A Phase 3 Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of Odevixibat (A4250) in Patients with Alagille Syndrome (ASSERT)

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Primary Objective:To demonstrate the efficacy of repeated daily doses of 120 µg/kg/day odevixibat in relieving pruritus in patients with ALGS.Secondary Objectives:To assess the impact of odevixibat on serum bile acid levels in patients with ALGS.To...

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

Summary

ID

NL-OMON51192

Source
ToetsingOnline

Brief title
Albireo A4250-012 (ASSERT) Study

Condition

- Hepatobiliary disorders congenital

Synonym
Alagille Syndrome

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Alagille Syndrome, Assert, Odevixibat (A4250)

Outcome measures

Primary outcome

Change from baseline in scratching to Month 6 (Weeks 21 to 24) as measured by

the Albireo ObsRO caregiver instrument.

Secondary outcome

Change in serum bile acid levels from baseline to the average of Week 20 and

Week 24

Study description

Background summary

Currently, there is no approved medical therapy for the treatment of pruritus in patients with ALGS. The majority of patients present with severe, intractable pruritus, which can be disabling. Attempts at managing pruritus are made by including ursodeoxycholic acid, cholestyramine, rifampin, ondansetron, or naltrexone in the patient*s treatment regimen; these agents are at best partially effective. Biliary diversion surgery is occasionally used to treat intractable pruritus with some success Treatment of persistent cholestasis and progressive liver cirrhosis is supportive and usually includes a choleretic agent. Kasai hepatoportoenterostomy (HPE) has been attempted in an effort to increase biliary flow from the liver to the intestine, but unlike patients with biliary atresia, those with ALGS who undergo the procedure have a worse outcome. Approximately 15% to 25% of patients with ALGS will require a liver transplant during childhood. For patients with ALGS there is a positive response to transplant with about 90% of patients showing improvement in liver parameters and some degree of catch-up growth. The 5-year survival post-transplant in this population is about 80%
By inhibiting IBAT with high selectivity and potency, odevixibat has the

potential to reduce the elevations in systemic bile acids that result from cholestasis and decrease pruritus, in patients with ALGS. The rationale for using odevixibat is to decrease serum bile acid levels, and to reduce the major morbidity of pruritus, improving the health and wellbeing of patients affected with ALGS. By reducing the elevations in systemic bile acids, odevixibat also has the potential to improve liver function and modify the progression of liver damage in patients with ALGS.

In adult healthy volunteers and pediatric patients with cholestatic liver disease, odevixibat has been generally safe and well tolerated in all completed studies. Reported AEs have primarily been of mild intensity. Abdominal pain and diarrhea have been the most common AEs in adults, and only 1 AE of diarrhea was reported in the pediatric Phase 2 study. Based on the mode of action of odevixibat as an IBAT inhibitor, loose stools or diarrhea are expected.
Infants with ALGS have elevated serum bile acids. Serum bile acids are an indicator of elevated bile acids within the liver, which in turn are thought to play a contributory role in hepatic oxidative stress and fibrosis. It has been shown that serum bile acid levels can predict long-term outcomes in patients with biliary atresia; even in patients with successful Kasai HPE procedures (defined as serum total bilirubin levels <1.5 mg/dL at 6 months post Kasai HPE); elevated serum bile acids may persist and can predict continued loss of hepatic function. Likewise, data from the Natural Course and Prognosis of Progressive Familial Intrahepatic Cholestasis (PFIC) and Effect of Biliary Diversion (NAPPED) consortium have shown that serum bile acid levels can predict long-term outcomes in patients with PFIC Type 1 and Type 2. These clinical observations, along with preclinical data demonstrating the adverse impact of elevated bile acids on the liver, provide support for the hypothesis that lowering serum bile acids may be of benefit in the long-term outcome of patients with cholestatic liver diseases including ALGS. By reducing the bile acid load, odevixibat has the potential not only to reduce the pruritus associated with chronic cholestasis, but also to ameliorate or slow hepatic injury or fibrosis and improve the long-term hepatic outcomes in patients with ALGS. The risk/benefit profile of odevixibat in patients with ALGS is considered acceptable

Study objective

Primary Objective:
To demonstrate the efficacy of repeated daily doses of 120 µg/kg/day odevixibat in relieving pruritus in patients with ALGS.

Secondary Objectives:
To assess the impact of odevixibat on serum bile acid levels in patients with ALGS.
To evaluate the safety and tolerability of odevixibat in patients with ALGS.

Study design

This is a Phase 3, double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of 120 µg/kg/day odevixibat in patients with ALGS.

Intervention

Patients will be randomized 2:1 to receive odevixibat 120 µg/kg/day or placebo.

Study burden and risks

See schedule of assessments on pages 23-26 of the protocol for more information.
Patient participation in this study will last approximately 36 weeks. During this period, the patient will visit the hospital at least 9 times. The screening visit and the treatment visits last 2 - 6 hours.
During these visits, the following tests and procedures will take place:
- physical examination is performed and questions are asked about medical history.
- weight, height, blood pressure, temperature and heart rate are measured
- blood and urine samples will be taken.
- The study doctor will also perform a pregnancy test on female subjects of childbearing age.
- Subjects are asked to keep an eDiary

Possible side effects that are already known are described in the IB and patient information letter.

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)

Inclusion criteria

1. A male or female patient (of any age) with genetically confirmed diagnosis of ALGS. A patient may be randomized based on genetic testing results in the medical record. If genetic testing results are not available, testing will be performed at Screening Visit 1, and the patient may not be randomized until the genetic diagnosis is confirmed
2. Patient must have a history of significant pruritus and a caregiver reported observed scratching or a patient-reported itching score at an average of >=2 (on 0 to 4 scale), as measured by the Albireo ObsRO instrument (for patients <18 years of age) or the PRO instrument (for patients >18 years of age) in the 14 days prior to randomization. For each AM and PM weekly assessment a minimum of 4 out of 7 expected scores must be recorded. The mean of the weekly AM and the mean of the weekly PM scores will be averaged to determine the pruritus score as measured by ObsRO or PRO, if the patient is >=18 years of age
3. Patient must have an elevated baseline serum bile acid level. Each of the serum bile acid levels obtained at Screening Visit 1 and Screening Visit 2 must be greater than the upper limit of normal (>ULN)
4. 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
5. Caregivers must be willing and able to use an eDiary device as required by the study and patients >=8 years of age must be willing to use an eDiary if able to do so
6. Sexually active males and females must agree to use a reliable contraceptive method with <=1% failure rate (such as hormonal contraception, intrauterine 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).

Exclusion criteria

1. 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) PFIC
c) Benign recurrent intrahepatic cholestasis
d) Suspected or proven liver cancer or metastasis to the liver on imaging studies
2. Patient with a past medical history or ongoing presence of any other disease or condition known to interfere with the absorption, distribution, metabolism (specifically bile acid metabolism), or excretion of drugs in the intestine, including but not limited to, inflammatory bowel disease
3. Patient with past medical history or ongoing chronic (i.e. >3 months) diarrhea requiring intravenous fluid or nutritional intervention for treatment of the diarrhea and/or its sequelae
4. Patient has a confirmed past diagnosis of infection with human immunodeficiency virus or other present and active, clinically significant chronic infection
5. Recent infection requiring hospitalization or treatment with parenteral anti-infective within 4 weeks of randomization (Study Day 1) or completion of oral anti-infective treatment within 2 weeks prior to start of Screening Period
6. Cancer within the last 5 years except for basal cell carcinoma
7. Cancer >5 years prior to screening except for non-liver cancers with no evidence of recurrence
8. Chronic kidney disease with an impaired renal function and a glomerular filtration rate <70 mL/min/1.73 m2
9. Patient with surgical history of disruption of the enterohepatic circulation (biliary diversion surgery) within 6 months prior to start of Screening Period
10. Patient has had a liver transplant or a liver transplant is planned within 6 months of randomization
11. Decompensated liver disease, history or presence of clinically significant ascites, variceal hemorrhage, and/or encephalopathy
12. INR >1.4 (the patient may be treated with Vitamin K intravenously, and if INR is <=1.4 at resampling the patient may be randomized)
13. Serum ALT >10 × ULN at Screening
14. Serum ALT >15 × ULN at any time point during the last 6 months unless an alternate etiology was confirmed for the elevation
15. Total bilirubin >15 × ULN at Screening
16. Patient suffers from uncontrolled, recalcitrant pruritic condition other than ALGS. Examples include, but not limited to, refractory atopic dermatitis or other primary pruritic skin diseases
17. Any patient who is pregnant or lactating or who is planning to become

pregnant within 24 weeks of randomization
18. Patient with a past medical history of alcohol or substance abuse. Patient must agree to refrain from illicit drug and alcohol use during the study
19. Administration of bile acid or lipid binding resins and medications that slow gastrointestinal motility
20. Patient has had investigational exposure to a drug, biologic agent, or medical device within 30 days prior to Screening, or 5 half-lives of the study agent, whichever is longer
21. Any other conditions or abnormalities which, in the opinion of the investigator 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
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):	16-12-2021
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	TBD
Generic name:	Odevixibat
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-12-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-06-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-08-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2020-004011-28-NL
ClinicalTrials.gov	NCT04674761
CCMO	NL75677.042.20