A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Odevixibat (A4250) in Children with Biliary Atresia Who Have Undergone a Kasai Hepatoportoenterostomy (BOLD)

Published: 28-04-2020
Last updated: 07-09-2024

This study has been transitioned to CTIS with ID 2024-512086-14-00 check the CTIS register for the current data. Primary Objective:The primary objective is to evaluate the efficacy of repeated once-daily doses of odevixibat versus placebo in...

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

Summary

ID

NL-OMON54084

Source
ToetsingOnline

Brief title
Albireo A4250-011 (BOLD) Study

Condition

- Hepatobiliary disorders congenital
- Bile duct disorders

Synonym
Biliary Atresia; Childhood disease of the liver

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Biliary Atresia, BOLD, Kasai Hepatoportoenterostomy, Odevixibat (A4250)

Outcome measures

Primary outcome

The primary efficacy endpoint is the time from randomization to first

occurrence of liver transplant, or death, during the 104-week treatment period.

Secondary outcome

• Proportion of patients who are alive and have not undergone a liver

transplant after 104 weeks.pharmacotherapeutic or procedural intervention such

as chronic diuretics or paracentesis.

• Time to onset of first sentinel event during the 104-week treatment period.

Sentinel events are defined in the protocol.

• Total bilirubin level after 13, 26, 52, and 104 weeks.

• Serum bile acid level after 13, 26, 52, and 104 weeks.

• Time to pediatric end-stage liver disease (PELD) score >=15.

• Safety parameters including AEs, SAEs, findings on physical examination,

laboratory assessments (including fat-soluble vitamins and lipids) and

abdominal ultrasound.

Study description

Background summary

There is no approved drug treatment for Biliary Atresia (BA) and the only available option is surgical Kasai Hepatoportoenterostomy (HPE). The chance of re-establishing bile flow strongly correlates with timing of the procedure. Even with a successful surgery that established drainage, children*s disease progressed and they developed portal fibrosis, cirrhosis, and portal hypertension. About half of the patients required a liver transplantation during the first 2 years of life. Approximately 80% of patients needed a transplant within the first 2 decades of life.There is clearly a need for new therapies to treat BA. Although Kasai HPE has become a lifesaver since its introduction, most patients with BA continue to experience gradual liver injury from excessive bile acids, and there are currently no approved treatments to limit this damage. Primarily, treatments are needed to prevent or reverse the damage to the bile ducts. However, therapies that directly target the cause of BA-associated liver damage, such as agents lowering bile acid levels, also have the potential to benefit patients. Liver damage in BA is characterized by rapid progression. By inhibiting the IBAT with high selectivity and potency, odevixibat may have the potential to relieve cholestasis and improve liver function in patients with BA. Early intervention is critical in slowing or preventing the complications of the disease. Therefore, the study aims to enroll patients as soon as possible after Kasai HPE (i.e. within 3 weeks).

Odevixibat has been tested in two Phase 3 studies in over 60 children with Progressive Familial Intrahepatic Cholestasis (PFIC). One study lasting for 6 months is completed, and one 72-week open-label study is ongoing. In the completed study, one patient stopped the study early due to an adverse event of diarrhea that was considered related to odevixibat. In the ongoing open-label study, three patients discontinued treatment due to adverse events of cholestasis (gallstones), acute pancreatitis (inflamed pancreas) and splenomegaly (enlarged spleen), hypophgia (decreased appetite), weight decrease and jaundice (yellowing of the skin). None of the events that led to treatment discontinuation were related to odevixibat. Odevixibat has also been tested in a 4-week Phase 2 study in 20 children with chronic liver disease and impaired bile flow and severe itch, including three patients with Biliary Atresia. No patients treated with odevixibat have died. In all studies described above, nine patients treated with odevixibat have been hospitalized. In all cases, the reason for hospitalization was unrelated to odevixibat.

Infants with BA have elevated serum bile acids. These levels remain high or continue to rise in patients with poor long-term outcomes but decrease over time in patients with better long-term outcomes. 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. Harpavat et

al. have shown that serum bile acid levels can predict long-term outcomes in patients with BA; 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. This clinical observation, along with the preclinical data demonstrating the adverse impact of elevated bile acids on the liver, provides support for the hypothesis that lowering serum bile acids may be of benefit in the long-term outcome of patients with BA. By reducing the bile acid load, odevixibat has the potential to ameliorate or slow hepatic injury or fibrosis and to improve the long-term outcomes of patients with BA. The risk/benefit profile of odevixibat in patients with BA is considered acceptable.

Study objective

This study has been transitioned to CTIS with ID 2024-512086-14-00 check the CTIS register for the current data.

Primary Objective:
The primary objective is to evaluate the efficacy of repeated once-daily doses of odevixibat versus placebo in children with biliary atresia (BA) post Kasai hepatoportoenterostomy(HPE) based native liver survival (NLS) of up to 104 weeks.

Secondary Objectives:
• To evaluate the effect of odevixibat compared to placebo on the time to onset of sentinel events.
• To evaluate the effect of odevixibat compared to placebo on total bilirubin after 13, 26, 52, and 104 weeks.
• To evaluate the effect of odevixibat compared to placebo on serum bile acids after 13, 26, 52, and 104 weeks.
• To assess the long-term safety and tolerability of repeated daily doses of odevixibat compared to placebo for 104 weeks in children with BA post. Kasai HPE

Exploratory Objectives
• To evaluate the effect of odevixibat compared to placebo on measures of overall hepatic health and function throughout the study treatment period
• To evaluate the effect of odevixibat compared to placebo on overall health of the patients throughout the study treatment period

Study design

This is a double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of odevixibat compared to placebo in children with BA who have undergone a Kasai HPE. The study includes a Screening Period of up to 3 weeks followed by a 104-week double-blind, placebo-controlled Treatment period.

Intervention

The study will consist of 2 parts, a Sentinel Cohort of up to 40 patients followed by the Primary Cohort. The Sentinel Cohort will consist of up to the first 40 patients and will be characterized by a different starting dose than the Primary Cohort, if dose escalation is recommended by the DMC. Initially, the first 20 patients will be randomized to odevixibat 40 µg/kg/day, or placebo in a ratio of 1:1. After one month of treatment, short-term safety will be assessed by the Medical Monitor and the Investigator to determine if the patient can dose escalate to 120 µg/kg/day. Patients randomized to placebo will remain on placebo.
After the initial 20 patients enrolled have received one month of therapy and the decision on dose escalation has been made for each individual patient, the cumulative data will be reviewed by the Data Monitoring Committee (DMC). If the DMC agrees that short-term safety has been demonstrated, subsequent patients randomized into the active treatment arm will receive 120 µg/kg/day of odevixibat as their initial dose and enrollment into the Primary Cohort will begin. If the DMC does not agree to increase the initial dose of the active treatment arm to 120 µg/kg/day, enrollment into the Sentinel Cohort will continue for another 20 patients.
Randomization will be stratified by age of the infant at the time of the Kasai HPE (<30 days, 30 to 60 days, and >60 to <=90 days) and by the presence or absence of splenic malformation syndrome. A patient may be dose-reduced due to adverse events (AEs) as per individual patient safety monitoring guidelines

Study burden and risks

Study subject*s participation will last about 2 years and contains a screening period of up to 3 weeks, a treatment period of 2 years, and a 4-week follow-up period. Study subject will need to come to the study center at least 11 times over this period. There will also be an additional follow-up telephone call near study completion. Subjects are expected to undergo procedures/assessments as described in the section 8.1.4. of the protocol, which include: Physical exam, vital signs, growth parameters, demographics and medical/surgical history, abdominal ultrasound, neurocognitive tests, blood and urine tests (including optional testing for Gilbert*s syndrome) and collection of stool samples.

Odevixibat has been tested in two Phase 3 studies in over 60 children with Progressive Familial Intrahepatic Cholestasis (PFIC). One study lasting for 6 months is completed, and one 72-week open-label study is ongoing. In the completed study, one patient stopped the study early due to an adverse event of diarrhea that was considered related to odevixibat. In the ongoing open-label study, three patients discontinued treatment due to adverse events of cholestasis (gallstones), acute pancreatitis (inflamed pancreas) and splenomegaly (enlarged spleen), hypophgia (decreased appetite), weight decrease

and jaundice (yellowing of the skin). None of the events that led to treatment discontinuation were related to odevixibat. Odevixibat has also been tested in a 4-week Phase 2 study in 20 children with chronic liver disease and impaired bile flow and severe itch, including three patients with Biliary Atresia. No patients treated with odevixibat have died. In all studies described above, nine patients treated with odevixibat have been hospitalized. In all cases, the reason for hospitalization was unrelated to odevixibat. The most common adverse effects considered related to odevixibat seen in children are listed below (of note these adverse effects were seen in patients with PFIC that participated in the Phase 3 studies).

The most common related adverse effects seen in research studies with odevixibat are listed below.
Very common (may affect more than 1 in 10 people):
• Blood bilirubin increased (an orange-yellow pigment formed in the liver by the breakdown of hemoglobin and excreted in bile) (14%)
Common (may affect up to 1 in 10 people):
• Alanine aminotransferase (ALT) increased (a substance produced by the liver that can be measured with a blood test) (10%)
• Aspartate aminotransferase (AST) increased (a substance produced by the liver that can be measured with a blood test) (6%)
• Diarrhea (6%)
• Pruritis (itchiness) (3%)
• International normalized ratio (INR) increased (test to see how well your blood clots and can be related to Vitamin K levels or function of the liver) (3%)
• Hepatic enzyme increased (a substance produced by the liver that can be measured with a blood test) (3%)
• Blood creatine phosphokinase increased (3%)
• Abdominal (stomach) pain (3%)

The adverse effects considered related to odevixibat seen in healthy adult volunteers in Albireo sponsored trials are listed below:
Very common (may affect more than 1 in 10 people):
• Diarrhea (45%)
• Abdominal (stomach) pain (29%)
Common (may affect up to 1 in 10 people):
• Upper abdominal (stomach) pain (10%)
• Nausea (Feeling like you might vomit) (9%)
• Headache (6%)
• Abdominal discomfort (discomfort in the stomach) (5%)
• Lower abdominal pain (pain in the lower part of the stomach) (3%)
• Abdominal distension (swollen belly) (2%)
• Constipation (difficulty passing stools) (2%)
• Dyspepsia (indigestion or upset stomach) (2%)
• Vomiting (2%)
• Anorectal discomfort (slight pain in rectum and/or anus) (2%)

• Feces discoloured (stool color different than usual) (2%)
• Feces soft (stool softer than usual) (2%)
• Feeling hot (2%)
• Decreased appetite (2%)
• Dizziness (2%)

RISKS RELATED TO STUDY PROCEDURES:
Placebo risk: Some participants in this study will receive a placebo. Taking a placebo is the same as not taking any active medicine. Study participant*s symptoms of BA may get worse, stay the same, or improve, just as it may do if he/she does not participate in the study.
Blood draws: A blood draw may cause faintness, inflammation of the vein, pain, bruising, swelling, or bleeding at the site of puncture. There is also a slight risk of infection. In very rare cases, there is a risk of blood clot or nerve injury after blood draw. Fasting: Fasting could cause dizziness, headache, stomach discomfort, or fainting.

There is no approved drug treatment for Biliary Atresia (BA) and the only available option is surgical Kasai Hepatoportoenterostomy (HPE). The chance of re-establishing bile flow strongly correlates with timing of the procedure. Even with a successful surgery that established drainage, children*s disease progressed and they developed portal fibrosis, cirrhosis, and portal hypertension. About half of the patients required a liver transplantation during the first 2 years of life. Approximately 80% of patients needed a transplant within the first 2 decades of life.There is clearly a need for new therapies to treat BA. Although Kasai HPE has become a lifesaver since its introduction, most patients with BA continue to experience gradual liver injury from excessive bile acids, and there are currently no approved treatments to limit this damage. Primarily, treatments are needed to prevent or reverse the damage to the bile ducts. However, therapies that directly target the cause of BA-associated liver damage, such as agents lowering bile acid levels, also have the potential to benefit patients. Liver damage in BA is characterized by rapid progression. By inhibiting the IBAT with high selectivity and potency, odevixibat may have the potential to relieve cholestasis and improve liver function in patients with BA. Early intervention is critical in slowing or preventing the complications of the disease. Therefore, the study aims to enroll patients as soon as possible after Kasai HPE (i.e. within 3 weeks).

Infants with BA have elevated serum bile acids. These levels remain high or continue to rise in patients with poor long-term outcomes but decrease over time in patients with better long-term outcomes. 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. Harpavat et al. have shown that serum bile acid levels can predict long-term outcomes in patients with BA; 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. This clinical observation, along with the preclinical data demonstrating the adverse impact of elevated bile acids on the liver, provides support for the hypothesis that lowering serum bile acids may be of benefit in the long-term outcome of patients with BA. By reducing the bile acid load, odevixibat has the potential to ameliorate or slow hepatic injury or fibrosis and to improve the long-term outcomes of patients with BA. The risk/benefit profile of odevixibat in patients with BA is considered acceptable.

Contacts

Public
Albireo AB

Arvid Wallgrens backe 20
Goteborg 413 46
SE
Scientific
Albireo AB

Arvid Wallgrens backe 20
Goteborg 413 46
SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. A male or female patient with a clinical diagnosis of BA
2. Age at Kasai HPE <=90 days

3. Eligible to start treatment within 3 weeks post-Kasai HPE

Exclusion criteria

• Patients with intractable ascites
• Ileal resection surgery
• ALT >=10× upper limit of normal (ULN) at Screening
• Patient reliant on total parenteral nutrition, or not able to take study drug orally, at randomization
• Acute ascending cholangitis (patients may be randomized after resolution of acute ascending cholangitis)
• Choledochal cystic disease
• INR >1.6 (the patient may be treated with Vitamin K intravenously, and if INR is <=1.6 at resampling the patient may be randomized)
• Patient has had exposure to an investigational drug or biologic agent within 30 days prior to randomization, or 10 half-lives of the study drug, whichever is longer
• Any other conditions or abnormalities, including congenital abnormalities, major cardiac surgery, hepatic, biliary, or GI disease which, in the opinion of the Investigator or Medical Monitor, may compromise the safety of the patient, the integrity of study results, or patient compliance with study requirements
• Weight < 3.5kg at randomization
• Known hypersensitivity to odevixibat or any component of the drug formulation

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: Recruiting

Start date (anticipated):	10-03-2021
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	TBD
Generic name:	odevixibat

Ethics review

Approved WMO Date:	28-04-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-12-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-02-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-03-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-06-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	02-08-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-12-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-12-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-09-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-04-2024
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
EU-CTR	CTIS2024-512086-14-00
EudraCT	EUCTR2019-003807-37-NL
ClinicalTrials.gov	NCT04336722
CCMO	NL73245.042.20