An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of A4250 in Children with Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC 2)

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Primary Objective (Cohort 1)To demonstrate a sustained effect of A4250 on serum bile acids and pruritus in children with progressive familial intrahepatic cholestasis (PFIC) Types 1 and 2.Primary Objective (Cohort 2)To evaluate the effect of A4250...

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

Summary

ID

NL-OMON54766

Source
ToetsingOnline

Brief title
PEDFIC 2 (2191/0009)

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

Primary Efficacy Endpoints

European Union (EU) and rest of world: Change from baseline in serum bile acids after 72 weeks of treatment.

US: Change in pruritus, as indexed by caregiver-reported observed scratching, from baseline over the treatment period i.e. up to 72 weeks, as measured by an overall mean of weekly averages of the worst daily scratch score using the Albireo observer-reported outcome (ObsRO) instrument.

Secondary outcome

Secondary Efficacy Endpoints

The baseline is calculated prior to initiation of A4250 treatment.

Secondary endpoints include:

• Proportion of positive pruritus assessments at the patient level over the 72 week treatment period using the Albireo ObsRO instrument.

• Change from baseline in serum bile acids to Week 76

• Proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level using the Albireo ObsRO instrument to Week 70

• Proportion of individual AM assessments meeting the definition of a positive pruritus assessment at the patient level using the Albireo ObsRO instrument to Week 72

• Proportion of individual PM assessments meeting the definition of a positive pruritus assessment at the patient level using the Albireo ObsRO instrument to Week 72

• All-cause mortality, number of patients undergoing biliary diversion surgery or liver transplantation. These parameters will be evaluated separately and together at weeks 24, 48, 72 and 76.

• Change in growth from baseline to Weeks 24, 48, 72 and 76 after initiation of A4250 treatment, defined as the linear growth deficit (height/length for age, weight for age, mid-arm circumference and body mass index [BMI]) compared to a standard growth curve (Z-score, standard deviation [SD] from P50)

• Change in aspartate aminotransferase (AST) to platelet ratio index (APRI) score and fibrosis-4 (Fib-4) score from baseline to Week 72

• Change in pediatric end-stage liver disease (PELD)/model for end-stage liver disease (MELD) score from baseline to Week 72

• Change in use of antipruritic medication at Weeks 24, 48, 72 and 76

Study description

Background summary

PFIC is a rare autosomal recessive cholestatic liver disease estimated to affect between one 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 subclassification is PFIC Types 1, 2, and 3 which is 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 is associated with BSEP dysfunction and is 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 (GGT) activity (the exception being MDR3 variants) and cholesterol [Hori 2010] are normal. 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 currently 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

Primary Objective (Cohort 1)
To demonstrate a sustained effect of A4250 on serum bile acids and pruritus in children with progressive familial intrahepatic cholestasis (PFIC) Types 1 and 2.

Primary Objective (Cohort 2)
To evaluate the effect of A4250 on serum bile acids and pruritus in patients with PFIC who either (1) do not meet eligibility criteria for Study A4250-005 (PEDFIC 1) or (2) who do meet the eligibility criteria for Study A4250-005 after recruitment of Study A4250-005 has been completed.

Study design

This is a Phase 3, multi-center, open-label extension study to investigate the long-term efficacy and safety of a 120 µg/kg/day daily dose of A4250 in patients with PFIC, including episodic forms also referred to as BRIC. Cohort 1 will consist of children with PFIC Types 1 and 2 who have participated in study A4250-005. Cohort 2 will consist of approximately 60 patients with PFIC who have elevated serum bile acids and cholestatic pruritus and who either (1) do not meet eligibility criteria for Study A4250-005 (PEDFIC 1) or (2) are eligible for enrolment in A4250-005 after recruitment of study A4250-005 has been completed. Up to 40 patients post biliary diversion surgery are allowed to participate in Cohort 2. Eligible patients will be enrolled into this open-label extension study and treated with a daily dose of 40 µg/kg/day1 or 120 µg/kg/day of A4250 for 72 weeks, or 40 µg/kg/day for the first 12 weeks followed by 120 µg/kg/day for the remaining 60 weeks1. Patients not tolerating the 120 µg/kg/day dose after a minimum of 1 week will have the option to down-titrate to a lower dose (40 µg/kg/day).

1 As of Protocol Amendment 6, patients entering Cohort 2 will start treatment at 40 µg/kg/day with the possibility to dose escalate to 120 µg/kg/day after 12 weeks if there is no improvement in pruritus based on investigator judgment.

Intervention

The treatment is a daily dose of A4250 capsules for 72 weeks.

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)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

Cohort 1:
1. Completion of the 24-week Treatment Period of Study A4250-005 or withdrawn from Study A4250-005 due to patient/caregiver judgment of intolerable symptoms after completing at least 12 weeks of treatment. Patients who withdraw from A4250-005 due to a study drug related AE will not be eligible.
2. Signed 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 to remain on the study
3. Patients expected to have a consistent caregiver for the duration of the study
4. Caregivers (and age appropriate patients) must be willing and able to use an eDiary device as required by the study

Cohort 2:
1. A male or female patient of any age, with a clinical diagnosis of PFIC, including episodic forms (i.e. benign recurrent intrahepatic cholestatis [BRIC]) and with a body weight greater or equal to 5 Kg at Visit S-1
2. Patient must have clinical genetic confirmation of PFIC.
3. Patients with PFIC, excluding BRIC, must have elevated serum bile acid concentration.
4, Patients with PFIC, excluding BRIC, must have history of significant pruritus
5. Patients with episodic forms of PFIC (i.e., BRIC) must have an emerging flare characterized by clinically significant pruritus and elevated serum bile acid levels/cholestasis as judged by the investigator.
6. Patient and/or legal guardian must sign informed consent (and assent) as appropriate.

7. Age appropriate patients are expected to have a consistent caregiver for the duration of the study.
8. Caregivers and age-appropriate patients (greater or equal to 8 years of age if able) must be willing and able to use an eDiary device as required by the study.

Exclusion criteria

Patients meeting any of the following criteria at Visit 1 will not be eligible for study participation:
Cohort 1:
1. Decompensated liver disease: coagulopathy, history, or presence of clinically significant ascites, variceal hemorrhage, and/or encephalopathy
2. Sexually active males and females who are not using a reliable contraceptive method with <=1% failure rate (such as barrier protection, hormonal contraception, intra-uterine device, or complete abstinence) throughout the duration of the study and 90 days thereafter (from signed informed consent through 90 days after last dose of study drug). See Appendix 6 for further details.
3. Patients not compliant with treatment in study A4250-005
4. Any other conditions or abnormalities which, in the opinion of the investigator or Medical Monitor, may compromise the safety of the patient, or interfere with the patient participating in or completing the study

Cohort 2:
1. Known pathologic variations of the ABCB11 gene that have been demonstrated to result in complete absence of the BSEP protein
2. Patient with past medical history or ongoing presence of other types of liver disease.
Note: Patients with clinically significant portal hypertension are allowed.
3. Patient has had a liver transplant, or a liver transplant is planned within 6 months of the Screening/Inclusion Visit
4. Decompensated liver disease, coagulopathy, history, or presence of clinically significant ascites, variceal hemorrhage, and/or encephalopathy.
5. INR >1.4 (the patient may be treated with Vitamin K intravenously, and if INR is less than or equal to 1.4 at resampling the patient may be included)
6. Serum ALT>10 x upper limit of normal (ULN) at Screening
7. Serum ALT>15 x ULN at any time point during the last 6 months unless an alternate etiology was confirmed for the elevation
8. Total bilirubin >5 x ULN at Screening
9. Patient suffers from uncontrolled, recalcitrant pruritic condition other that PFIC.
10. Administration of bile acid or lipid binding resins and medications that slow GI motility.
11. Any other conditions or abnormalities which, in the opinion of the

investigator or Medical Monitor, may compromise the safety of the patient, or interfere with the patient participating in or completing the study

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-12-2018
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not available yet
Generic name:	not available yet

Ethics review

Approved WMO Date:	01-08-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-10-2018
Application type:	First submission

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-01-2019
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:	27-05-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-12-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-01-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-05-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-06-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-11-2020
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-01-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-03-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-03-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-04-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-06-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-12-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-02-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-02-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-03-2022
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-02-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-02-2023
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
Other	2017-002325-38
EudraCT	EUCTR2017-002325-38-NL
CCMO	NL63749.028.18