16 July 2021
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment report

Bylvay (Odevixibat)
Treatment of progressive familial intrahepatic cholestasis
EU/3/12/1028

Sponsor: Albireo AB

Note
Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	(2S)-2-{[(2R)-2-[({[3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro- 1,2,5-benzothiadiazepin-8-yl]oxy}acetyl)amino]-2-(4-hydroxyphenyl)acetyl]amino}butanoic acid
Other name(s)	Bylvay
International Non-Proprietary Name	Odevixibat
Tradename	Bylvay
orphan condition	Treatment of progressive familial intrahepatic cholestasis
Sponsor's details:	Albireo AB Arvid Wallgrens Backe 20 Goteborgs Annedal 413 46 Goteborg Vastra Gotalands Lan Sweden
Orphan medicinal product designation procedural history	
Sponsor/applicant	Albireo AB
COMP opinion	13 June 2012
EC decision	17 July 2012
EC registration number	EU/3/12/1028
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johann Lodewijk Hillege / Jayne Crowe
Applicant	Albireo AB
Application submission	06 November 2020
Procedure start	26 November 2020
Procedure number	EMA/H/C/004691
Invented name	Bylvay
Proposed therapeutic indication	Bylvay is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older Further information on Bylvay can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Bylvay
CHMP opinion	20 May 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Olimpia Neagu
Sponsor's report submission	30 November 2020
COMP discussion and adoption of list of questions	13-15 April 2021
Oral explanation	N/A
COMP opinion (adoption via written procedure)	21 May 2021

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2012 designation was based on the following grounds:

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- Progressive familial intrahepatic cholestasis (hereinafter referred to as "the condition") was estimated to be affecting not more than 0.2 in 10,000 persons in the European Union, at the time the application was made; the sponsor has based this on a literature search; this is not more than 5 in 10,000 persons as established in Article 3(1) (a) of Regulation (EC) 141/2000;
- the condition is chronically debilitating due to symptoms which develop early, median time at onset of symptoms being 2 months with 78% of patients developing jaundice. The natural history and complications of hepatic dysfunction (portal hypertension, liver failure, cirrhosis, hepatocellular carcinoma) are associated with the condition. Portal hypertension can develop. The condition is life-threatening due to death secondary to complications of end-stage liver disease. In general, without treatment, PFIC will lead to cirrhosis by age 10-20 years, and frequently even earlier. The survival in those not coming to surgery is 50% at the age of 10 and almost none at the age of 20 years;
- there is, at present, no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

The COMP recommends the designation of this medicinal product, containing (2S)-2-{[(2R)-2-[({[3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro- 1,2,5-benzothiadiazepin-8-yl]oxy}acetyl)amino]-2-(4-hydroxyphenyl)acetyl]amino}butanoic acid, as an orphan medicinal product for the orphan indication: treatment of progressive familial intrahepatic cholestasis.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor is proposing that progressive familial intrahepatic cholestasis continues to be an orphan condition.

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of rare autosomal recessive liver disorders of childhood characterized by mutations in genes encoding proteins involved in the hepatocellular transport system.

Three main subtypes of PFIC (PFIC1, PFIC2, PFIC3) have been identified.

- PFIC1, also known as Byler's disease, is caused by mutations in the *ATPase phospholipid transporting 8B1* gene (*ATP8B1*), located on chromosome 18, which encodes a phospholipid transporting transmembrane P-type adenosine triphosphatase known as FIC1. This 'flippase' is involved in maintaining an asymmetric distribution of phospholipids across the canalicular membrane bilayer of hepatocytes, thereby protecting the canalicular membrane from hydrophobic bile acids and maintaining its integrity.
- PFIC2 is caused by mutations in the *ATP binding cassette subfamily B member11 gene* (*ABCB11*), located on chromosome 2, which encodes the bile salt export pump (BSEP), the main transporter of bile acids from hepatocytes to the canalicular lumen.
- PFIC3 is caused by mutations in the *ATP binding cassette subfamily B member 4* gene (*ABCB4*), located on chromosome 7, which encodes multidrug-resistance protein 3 (MDR3/ABCB4); this protein transports phospholipids into the canalicular lumen to neutralize bile salts and prevent injury to biliary epithelia and bile canaliculi.

In addition, at least 3 other subtypes have been described in the literature (PFIC4-6).

The main clinical features of PFIC include cholestasis, jaundice and pruritus, with symptoms typically appearing in infancy or early childhood. PFIC is associated with a range of potentially fatal complications of the liver, including portal hypertension, liver failure, cirrhosis and hepatocellular carcinoma (HCC; PFIC2), as well as extrahepatic manifestations (PFIC1). The biochemical features of PFIC1 and PFIC2 are low levels of γ-glutamyl transferase (GGT) with elevated serum bile acid and decreased primary bile acid concentrations, while PFIC3 is associated with high levels of GGT. Historically, diagnosis of PFIC has been based on a combination of clinical and laboratory or biochemical approaches but, more recently, genetic testing has become available (Clinics and Research in Hepatology and Gastroenterology (2019) **43**, 20—36).

The COMP continues to designate this condition as an orphan condition.

The current proposed therapeutic indication "*Bylvay is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older (see sections 4.4 and 5.1).*" falls within the scope of the designated orphan condition "Treatment of progressive familial intrahepatic cholestasis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by a positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

Symptoms of the disease develop early, median time of onset of symptoms being 2 months and 78% of PFIC patients develop jaundice. Icterus (itching) is often seriously debilitating and could lead to auto-mutilation of the skin, irritability and sleeplessness. Several complications of hepatic dysfunction (portal hypertension, liver failure, cirrhosis) and hepatocellular carcinoma are associated with the condition. Due to malabsorption of fat and in fat soluble vitamins, young patients commonly show signs of "failure to thrive".

PFIC can lead to death secondary to complications of end-stage liver disease. In general, without treatment, PFIC 1 and 3 will lead to end-stage liver disease by age 10-20 years, and even earlier in PFIC 2. The survival in those not coming to surgery is 50% at the age of 10 and almost none at the age of 20 years. The rates of liver transplant (LT) for patients with PFIC1 and PFIC2 (40—100%)

suggest that the highest reported mortality figure (87%) is probably most representative of the natural history of untreated PFIC.

Reasons for death included infections, bleeding (cerebral, gastrointestinal, splenic), liver failure, liver transplant-related complications, hepatocellular carcinoma, and complications secondary to cholestasis, including acute infections, dehydration and gastrointestinal bleeding (Clinics and Research in Hepatology and Gastroenterology (2019) **43**, 20—36).

Number of people affected or at risk

The sponsor has provided an updated bibliographical search and used 5 publications for the purpose of establishing a prevalence estimate. The table below summarises four of the key publications. The fifth is a recent review publication by Baker et al from 2019.

Reference	**Country**	**Key findings**
Henriksen, 1981	Norway	The incidence of intrahepatic cholestasis between 1955 and 1974 was 1/18,000 live births.
Nielsen, 2004	Greenland	46 cases of PFIC were identified during a 60-year observation period, mostly from related subjects. Incidence and prevalence were not described.
Fischler, 2001	Sweden	12.9% of cases of intrahepatic cholestasis were diagnosed as PFIC
Ruth, 2014	World-wide	9.0% of cases of intrahepatic cholestasis were diagnosed as PFIC

Two publications reported population-level epidemiology data for PFIC (Henriksen, 1981; Nielsen, 2004). A retrospective study assessed 124 infants admitted to hospitals in Norway with cholestatic jaundice during the first 3 months of life between 1955 and 1974, of whom 60 had intrahepatic cholestasis. These figures result in an incidence of intrahepatic cholestasis, including but not limited to PFIC, of approximately 1 per 18,000 live births (Henriksen, 1981). However, molecular genetic diagnostics for PFIC were not available at the time of data collection (1955—1974). A later study that analysed death registers and case records from two hospitals in Greenland for the period 1943—2002 reported 46 cases of PFIC1 diagnosed by liver biopsy, biochemistry and/or molecular genetic testing (ATP8B1) (Nielsen, 2004). In this study, many cases occurred in patients originating from indigenous populations described by the authors as ‘‘highly inbred’’. The overall study population size and incidence were not reported.

The other two publications reported the prevalence of PFIC among patients with liver-related disease (Fischler, 2001; Ruth, 2014), based on genetic testing for PFIC diagnosis.

The Swedish study (Fischler, 2001) was a tertiary referral centre study that included infants with neonatal cholestasis with an onset in the first 6 months of life. The proportion of cases of PFIC among this study population was 12.9%.

The worldwide multicentre study included infants with cholestasis, acute liver failure or splenomegaly (Ruth, 2014). In this study the proportions of intrahepatic cholestasis cases which were PFIC was 9.0%.

Baker et al 2019 (Clinics and Research in Hepatology and Gastroenterology (2019) **43**, 20—36) offers a more extensive epidemiological overview. The table from the publication is presented below:

Table 1 Summary of included publications.

Reference	Study design	Study population	*n*	Patients with PFIC, *n*	Genetic diagnosis	Country/region	Study period	Reported data					
								PFIC epidemiology	PFIC subtype	At pre-sentation	At follow-up	Mortality	HRQoL and/or pruritus
Henriksen et al., 1981 [10]	Retrospective chart review	Infants with cholestatic jaundice	124	60	No	Norway	1955–1974 (follow-up in 1978)	Incidence: 1/18,000 live births	NS	Yes	Yes	43%	No
Whitington et al., 1994 [26]	Retrospective chart review	Patients with PFIC (with chronic cholestasis but excluding other chronic cholestatic conditions)	33	33	No	North America	1978–1991	No	NS	Yes	Yes	21%	No
Fischler et al., 2001 [14]	Retrospective chart review	Infants with neonatal cholestasis	85	11	Yes	Sweden	1988–1995	Prevalence: 12.9%	PFIC2: 91% Others: NS	No	No	No	No
Nielsen and Eiberg, 2004 [11]	Retrospective review of death register and hospital records	Patients with PFIC1	46	46	Yes[a]	Greenland	1943–2002	No	PFIC1: 100%	Yes	No	87%	No
Wanty et al., 2004 [24]	Retrospective chart review	Patients with PFIC (based on chronic cholestasis)	49	49	Yes[b]	Belgium	NR	No	PFIC1/2: 61% PFIC3: 39%	Yes	Yes	8%	No
Chaabouni et al., 2007 [13]	Retrospective review of hospital records	Children with cirrhosis	71	9	No	Tunisia	1990–2004	Prevalence: 12.7%	NS	No	No	33%	No
Englert et al., 2007 [20]	Retrospective chart review	Patients with PFIC treated with UDCA plus PEBD and/or LT	42	42	Yes	Germany	NR	No	PFIC2: 62% PFIC3: 38%	Yes	Yes	0%	No
Monajemzadet et al., 2009 [15]	Cross-sectional, diagnostic	Children referred for liver needle biopsy excluding those with thalassemia	321	20	No	Iran	2004–2006	5.0%	NS	No	No	No	No
Lee et al., 2009 [23]	Case series	Infants with PFIC (based on chronic cholestasis)	5	5	No	Malaysia	1996–2004	No	PFIC1/2: 80% PFIC3: 20%	Yes	Yes	80%	Pruritus scores
Yang et al., 2009 [30]	Retrospective chart review	Children with PFIC who underwent PEBD	11	11	Partial	Netherlands	2000–2005	No	PFIC2: 73% Others: NS	No	No	No	HRQoL
Miyagawa-Hayashino et al., 2009 and Hori et al., 2011 [22,25] [c]	Retrospective chart review	Children who underwent LT	725	14	Yes	Japan	1990–2008	No	PFIC1: 78.6% PFIC2: 21.4%	No	Yes	21.4%	No
Lind et al., 2010 [29]	Prospective PFIC/ALGS database	Children/adolescents with PFIC/ALGS who underwent PEBD	8	8	NS	NR	NR	No	No	No	No	No	Yes

Table 1 (*Continued*)

Reference	Study design	Study population	*n*	Patients with PFIC, *n*	Genetic diagnosis	Country/region	Study period	Reported data					
								PFIC epidemiology	PFIC subtype	At pre-sentation	At follow-up	Mortality	HRQoL and/or pruritus
Davit-Spraul et al., 2010 [8]	Retrospective chart review	Children with hepatocellular cholestasis, pruritus, elevated serum bile acid, and normal serum GGT activity	62	62	Yes	France	1978–2007	No	PFIC1: 21%[d] PFIC2: 63%[d] Others: NS[d]	Yes	Yes	10%	No
Schukfeh et al., 2012 [27]	Retrospective chart review	Children with PFIC who underwent PEBD	24	24	Partial	Germany	1994–2008	No	NS	No	No	No	Pruritus scores
Alam et al., 2013 [12]	Protocol-based screening study	Children with encephalopathy, acute liver failure, cholestasis, hepatomegaly, or chronic liver disease	288	7	NS	India	NR	Prevalence: 2.4%	PFIC2: 100%	No	No	No	No
Al Mehaidib et al., 2013 [19]	Retrospective chart review	Patients with cholestasis and suspected PFIC	68	48	Yes	Saudi Arabia	2002–2012	No	PFIC1: 10.4% PFIC2: 56.3% PFIC3: 33.3%	Yes	Yes	6%	No
Gray et al., 2013 [21]	Prospective, genetic	Infants < 2 years of age with cholestasis, acute liver failure, or splenomegaly and with DNA sequencing data	87	8	Yes	Int. (13 centres)	NR	No	PFIC1: 37.5%[e] PFIC2: 37.5%[e] PFIC3: 37.5%[e]	No	No	No	No
Ruth et al., 2014 [16]	Prospective, genetic	Infants < 2 years of age with cholestasis, acute liver failure, or splenomegaly	238	NR[f]	Yes	International (13 centres)	NR	Prevalence: 9%	NS	No	No	No	No
Vasishta et al., 2015 [18]	Retrospective, postmortem	Children with hepatic disease	181	NR[f]	NS	North India	NR	Prevalence: 0.6%	NS	No	No	No	No
Kamath et al., 2015 [17]	Cross-sectional sub-study	Children with chronic intrahepatic cholestasis	214	25	Yes	North America (16 centres)	NR	Prevalence: 11.7%	PFIC1: 24.0% PFIC2: 48.0% PFIC3: 28.0%	No	No	No	HRQoL

A1ATD: α-1-antitrypsin deficiency; ALGS: Alagille syndrome; BSEP: bile salt export pump; GGT: γ-glutamyl transferase; HRQoL: health-related quality of life; Int: international; LT: liver transplantation; NR: not reported; NS: type of PFIC diagnosis not specified; PEBD: partial external biliary diversion; PFIC: progressive familial intrahepatic cholestasis; UDCA: ursodeoxycholic acid.

[a] PFIC diagnosed by molecular testing, liver biopsy, and/or biochemistry.

[b] Genetic analysis was performed where possible only for PFIC2 mutations.

[c] Miyagawa-Hayashino et al. (journal article) and Hori et al. (subsequent congress abstract) reported on the same study population. Hori et al. included one additional patient (who had PFIC2 and survived); and reported death of one more of the original patients (who had PFIC1).

[d] PFIC subtype remained unknown in 10 patients (16%).

[e] There were 3/8 patients with each subtype; one patient had both PFIC1 and PFIC3.

[f] Proportion, but not number, of cases reported.

Six publications reported the prevalence of PFIC among patients with liver-related disease (Table 1). Of these, three studies used genetic testing for PFIC diagnosis: a multicentre study from North America in children with intrahepatic cholestasis, a Swedish tertiary referral centre study that included infants with neonatal cholestasis with an onset in the first 6 months of life, and a worldwide multicentre study in infants with cholestasis, acute liver failure or splenomegaly. In these three studies, the proportions of cases of PFIC among the study populations were 11.7% (North America), 12.9% (Sweden), and 9.0%(International), respectively.

In the remaining three studies the basis of PFIC diagnosis was either clinical, biochemical and histological, or was not reported. The other European Centers (Germany, France, Belgium and The Netherlands) do not report the percentage of PFIC cases for intrahepatic cholestasis cases. From the international study it is apparent that an average range around the world is ~9% for which PFIC will be diagnosed. It also appears that there is variability in the prevalence in Europe.

Altogether, the incidence referenced in the literature review by Baker et al (Baker 2019) and also published by Jacquemin 2012, results in a birth incidence for PFIC of 0.13/10 000 (approximately 1 per 75,000 live births). A birth incidence of 0.13/10 000 gives a total of (4.2 million babies born in the EU in 2019; https://ec.europa .eu/eurostat/statistics-explained/index.php/Fertility_statistics) = 56 PFIC patients born/year, corresponding to a yearly birth incidence of **0.001/10 000** (56/(519 200 000x10 000)).

Taking into account that most liver transplants occur in childhood, a conservative average life span of 30 years for patients with PFIC is estimated. Based on this, the prevalence can be calculated as follows using the incidence x duration formula: 0.001/10 000 x 30 years = **0.03/10 000.**

This was accepted by the COMP.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Ursodeoxycholic acid (UDCA) has national marketing approval for PFIC subtype 3 in France.

The EASL Clinical Practice Guidelines (2009) recommends UDCA for PFIC 3 and biliary diversion surgery (Management of cholestatic liver diseases Journal of Hepatology 51 (2009) 237–267). There has been no recent update of the EASL Clinical Practice Guidelines.

There is currently no medicinal product approved which covers the full PFIC population. Supplementation with medium chain triglycerides and fat-soluble vitamins is generally recommended in children. UDCA has been reported to improve biochemical tests in almost 50% of patients with PFIC3, but generally does not affect PFIC1 and PFIC2 although it is widely prescribed off-label. In fact, 80% of the PFIC 1 or 2 patients in the Bylvay trials had been treated with UDCA. Rifampicin may alleviate pruritus, but it is also use if off-label in PFIC.

Partial biliary diversion reduces serum bile acids and pruritus and prevent hepatic fibrosis. However, the external stoma may lead to complications, such as cholangitis. Effects of this surgery have been reported to be temporary. Liver transplantation is the recommended treatment of end-stage liver

disease in PFIC. Liver transplantation requires extensive surgery, and life-long immune-suppression thereafter to counterfeit rejection reaction. There is also a shortage of suitable donors.

As the agreed therapeutic indication of Bylvay is broader and covers more patients, including patients with PFIC 1 and 2, than the approved UDCA, there are no satisfactory methods to treat the entirety of patients.

Significant benefit

NA

4. COMP position adopted on 21 May 2021

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of progressive familial intrahepatic cholestasis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.03 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to symptoms which develop early, median age of onset of symptoms being 2 months with 78% of patients developing jaundice. The complications of hepatic dysfunction (portal hypertension, liver failure, cirrhosis, hepatocellular carcinoma) are associated with the condition. It is life-threatening due to death secondary to complications of end-stage liver disease. In general, without treatment, PFIC will lead to cirrhosis by age 10-20 years, and frequently even earlier. The survival in those not coming to surgery is 50% at the age of 10 and almost none at the age of 20 years;
- at present no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Bylvay.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Bylvay, (2S)-2-{[(2R)-2-[({[3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro- 1,2,5-benzothiadiazepin-8-yl]oxy}acetyl)amino]-2-(4-hydroxyphenyl)acetyl]amino}butanoic acid, odevixibat, for treatment of progressive familial intrahepatic cholestasis (EU/3/12/1028) is not removed from the Community Register of Orphan Medicinal Products.