Health Technology Briefing
April 2022

Odevixibat for cholestatic liver disease in Alagille syndrome patients

Company/Developer | Albireo Pharma Inc

☐ New Active Substance  ☑ Significant Licence Extension (SLE)

NIHRIO ID: 30949  NICE ID: 10643  UKPS ID: Not available

Licensing and Market Availability Plans
Currently in phase III clinical development.

Summary

Odevixibat is currently in clinical development for the treatment of cholestatic liver disease in Alagille syndrome (ALGS) patients. ALGS is an inherited developmental disorder, caused by a mutation in the JAGGED1 gene or in the NOTCH2 gene. The mutation causes problems with early embryonic development leading to abnormalities in various parts of the body. ALGS is a rare multisystem disorder with a wide variety of clinical manifestations affecting the liver, heart, skeleton, eyes, central nervous system, kidneys, and facial features. Most patients with this disorder have liver abnormalities resulting from having too few bile ducts as well as other physiological indicators such as a small chin or deep-set eyes. Due to the reduced number of ducts, bile acids build up in the liver and damage the liver tissue as well as causing severe itching which can significantly limit quality of life and sleep. ALGS is a long-term debilitating and life-threatening disease that has no approved treatments, and many patients require liver transplants before adulthood.

Odevixibat is an orally administered intervention to decrease the reabsorption of bile acids. Through this inhibition, odevixibat is expected to decrease damage to the liver cells and improve the debilitating pruritus, therefore providing a better quality of life for individuals with ALGS. If licenced, odevixibat will provide a novel treatment option for patients with ALGS that have cholestatic liver disease.
## Proposed Indication

For the treatment of patients with Alagille syndrome (ALGS).¹²

## Technology

### Description

Odevixibat (Bylvay, A4250) is an ileal sodium/bile acid cotransporter (IBAT) inhibitor.³ Odevixibat acts locally in the distal ileum to decrease the reuptake of bile acids and increase the clearance of bile acids through the colon, reducing the concentration of bile acids in the serum.⁴ It exhibits therapeutic intervention by checking the transport of bile acids.⁵

Odevixibat is currently in phase III clinical development for the treatment of patients with ALGS. In these trials, odevixibat is administered orally once daily for 24 weeks (NCT04674761, ASSERT) and once daily for 72 weeks (NCT05035030, ASSERT-EXT).¹²

## Key Innovation

The management of ALGS depends on the clinical manifestations and there are currently no treatments licensed directly for the treatment of ALGS liver disease.⁶ Research has shown odevixibat has the potential to decrease the damage in the liver cells. In a phase 2 study (NCT02630875), the mean baseline serum bile acid levels were reduced in the majority of the patients. All patients completed the study, and no serious adverse events were treatment related; most adverse events, including increased transaminases, were transient.⁷

In studies for other indications, odevixibat showed a reduction in serum bile acids and pruritus in most patients and exhibited a favourable overall tolerability profile.⁵ If approved, odevixibat would offer the first available treatment option for ALGS patients.

## Regulatory & Development Status

Odevixibat has Marketing Authorisation in the EU/UK for progressive familial intrahepatic cholestasis (PFIC) in patients 6 months or older.⁴ The EMA marketing authorisation for PFIC was granted on July 2021 and MHRA approval was granted on Sept 2021.⁸

Odevixibat also has FDA approval for the treatment of pruritus in patients aged 3 months or older with PFIC, granted July 2021.⁹

Odevixibat is currently in phase III clinical development for the treatment of biliary atresia.¹⁰

## Patient Group

### Disease Area and Clinical Need

ALGS is a rare autosomal dominant, multisystem disorder typically manifesting as cholestasis, and potentially leading to end-stage liver disease and death.¹¹ ALGS is a disorder that can have a wide range of clinical variability and this variability is visible even in individuals from the same family.¹² ALGS is
attributable to a mutation or deletion in one of two genes that are associated with the NOTCH signalling pathways. The majority of individuals with ALGS have a mutation in the JAGGED1 gene and the NOTCH2 gene is affected in a small minority of people with ALGS.\textsuperscript{11,13} ALGS can manifest in neonates through prolonged jaundice due to conjugated hyperbilirubinemia, and/or cardiac signs and symptoms.\textsuperscript{14} Other major manifestations of ALGS include bile duct paucity on liver biopsy, cholestasis, butterfly vertebrae, ophthalmologic abnormalities, and characteristic facial features such as prominent forehead, deep-set eyes and a small chin.\textsuperscript{12,13} Approximately 95% of patients with ALGS present with chronic cholestasis, usually within the first 3 months of life.\textsuperscript{14} Laboratory evaluation of these patients revealed elevated serum bile acids, elevated liver function tests (LFTs), and conjugated hyperbilirubinemia. Associated symptoms include xanthomas, growth failure, and pruritus.\textsuperscript{11}

ALGS affects approximately one in every 30,000 live births in the UK.\textsuperscript{13} The 2020-21 Hospital Episodes Statistics for England recorded a total of 86 finished consultant episodes (FCE) for congenital malformations of the liver (ICD 10, code Q44.7), resulting in 64 hospital admissions, 622 FCE bed days and 26 day cases.\textsuperscript{15}

### Recommended Treatment Options

Liver transplantation is the current treatment option available for patients with ALGS.\textsuperscript{16} There are no authorised pharmacologic treatments in the EU or Great Britain for ALGS.\textsuperscript{17}

### Clinical Trial Information

| Trial | NCT04674761, ASSERT; A Phase 3 Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of Odevixibat (A4250) in Patients With Alagille Syndrome  
Phase III – Active, not recruiting  
Location(s): 6 EU countries, UK, USA, Canada, and other countries  
Primary completion date: June 2022  
Study ID: A4250-012 |
| --- | --- |
| N= 52; Child and adult subjects with genetically confirmed diagnosis of ALGS and a history of significant pruritus | Odevixibat administered orally once daily for 24 weeks  
Comparator(s): Placebo orally administered once daily 24 weeks  
Outcome(s): Primary outcome measure: |
| NCT05035030, ASSERT-EXT; An Open Label Study to Evaluate the Long-term Safety and Efficacy of Odevixibat (A4250) in Patients With Alagille Syndrome  
Phase III – Enrolling by invitation  
Location(s): 6 EU countries, UK, USA, Canada, and other countries  
Primary completion date: October 2023  
Study ID: A4250-015 |
| N= 52 (estimated); Child and adult subjects who have completed of the 24-week Treatment Period of Study A4250-012 | Odevixibat administered orally once daily for 72 weeks  
Comparator(s): No comparator  
Outcome(s): Primary outcome measure: |
### Change from baseline in scratching score [Time frame: from baseline to week 24]

See trial record for full list of all outcomes

### Change in pruritus [Time frame: baseline to week 72]

See trial record for full list of all outcomes

### Results (efficacy)

- 

### Results (safety)

- 

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### Trial

**Trial ID:** NCT02630875; An Exploratory Phase II Study to Demonstrate the Safety and Efficacy of A4250 in Children With Cholestatic Pruritus

**Phase:** II – Completed

**Location(s):** 4 EU countries and UK

**Study completion date:** March 2017

### Trial Design

Non-randomised, open label, single group assignment

### Population

N= 24 (actual); Subjects with a diagnosis of pruritus due to chronic cholestasis based on history and investigator judgment. This will include but will not be restricted to patients with PFIC, ALGS, Biliary Atresia and Sclerosing Cholangitis

### Intervention(s)

Odevixibat administered in 6 different doses

### Comparator(s)

- 

### Outcome(s)

**Primary outcome measure:**

- Adverse events evaluation [Time frame: 4 weeks]

See trial record for full list of all outcomes

### Results (efficacy)

- 

### Results (safety)

- 

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### Estimated Cost

The list price of odevixibat for PFIC is: 18

- 200mcg: £2,620 ex-VAT
- 400mcg: £5,240 ex-VAT
- 600mcg: £7,860 ex-VAT
- 1200mcg: £15,720 ex-VAT

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### Relevant Guidance

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### NICE Guidance

No guidance available

### NHS England (Policy/Commissioning) Guidance


### Other Guidance


### Additional Information


**NB:** This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.