Health Technology Briefing
January 2024

Odevixibat for treating biliary atresia in children following Kasai hepatoportoenterostomy

Company/Developer	Ipsen Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29875	NICE ID: Not Available	UKPS ID: 670913

Licensing and Market Availability Plans

Currently in phase III trials.[1,2]

Summary

Odevixibat is in clinical development for the treatment of children with biliary atresia (BA) following a Kasai hepatoportoenterostomy (HPE). BA is a rare gastrointestinal disorder where either all or a portion of the bile duct on the outside of the liver is absent or destroyed. As a result, bile acids accumulate in the liver causing liver damage. The only currently available treatment option for BA is a Kasai HPE procedure where a surgeon replaces the damaged bile ducts with a portion of the patients small intestine, enabling bile to flow from the liver to the intestine. Although this procedure is typically successful most patients still require a liver transplant later in childhood.

Odevixibat is an orally administered medicinal product which blocks the action of ileal bile acid transporters (IBAT), a protein which transports bile acid from the small intestine back into the liver. Therefore, by blocking IBAT, odevixibat can reduce the build-up of bile acids in the liver and increase the loss of bile through the digestive system, thus limiting damage to the liver. Odevixibat will offer a novel treatment for patients with BA following a Kasai HPE, with the potential to reduce the build-up of bile acids and associated liver damage therefore delaying the need for liver transplantation in childhood.

Proposed Indication

Treatment of biliary atresia (BA) in paediatric patients who have previously undergone a Kasai hepatoportoenterostomy (HPE) procedure.[1]

Technology

Description

Odevixibat (Bylvay, A4250) is a selective inhibitor of the ileal bile acid transporter (IBAT).[3] IBAT is a protein found in the intestine which transports bile acid from the small intestine for circulation back into the liver.[4,5] Odevixibat inhibits absorption of bile acids via IBAT therefore reducing the amount of bile acids being directed to the liver and increasing their excretion from the body through the colon.[5] As a result the amount of bile acid build-up in the liver is reduced and associated liver damaged is limited.[3,4]

Odevixibat is currently in phase III clinical development for the treatment of paediatric patients with BA following a Kasai HPE procedure. In these trials, odevixibat is administered orally once daily for 104 weeks (NCT04336722, BOLD and NCT05426733, BOLD-EXT).[1,2]

Key Innovation

For patients with BA, treatment focus includes restoring bile flow, improving long-term survival of the native liver and management of symptoms.[6] Currently, there are no pharmacologic therapies available for BA and the main treatment option is to carry out a Kasai HPE; a procedure involving the removal of the damaged bile ducts outside the liver.[6-8] The aim of this surgery is to limit or delay the need for liver transplantation as BA is the leading cause of liver transplantation in childhood.[9,10] One study showed that only 23% of children had 20 year survival with their native liver.[11] Other medicines such as glucocorticoids, ursodeoxycholic acid and cholestyramine can be used off-label in BA to promote bile flow however, evidence of efficacy is limited.[12] This demonstrates an unmet need for improved pharmacological interventions to reduce liver damage associated with BA thus reducing the need for liver transplantation.[10]

Odevixibat has been shown to reduce bile acids in the blood by around 50% in patients with BA whilst also reducing pruritus (itch), a common symptom of cholestatic liver diseases. There were also no serious adverse events experiences in patients with BA when treated with odevixibat.[13] Therefore, if licensed, odevixibat will offer a novel treatment for patients with BA following a Kasai HPE.[10,12,13]

Regulatory & Development Status

Odevixibat has Marketing Authorisation in the UK for the treatment of progressive familial intrahepatic cholestasis (PFIC) in adult patients.[3]

Odevixibat was granted an orphan drug designation in the EU in 2018 for BA.[14] Odevixibat was also granted an FDA orphan drug designation in 2019 for BA.[15]

Patient Group

Disease Area and Clinical Need

BA is a rare gastrointestinal disorder characterised by destruction or absence of all or a portion of the bile duct that lies outside the liver (extrahepatic bile duct). The bile duct is a tube that allows the passage of bile from the liver into the gall bladder and, eventually, the small intestine. Bile is a liquid secreted by the liver that plays an essential role in carrying waste products from the liver and promoting absorption of fats and vitamins by the intestines. In BA, absence or destruction of the bile ducts results in the abnormal accumulation of bile in the liver. Affected infants have yellowing of the skin and whites of the eyes (jaundice) and scarring of the liver (fibrosis). In some cases, additional abnormalities may be present, including heart defects and intestinal, spleen and kidney malformations. The exact cause of BA is unknown, but several factors contribute to the development of the disorder, including immunologic, infectious/toxic, and genetic factors. Although the bile ducts may be normal at birth, one or more of these factors initiate epithelial damage (independently or with the help of an activated immune system) and trigger rapid production of fibrous tissue (sclerosis) causing an obstruction of bile ducts. Several viruses, including cytomegalovirus, reovirus type 3 and rotavirus infections are being studied as possible causative agents. A minority of cases may be caused by defects during the development (morphogenesis) of the liver and biliary tree during pregnancy. Some of these cases may be diagnosed during gestation by a prenatal ultrasound that shows a cyst in the biliary system.[16]

The incidence of BA in the UK was calculated to be 1 in 16,700 births in 1999.[17] In 2006, the incidence of BA was estimated at 1 in 17,049 births in England and Wales.[18] In England, 2022-23 there were 360 finished consultant episodes (FCE) and 331 admissions for atresia of the bile ducts (ICD-10 Code Q44.2) which resulted in 1,725 FCE bed days and 152 day cases.[19]

Recommended Treatment Options

There are currently no National Institute for Health and Care Excellence (NICE) recommended treatment options for BA. The main treatment option is for patients to undergo a Kasai HPE; a procedure involving the removal of the damaged bile ducts outside the liver.[6-8] Medicines such as glucocorticoids, ursodeoxycholic acid and cholestyramine can be used off-label to promote bile flow.[12] Whilst antibiotics are often given to limit the risk of cholangitis following surgery.[7,12]

Clinical Trial Information

Trial	**BOLD**, NCT04336722, EudraCT-2019-003807-37; 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 **Phase III –** Recruiting **Locations:** Eight EU countries, UK, USA, Canada and other countries **Primary completion date:** June 2026	**BOLD-EXT**, NCT05426733; An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of Odevixibat (A4250) in Children With Biliary Atresia (BOLD-EXT) **Phase III –** Enrolling by invitation **Locations:** Six EU countries, USA, Canada and other countries **Primary completion date:** December 2024
Trial Design	Randomised, parallel assignment, double-blind, placebo-controlled	Open label, single group assignment
Population	N=245 (estimated); subjects with clinically diagnosed biliary atresia who were aged 90 days or less when	N=180 (estimated); subjects who completed the 104 week treatment

	undergoing Kasai Hepatoportoenterostomy; aged up to 111 days	period of BOLD trial; aged 1 year to 18 years
Intervention(s)	Oral Odevixibat capsules once daily	Oral Odevixibat capsules once daily
Comparator(s)	Matched placebo	No comparator
Outcome(s)	**Primary outcome:** Proportion of patients who are alive and have not undergone a liver transplant after 104 weeks of study treatment.	**Primary outcome:** Proportion of patients who are alive and have not undergone a liver transplant
Results (efficacy)	-	-
Results (safety)	-	-

Estimated Cost

Odevixibat is already marketed in the UK for the treatment of progressive familial intrahepatic cholestasis; Odevixibat is available as a pack of 30 capsules. The cost per pack of 200 microgram capsules is £3,085, per pack of 400 microgram capsules is £6,170, per pack of 600 microgram capsules is £9,255 and per pack of 1,200 microgram capsules is £18,510. The company has a commercial arrangement. This makes odevixibat available to the NHS with a discount.[5,20]

Relevant Guidance

NICE Guidance

No relevant guidance identified

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract Specialist Liver Disease Service (Children) E03/S(HSS)/d

Other Guidance

- National Institute of Diabetes and Digestive and Kidney Diseases. Treatment for Biliary Atresia. 2017.[7]
- Childrens Liver Disease Foundation. Biliary Atresia. 2019.[21]
- D A Kelly and M Davenport. Current management of biliary atresia. 2007[22]

Additional Information

References

1 clinicaltrials.gov. *Efficacy and Safety of Odevixibat in Children With Biliary Atresia Who Have Undergone a Kasai HPE (BOLD)*. *Trial ID: NCT04336722*. Status: Recruiting. Available from: https://clinicaltrials.gov/study/NCT04336722 [Accessed 7 November 2023].

2 clinicaltrials.gov. *An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of Odevixibat in Children With Biliary Atresia (BOLD-EXT)*. *Trial ID: NCT05426733*. 2022. Status: Enrolling by invitation. Available from: https://clinicaltrials.gov/study/NCT05426733 [Accessed 10 October 2023].

3 National Institute for Health and Care Excellence (NICE). *Odevixibat*. Available from: https://bnf.nice.org.uk/drugs/odevixibat/ [Accessed 10 October 2023].

4 European Medicines Agency (EMA). *Bylvay*. 2021. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/bylvay [Accessed 10 October 2023].

5 National Institute for Health and Care Excellence (NICE). *Odevixibat for treating progressive familial intrahepatic cholestasis*. 2022. Available from: https://www.nice.org.uk/guidance/hst17 [Accessed 9 October 2023].

6 Karpen SJ, Kelly D, Mack C, Stein P. Ileal bile acid transporter inhibition as an anticholestatic therapeutic target in biliary atresia and other cholestatic disorders. *Hepatol Int*. 2020;14(5):677-89. Available from: https://doi.org/10.1007/s12072-020-10070-w.

7 National Institute of Diabetes and Digestive and Kidney Diseases. *Treatment for Biliary Atresia*. 2017. Available from: https://www.niddk.nih.gov/health-information/liver-disease/biliary-atresia/treatment [Accessed 9 October 2023].

8 Patient. *Biliary Atresia*. 2022. Available from: https://patient.info/doctor/biliary-atresia [Accessed 16 October 2023].

9 Wildhaber BE. Biliary atresia: 50 years after the first kasai. *ISRN Surg*. 2012;2012:132089. Available from: https://doi.org/10.5402/2012/132089.

10 Laue T, Baumann U. Odevixibat: an investigational inhibitor of the ileal bile acid transporter (IBAT) for the treatment of biliary atresia. *Expert Opin Investig Drugs*. 2022;31(11):1143-50. Available from: https://doi.org/10.1080/13543784.2022.2151890.

11 Lykavieris P, Chardot C, Sokhn M, Gauthier F, Valayer J, Bernard O. Outcome in adulthood of biliary atresia: a study of 63 patients who survived for over 20 years with their native liver. *Hepatology (Baltimore, Md)*. 2005;41(2):366-71. Available from: https://doi.org/10.1002/hep.20547.

12 Fligor SC, Hirsch TI, Tsikis ST, Adeola A, Puder M. Current and emerging adjuvant therapies in biliary atresia. *Front Pediatr*. 2022;10:1007813. Available from: https://doi.org/10.3389/fped.2022.1007813.

13 Baumann U, Sturm E, Lacaille F, Gonzalès E, Arnell H, Fischler B, et al. Effects of odevixibat on pruritus and bile acids in children with cholestatic liver disease: Phase 2 study. *Clinics and Research in Hepatology and Gastroenterology*. 2021;45(5):101751. Available from: https://doi.org/10.1016/j.clinre.2021.101751.

14 European Medicines Agency (EMA). *EU/3/18/2103: Orphan designation for the treatment of biliary atresia*. 2018. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3182103 [Accessed 23 October 2023].

15 U.S. Food and Drug Administration (FDA). *Search Orphan Drug Designations and Approvals*. 2019. Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=658118 [Accessed 23 October 2023].

16 National Organization for Rare Disorders (NORD). *Biliary Atresia*. 1986. Available from: https://rarediseases.org/rare-diseases/extrahepatic-biliary-atresia/ [Accessed 16 October 2023].

17 McKiernan PJ, Baker AJ, Kelly DA. The frequency and outcome of biliary atresia in the UK and Ireland. *The Lancet*. 2000;355(9197):25-9. Available from: https://doi.org/10.1016/S0140-6736(99)03492-3.

18 Livesey E, Borja MC, Sharif K, Alizai N, McClean P, Kelly D, et al. Epidemiology of biliary atresia in England and Wales (1999–2006). *Archives of Disease in Childhood - Fetal and Neonatal Edition*. 2009;94(6):F451. Available from: https://doi.org/10.1136/adc.2009.159780.

19 National Health Service (NHS). *Hospital Admitted Care Activity, 2022-23: Diagnosis* 2023. Available from: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2F34%2FC4E943%2Fhosp-epis-stat-admi-diag-2022-23-tab.xlsx&wdOrigin=BROWSELINK.

20 National Institute for Health and Care Excellence (NICE). *Odevixibat Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/odevixibat/medicinal-forms/ [Accessed 23 October 2023].

21 Childrens Liver Disease Foundation. *Biliary Atresia A Guide*. 2019. Available from: https://childliverdisease.org/wp-content/uploads/2019/07/Biliary-Atresia.pdf [Accessed 13 November 2023].

22 Kelly DA, Davenport M. Current management of biliary atresia. *Archives of disease in childhood*. 2007;92(12):1132-5. Available from: https://doi.org/10.1136/adc.2006.101451.

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