



Odevixibat: First Approval

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Abstract

Odevixibat (Bylvay™) is a small molecule inhibitor of the ileal bile acid transporter being developed by Albireo Pharma, Inc. for the treatment of various cholestatic diseases, including progressive familial intrahepatic cholestasis (PFIC). In July 2021, odevixibat received its first approval in the EU for the treatment of PFIC in patients aged ≥ 6 months, followed shortly by its approval in the USA for the treatment of pruritus in patients aged ≥ 3 months with PFIC. Odevixibat is also in clinical development for the treatment of other cholestatic diseases, including Alagille syndrome and biliary atresia, in various countries. This article summarizes the milestones in the development of odevixibat leading to this first approval for PFIC.

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Odevixibat (Bylvay™): Key points

Small molecule inhibitor of the ileal bile acid transporter being developed by Albireo Pharma, Inc. for the treatment of various cholestatic diseases, including PFIC.

Received its first approval on 16 July 2021 in the EU.

Approved for the treatment of PFIC in patients aged ≥ 6 months in the EU and for treatment of pruritus in patients aged ≥ 3 months with PFIC in the USA.

1 Introduction

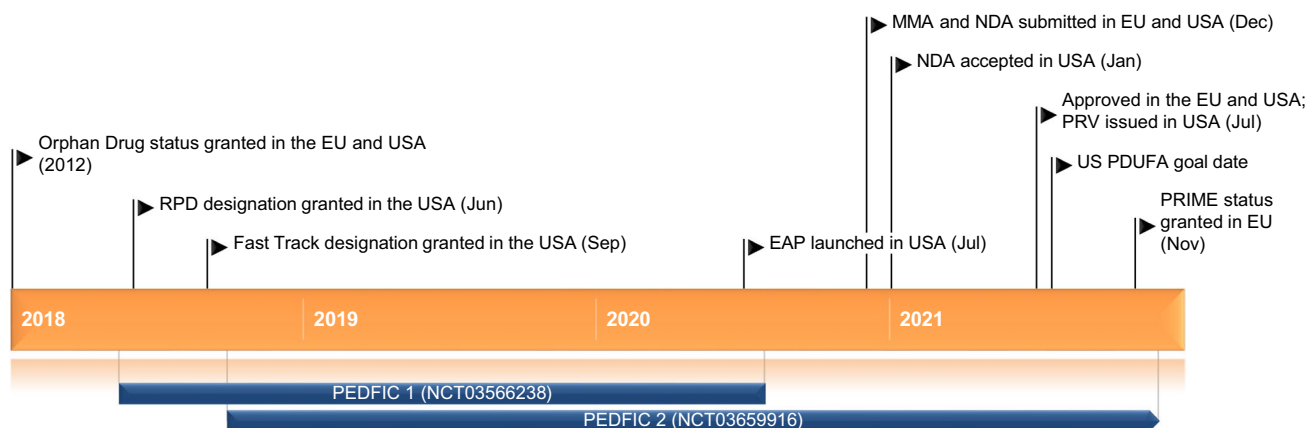
Cholestatic liver diseases are typified by the accumulation of biliary components resulting from impaired bile formation and/or bile flow, with liver injury, inflammation and fibrosis being driven largely by bile acid (BA) retention [1, 2]. Symptoms can include pruritus, fatigue and jaundice, with progression to end stage liver disease in many cases requiring liver transplant [3]. Asymptomatic cases can also occur and are often identified by elevated levels of certain liver enzymes upon routine laboratory testing or tests for another condition [3].

Odevixibat (Bylvay™) is a small molecule inhibitor of the ileal BA transporter (IBAT) [4, 5]. Odevixibat is being developed by Albireo Pharma, Inc. (Albireo) for the treatment of cholestatic liver diseases, including progressive familial intrahepatic cholestasis (PFIC), biliary atresia and Alagille syndrome. In July 2021, odevixibat was approved in the EU for the treatment of PFIC in patients aged ≥ 6 months [5, 6] and in the USA for the treatment of pruritus in patients aged ≥ 3 months with PFIC [4, 7]. Odevixibat is available as 4 strengths in 2 different sized capsules; smaller capsules (400 and 1200 μg) are intended to be swallowed, while the larger capsules (200 and 600 μg strength) are intended to be opened and the contents (oral pellets) sprinkled on soft food [4, 5]. The recommended dosage is 40 $\mu\text{g}/\text{kg}$ once daily, administered orally in the morning, with (EU; USA) [4, 5] or without (EU) [5] food. In the

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Key milestones in the development of odevixibat, focusing on its use in the treatment of progressive familial intrahepatic cholestasis. *EAP* Expanded Access Programme, *MMA* Marketing Authorization Appli-

cation, *NDA* New Drug Application, *PDUFA* Prescription Drug User Fee Act, *PRIME* PRIority Medicines, *PRV* Paediatric Disease Priority Review Voucher, *RPD* Rare Paediatric Disease

EU and US, if an adequate clinical response has not been achieved after 3 months of continuous therapy with odevixibat, the dose may be increased to 120 µg/kg/day [4, 5]; in the US this can be achieved by increasing the dose in increments of 40 µg/kg [4]. The maximum daily dose of odevixibat is 7.2 mg per day in the EU [5] and the daily dose must not exceed 6 mg in the US [4].

Odevixibat continues to be assessed for PFIC in an ongoing open-label, phase III extension study for long term safety and efficacy, and is also in phase III development for other cholestatic diseases, including Alagille syndrome and biliary atresia. Odevixibat has orphan designations for the treatment of Alagille syndrome, biliary atresia and primary biliary cholangitis in both the USA and EU [8–10].

1.1 Company Agreements and Patent Information

In February 2021, Albireo entered into a limited co-promotion agreement (for 2 years, with option of extending) with Travere Therapeutics in the USA [11] and entered a marketing agreement with Medison Pharma Ltd for commercialization of odevixibat in Israel [12]. In May 2021, Albireo also entered into license and distribution agreements for the commercialization of odevixibat with Genpharm Services (in Saudi Arabia and other Gulf countries) and Gen Ilac (in Turkey) [13].

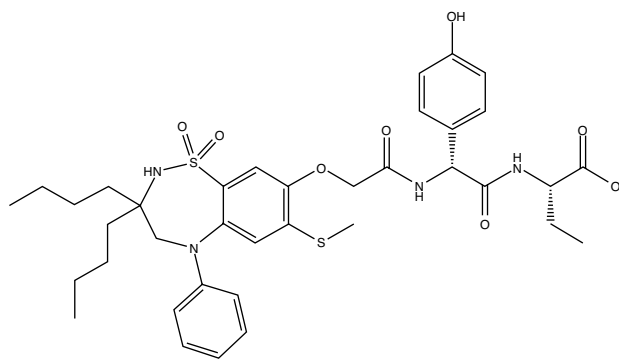
In 2006, Albireo was issued patents covering the composition-of-matter for odevixibat in the USA and > 50 other countries, and in May 2017 was issued a method-of-treatment patent for odevixibat in PFIC and other specified liver diseases in the USA, corresponding method-of-use patents in Europe and Japan, and a method-of-treatment patent in NASH in the USA [14]. As of December 2020, Albireo has patent protection for odevixibat composition-of-matter expiring in September 2022, and protection in the USA for

the method of using certain IBAT inhibitor(s) to treat certain liver diseases, expiring in November 2031, not including a patent term extension. Albireo also has a European patent for the method of using certain IBAT inhibitor(s) in combination with a BA binder to treat certain liver diseases (expires November 2031), with the same patent pending in the USA. An Albireo patent for crystal modifications of odevixibat is now issued in the USA (expiring in June 2039) and is currently pending in Europe. Similarly, patents for formulations of odevixibat are pending in the USA and Europe and, if granted, will expire in June 2039 [10].

2 Scientific Summary

2.1 Pharmacodynamics

Odevixibat displays selective, reversible inhibition of the IBAT [5]. The drug reduces the level of BAs in the plasma/serum by reducing the reuptake of BAs in the distal ileum



Chemical structure of odevixibat

and increasing colon clearance of BAs [5, 15]. There is no correlation between the degree by which serum BA (sBA) levels are reduced and the systemic pharmacokinetics of odevixibat, given the drug acts locally in the intestine with minimal systemic exposure [5].

In a mouse model of sclerosing cholangitis, odevixibat ameliorated cholestatic liver and bile duct injury and appeared to have anti-fibrotic as well as anti-inflammatory effects [16].

2.2 Pharmacokinetics

After oral administration, odevixibat absorption is minimal [4, 5]. In paediatric patients with PFIC aged 0.5–17 years treated once daily with odevixibat 40 or 120 µg/kg, plasma concentrations of odevixibat were generally below the limit of quantification [4]. Simulated in a paediatric PFIC population, odevixibat 40 or 120 µg/kg/day had maximum plasma concentrations of 0.21 and 0.62 ng/mL and area under the plasma concentration time-curve values of 2.26 and 5.99 ng · h/mL [5]. Taking odevixibat with food, or after sprinkling odevixibat pellets on soft food, has no clinically relevant impact on systemic exposure to the drug [4]. There is minimal [5] to no [4] accumulation of odevixibat after once-daily administration. Odevixibat is > 99% plasma protein bound [4, 5]. Dosages of 40 or 120 µg/kg/day have mean bodyweight-adjusted apparent volumes of distribution of 40.3 and 43.7 L/kg in paediatric patients [5]. Metabolism of odevixibat is minimal in humans [5], and occurs via mono-hydroxylation in vitro [4]. In healthy adults, elimination of odevixibat after a single oral dose occurred mainly via the faeces (82.9%), with only 0.002% of the dose eliminated via the urine [17]. In paediatric patients who received odevixibat 40 or 120 µg/kg/day, the mean

bodyweight-normalized apparent total clearance values were 26.4 and 23.0 L/kg/h; the mean half-life of the drug is ≈ 2.5 h [5].

Absorption of fat-soluble vitamins (FSVs) may be reduced by odevixibat; monitoring of FSVs is therefore advised [4, 5]. Similarly, odevixibat may impact the absorption of lipophilic oral contraceptives and other fat-soluble medications [5]. Odevixibat may be bound by BA-binding resins in the gut; thus, staggered administration is recommended [4]. Odevixibat is a P-glycoprotein substrate [4, 5]; its exposure may therefore increase if coadministered with the strong P-glycoprotein inhibitor itraconazole, although this interaction is not expected to be clinically relevant [18, 19]. Although odevixibat is an inhibitor of CYP3A4/5, it does not alter exposure to the CYP3A4 substrate midazolam [4, 5, 19] or its 1-hydroxy metabolite [4, 5] to any clinically relevant extent.

2.3 Therapeutic Trials

2.3.1 Progressive Familial Intrahepatic Cholestasis

Odevixibat was effective in reducing pruritus and sBAs in children with PFIC in a randomized, double-blind, phase III trial (NCT03566238; PEDFIC 1) [5, 20]. Patients aged 0.5–18 years with PFIC (type 1 or 2), elevated sBAs and a history of significant pruritus were randomized to odevixibat 40 µg/kg (*n* = 23), odevixibat 120 µg/kg (*n* = 19) or placebo (*n* = 20) once daily [20]. Over the 24-week treatment period, the mean proportion of positive pruritus assessments (defined as a scratching score of ≤ 1 or ≥ 1-point improvement from baseline on a 5-point scale of an observer-reported instrument) [primary endpoint in USA] was

Features and properties of odevixibat

| | |
|------------------------------|---|
| Alternative names | Bylvay; A4250 |
| Class | Acetamides, butyric acids, hepatoprotectants, small molecules, sulfones, thiazepines |
| Mechanism of action | Sodium-bile acid cotransporter inhibitors |
| Route of administration | Oral |
| Pharmacodynamics | Selectively and reversibly inhibits the ileal BA transporter; reduces BA levels in serum/plasma by reducing BA reuptake in the distal ileum and increasing colon clearance of BAs |
| Pharmacokinetics | Minimal absorption and metabolism; eliminated mainly via the faeces; half-life ≈ 2.5 h |
| Most frequent adverse events | Diarrhoea, increased hepatic enzymes (including alanine transferase and aspartate transferase), increased blood bilirubin, increased international normalized ratio |
| ATC codes | |
| WHO ATC code | A05A-X05 (odevixibat) |
| EphMRA ATC code | A5A (bile therapy and chologogues) |
| Chemical name | (S)-2-((R)-2-(2-((3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,5]thiadiazepin-8-yl)oxy)acetamido)-2-(4-hydroxyphenyl)acetamido)butanoic acid |

BA bile acid

58.3% with odevixibat 40 µg/kg/day, 47.7% with odevixibat 120 µg/kg/day and 28.7% with placebo, with the difference between each odevixibat group and placebo being significant (based on 95% CIs) [5]. In addition, significantly (one-sided $p < 0.02$) more patients achieved an sBA response (defined as a $\geq 70\%$ reduction from baseline or a level ≤ 70 µmol/L at week 24) [primary endpoint in Europe/rest of world] with odevixibat 40 µg/kg/day (43.5%; 10/23 patients) or 120 µg/kg/day (21.1%; 4/19 patients) than with placebo (0%; 0/20 patients). Each odevixibat dosage group had favourable mean changes from baseline in growth parameters, including height and weight Z scores, versus placebo, although the between-group differences were not significant [5]. Odevixibat appeared to improve both patient and family health-related quality of life (QoL), as assessed by caregivers of patients aged ≥ 2 years using the Pediatric QoL Inventory questionnaire, with mean improvements from baseline in both total score and family impact total score numerically favouring odevixibat (40 and 120 µg/kg/day pooled) over placebo [21].

Longer-term clinical benefit of odevixibat has been demonstrated in an ongoing, open-label, phase III, extension study (NCT03659916; PEDFIC 2) [22]. Patients in this trial either had PFIC type 1 or 2 and had been treated with odevixibat (40 or 120 µg/kg/day) ($n = 34$) or placebo ($n = 19$) in the PEDFIC 1 trial or were new patients with any type of PFIC ($n = 16$). The previously treated patients were defined as the P10 cohort, whereas the latter two patient groups were combined into a single ‘treatment-naïve’ (TN) cohort. All patients received odevixibat 120 µg/kg/day in the extension study. In an interim analysis (data cutoff July 2020), mean sBA levels in the P10 cohort significantly ($p < 0.0001$) declined from 251.8 µmol/L at the PEDFIC 1 baseline to 85.1 µmol/L after 24 weeks of treatment in the extension (i.e. total of 48 weeks’ therapy). In the P10 cohort, there were also significant improvements in mean

monthly pruritus scores (from 3.0 to 1.4, $p < 0.0001$), height Z scores (from -1.6 to -0.5 , $p = 0.02$) and weight Z scores (from -0.9 to 0.2 , $p = 0.03$) [22, 23]. Data for these outcomes in the TN cohort over the course of the extension (i.e. over 24 weeks’ treatment) showed a similar trend [22, 23].

The efficacy of odevixibat has been further assessed in a pooled analysis of the PEDFIC 1 and 2 trials [24–26]. This analysis included 77 patients who received odevixibat in one or both of the studies; 42 were treated with the drug in PEDFIC 1 (34 of these entered PEDFIC 2), 19 had received placebo in PEDFIC 1 (all entered PEDFIC 2) and 16 were patients newly enrolled into PEDFIC 2. In this analysis, improvements in sBA and pruritus were observed with odevixibat regardless of whether patients had type 1 ($n = 20$) or type 2 ($n = 51$) PFIC [24]; the improvements occurred within the first 4 weeks of treatment and were sustained up to week 48 [25, 26]. In addition to improvements in sBA and pruritus, there were also continued clinically meaningful benefits seen in terms of growth, and sleep parameters over 48 weeks of treatment [26].

2.3.2 Other Cholestatic Disease Studies

Odevixibat demonstrated promise as a treatment for paediatric patients with various cholestatic liver diseases and pruritus in an open-label, multicentre, phase II study (NCT02630875) [27]. Eligible patients were aged 1–18 years with pruritus caused by a chronic cholestatic disease (e.g. PFIC, Alagille syndrome, biliary atresia or primary sclerosing cholangitis). Patients received a single dose of odevixibat (10–200 µg/kg, depending on the cohort) prior to a 2-week safety observation period, then received that same dose daily for 4 weeks; 20 patients participated, with 4 entering the study again after completing their first dose level. At the end of the 4-week treatment period, overall (i.e. all cohorts combined), the mean change from baseline in sBA

Key clinical trials of odevixibat (all sponsored by Albioreo Pharma, Inc.)

| Drug(s) | Indication | Phase | Status | Location(s) | Identifier |
|---------------------|--------------------|-------|------------|---------------|--|
| Odevixibat, placebo | PFIC (type 1 or 2) | III | Completed | Multinational | NCT03566238; PEDFIC 1; EudraCT2017-002338-21 |
| Odevixibat | PFIC (any type) | III | Recruiting | Multinational | NCT03659916; PEDFIC 2; EudraCT2017-002325-38 |
| Odevixibat, placebo | Alagille syndrome | III | Recruiting | Multinational | NCT04674761; ASSERT; EudraCT2020-004011-28 |
| Odevixibat, placebo | Biliary atresia | III | Recruiting | Multinational | NCT04336722; BOLD; EudraCT2019-003807-37 |
| Odevixibat | Cholestasis | II | Completed | Europe | NCT02630875; EudraCT2015-001157-32 |

PFIC progressive familial intrahepatic cholestasis

level (primary endpoint) was $-123.1 \mu\text{mol/L}$ ($235 \mu\text{mol/L}$ at baseline). Mean changes from baseline in pruritus scores were -2.2 on the visual analogue-itch scale (baseline 6.2; 0–10 scale), -2.0 on the Partial Patient-Oriented Scoring Atopic Dermatitis itch scale (baseline 6.0; 0–10 scale) and -0.8 on the Whittington itch scale (baseline 2.6; 0–4 scale); lower scores indicate improvements [27].

2.4 Adverse Events

Odevixibat was generally well tolerated in paediatric patients with cholestatic liver diseases in clinical studies [20, 23, 27, 28], with the focus here being the phase III PEDFIC 1 and 2 trials.

In the 24-week PEDFIC 1 study, 33.3% of all odevixibat (40 or 120 $\mu\text{g/kg/day}$) recipients and 15.0% of placebo recipients had treatment-related adverse events (AEs) [28]. The most common of these to occur with odevixibat included diarrhoea, alanine aminotransferase (ALT) increased, blood bilirubin increased (incidence of each was 8.7% [2/23 patients] with 40 $\mu\text{g/kg/day}$ and 10.5% [2/19] with 120 $\mu\text{g/kg/day}$ vs 5.0% [1/20] with placebo) and aspartate aminotransferase increased (8.7% [2/23] with 40 $\mu\text{g/kg/day}$ and 5.3% [1/19] with 120 $\mu\text{g/kg/day}$ vs 5.0% [1/20] with placebo). One discontinuation occurred (in the odevixibat 120 $\mu\text{g/kg/day}$ arm) because of an AE (diarrhoea) [28].

The tolerability profile of odevixibat in the PEDFIC 2 extension study was consistent with these findings. Interim tolerability data from PEDFIC 2 were grouped into two cohorts: patients who had received odevixibat ($n = 34$) or placebo ($n = 19$) in PEDFIC 1 (cohort 1) and patients who were newly enrolled into PEDFIC 2 (cohort 2; $n = 16$) [28]. The incidence of treatment-related AEs with odevixibat 120 $\mu\text{g/kg/day}$ from 24 weeks was 26.3–31.3% across cohorts 1 and 2 and 29% (20/69 patients) overall. In cohort 1 the most common treatment-related AEs were blood bilirubin increased (8.8%; 3/34 patients) and hepatic enzyme increased (5.9%; 2/34 patients) in patients who had received odevixibat in PEDFIC 1, and blood bilirubin increased (10.5%; 2/19 patients) and ALT increased (5.3%; 1/19 patients) in patients who had received placebo in PEDFIC 1. Similarly, in cohort 2, blood bilirubin increased, ALT increased and international normalized ratio increased were the most frequent treatment-related AEs (12.5% incidence for each; 2/16 patients). One discontinuation occurred primarily because of an AE (worsening cholestasis) [28].

In PEDFIC 1 or 2, there were no liver decompensation events, new FSV deficiency events (refractory to clinically recommended vitamin supplementation), deaths or serious treatment-related AEs, and no clinically relevant changes in haematology, serum biochemistry or urinalysis test values [28].

2.5 Ongoing Clinical Trials

In addition to the previously discussed ongoing, open label, long-term phase III PEDFIC 2 trial (NCT03659916) evaluating the safety and efficacy of odevixibat, recruitment is underway in two phase III trials evaluating the efficacy and safety of odevixibat in children and adults with Alagille syndrome (NCT04674761; ASSERT) and children with biliary atresia who have undergone a Kasai hepatoportoenterostomy (NCT04336722; BOLD).

3 Current Status

Odevixibat received its first approval on 16 July 2021 for the treatment of PFIC in patients aged ≥ 6 months in the EU [5, 6] and on 20 July 2021 in the USA for the treatment of pruritus in patients aged ≥ 3 months with PFIC [4, 7].

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40265-021-01594-y>.

Declarations

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Ethics approval, Consent to Participate, Consent to Publish, Availability of Data and Material, Code Availability Not applicable.

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