, later, the appearance of portal fibrosis. Serum biochemistry indicates cholestasis with hyperbilirubinemia, elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The concentrations of bile acids in serum are very high, while serum gamma-glutamyl transferase activity (exception being MDR3

variants) and cholesterol are normal [Hori 2010]. Symptoms of portal hypertension and liver failure will develop during the course of the disease [Davit-Spraul 2009; Alissa 2008]. Symptoms develop early; median age at onset of symptoms is 2 months, and 78% of PFIC patients present with jaundice [Pawlikowska 2010]. The life threatening and debilitating nature of PFIC is reflected by the fact that survival in those not resorting to surgery is 50% at 10 years of age and almost zero at 20 years of age. Approximately half of PFIC patients undergo liver transplantation [Davit-Spraul 2009] and treatment resistant pruritus is the leading indication for the surgical procedure partial external biliary diversion, mostly in PFIC Type 1 and 2 patients.
PFIC is life threatening and debilitating. Currently, the treatment for PFIC is palliative and there is no pharmaceutical treatment approved for use in PFIC. The therapeutic choices are restricted to non specific therapy of the symptoms and signs of the disease such as nutritional support, preventing vitamin deficiencies, and treatment of extrahepatic features. Medical treatment options include off label use of ursodeoxycholic acid, rifampin, antihistamines, and naltrexone. A minority of patients respond nominally and transiently to these interventions. Biliary diversion is used to decrease systemic bile acids through interruption of the enterohepatic circulation and so avoid transplantation. Liver transplantation is typically only viewed as an option when patients have failed medical treatment and/or biliary diversion and have liver failure or persistent uncontrolled pruritus.

Study objective

To demonstrate the efficacy of repeated daily doses of 40 µg/kg/day and 120 µg/kg/day A4250 in children with progressive familial intrahepatic cholestasis (PFIC) Types 1 and 2, as determined by the following:
* Proportion of patients experiencing at least a 70% reduction in fasting serum bile acid (s-BA) concentration from baseline to end of treatment or reaching a level *70 µmol/L compared to placebo after 24 weeks of treatment
* The proportion of positive pruritus assessments at the subject level over the 24-week Treatment Period

Study design

The study includes a 35- to 56 day Screening Period followed by a 24 week Treatment Period and a 4 week Follow-Up Period. After completion of the Screening Period, eligible patients (20 per treatment group) will be randomized on Day 0 (Visit 3) in a 1:1:1 fashion to receive 40 µg/kg/day or 120 µg/kg/day of A4250, or a matching placebo. Patients who complete the Treatment Period and Visit 9 (Day 168) in this study will be invited to participate in a 72 week open label extension study (A4250 008) in which all patients will receive active treatment. A patient who prematurely withdraws due to no improvement/intolerable symptoms, and has completed at least 12 weeks of the Treatment Period and End of Treatment (EOT) Visit, will also be offered the

opportunity to enter Study A4250 008.

There will be up to 10 clinic visits during the study and one scheduled telephone contact.

Intervention

There are three treatment groups to which the subject can be assigned to in a 1:1:1 chance:
* Group A: A4250 at a dose of 40 micrograms (mcg) per kilogram (kg) of body weight
* Group B: A4250 at a dose of 120 mcg per kg of body weight
* Group C: Matching placebo capsules

Study burden and risks

A4250 has been evaluated in three Albireo sponsored clinical studies: a double blind placebo controlled study in healthy volunteers, a single dose ADME study, and a Phase 2 study in children with cholestatic pruritus. In addition, an investigator sponsored study has been conducted in patients with PBC.
A total of 98 subjects/patients have been exposed to A4250. Healthy subjects have been exposed to up to 10 mg as a single dose and up to 3 mg daily as part of a multiple dose evaluation. Children with cholestatic liver disease have been treated with up to 0.2 mg/kg/day (200 µg/kg/day) for 4 weeks. In total, 2 SAEs have been reported; both were judged by the physician to be not related to the study drug.
Patients with cholestatic liver diseases suffer from excess bile acids in the liver resulting in tissue damage. A commonly used treatment in these patients is bile diversion surgery, whereby approximately 50% to 100% of the enterohepatic circulation of bile acids is interrupted. Inhibition of IBAT with A4250, thereby interrupting the enterohepatic circulation of bile acids, is therefore a potential medical alternative to surgery which could be of benefit to these patients if shown to be effective and safe. Data from the Phase 2 study showed efficacy of A4250 in reducing s BA concentrations and pruritus in such patients.
Based on the mode of action of an IBAT inhibitor, loose stools or diarrhea could be expected. However, in the pediatric Phase 2 study with 4 weeks daily treatment, only one patient had mild transient diarrhea after a single dose that did not recur on multiple dosing.

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. A male or female patient, with clinical diagnosis of PFIC Type 1 or 2, between the ages of *6 months and *18 years at Visit 1 with a body weight above 5 kg
2. Patient must have clinical genetic confirmation of PFIC-1 or PFIC-2 through identification of biallelic pathogenic variants in either the ATP8B1 or ABCB11 genes
3. Patient must have elevated s-BA concentration, specifically measured to be *100 *mol/L,taken as the average of 2 samples at least 7 days apart (Visits 1 and 2) prior to randomization
4. Patient must have history of significant pruritus and a caregiver reported observed scratching in the eDiary in the 2 weeks prior to randomization
5. Patient and/or legal guardian must sign informed consent (and assent) as appropriate. Patients who turn 18 years of age (or legal age per country) during the study will be required to re-consent in order to remain in the study
6. Patients will be expected to have a consistent caregiver for the duration of the study
7. Caregivers and age-appropriate patients (*8 years of age) must be willing and able to use an eDiary device as required by the study

Exclusion criteria

1. Patient with pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein
2. Patient with past medical history or ongoing presence of other types of liver disease including, but not limited to, the following:
a. Biliary atresia of any kind
b. Benign recurrent intrahepatic cholestasis
c. Suspected or proven liver cancer or metastasis to the liver on imaging studies
d. Histopathology on liver biopsy is suggestive of alternate non-PFIC related etiology of cholestasis
3. Patient with past medical history of ongoing chronic diarrhea
4. Any patient with suspected or confirmed cancers except for basal cell carcinoma
5. Patient with a past medical history of chronic kidney disease with an impaired renal function and a glomerular filtration rate <70 mL/min/1.73 m2
6. Patient with surgical history of disruption of the enterohepatic circulation (biliary diversion surgery) within 6 months prior to start of Screening period)
7. Patient has had a liver transplant or a liver transplant is planned within 6 months of randomization
8. Decompensated liver disease, coagulopathy, history or presence of clinically significant ascites, variceal hemorrhage, and/or encephalopathy
9. Patient suffers from uncontrolled, recalcitrant pruritic condition other than PFIC.
10. Patient who has been previously treated with an IBAT inhibitor whose pruritus has not responded to treatment

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):	20-09-2018
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	A4250
Generic name:	A4250

Ethics review

Approved WMO Date:	19-02-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-05-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-06-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-06-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-08-2018
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-06-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2017-002338-21-NL
ClinicalTrials.gov	NCT03566238
CCMO	NL63688.028.18