

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Bylvay 200 micrograms hard capsules  
Bylvay 400 micrograms hard capsules  
Bylvay 600 micrograms hard capsules  
Bylvay 1,200 micrograms hard capsules

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

#### Bylvay 200 mcg hard capsules

Each hard capsule contains odeixibat sesquihydrate equivalent to 200 micrograms odeixibat

#### Bylvay 400 mcg hard capsules

Each hard capsule contains odeixibat sesquihydrate equivalent to 400 micrograms odeixibat

#### Bylvay 600 mcg hard capsules

Each hard capsule contains odeixibat sesquihydrate equivalent to 600 micrograms odeixibat

#### Bylvay 1,200 mcg hard capsules

Each hard capsule contains odeixibat sesquihydrate equivalent to 1,200 micrograms odeixibat

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Hard capsule

#### Bylvay 200 mcg hard capsules

Size 0 capsule with ivory opaque cap and white opaque body; imprinted "A200" with black ink.

#### Bylvay 400 mcg hard capsules

Size 3 capsule with orange opaque cap and white opaque body; imprinted "A400" with black ink.

#### Bylvay 600 mcg hard capsules

Size 0 capsule with ivory opaque cap and body; imprinted "A600" with black ink.

#### Bylvay 1,200 mcg hard capsules

Size 3 capsule with orange opaque cap and body; imprinted "A1200" with black ink.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

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).

#### 4.2 Posology and method of administration

Treatment must be initiated and supervised by physicians experienced in the management of PFIC.

##### Posology

The recommended dose of odevixibat is 40 mcg/kg administered orally once daily in the morning. Odevixibat can be taken with or without food.

Table 1 shows the strength and number of capsules that should be administered daily based on body weight to approximate a 40 mcg/kg/day dose.

**Table 1: Number of Bylvay capsules needed to achieve the nominal dose of 40 mcg/kg/day**

Body weight (kg)	Number of 200 mcg capsules		Number of 400 mcg capsules
4 to < 7.5	<b>1</b>	or	N/A
7.5 to < 12.5	<b>2</b>	or	1
12.5 to < 17.5	<b>3</b>	or	N/A
17.5 to < 25.5	<b>4</b>	or	2
25.5 to < 35.5	6	or	<b>3</b>
35.5 to < 45.5	8	or	<b>4</b>
45.5 to < 55.5	10	or	<b>5</b>
≥ 55.5	12	or	<b>6</b>

Capsule strength/number in **bold** is recommended based on predicted ease of administration.

##### *Dose escalation*

Improvement in pruritus and reduction of serum bile acid levels may occur gradually in some patients after initiating odevixibat therapy. If an adequate clinical response has not been achieved after 3 months of continuous therapy, the dose may be increased to 120 mcg/kg/day (see section 4.4.).

Table 2 shows the strength and number of capsules that should be administered daily based on body weight to approximate a 120 mcg/kg/day dose, with a maximum daily dose of 7,200 mcg per day.

**Table 2: Number of Bylvay capsules needed to achieve the nominal dose of 120 mcg/kg/day**

Body weight (kg)	Number of 600 mcg capsules		Number of 1,200 mcg capsules
4 to < 7.5	<b>1</b>	or	N/A
7.5 to < 12.5	<b>2</b>	or	1
12.5 to < 17.5	<b>3</b>	or	N/A
17.5 to < 25.5	<b>4</b>	or	2
25.5 to < 35.5	6	or	<b>3</b>
35.5 to < 45.5	8	or	<b>4</b>
45.5 to < 55.5	10	or	<b>5</b>
≥ 55.5	12	or	<b>6</b>

Capsule strength/number in **bold** is recommended based on predicted ease of administration.

Alternative treatment should be considered in patients for whom no treatment benefit can be established following 6 months of continuous daily treatment with odevixibat.

##### *Missed doses*

If a dose of odevixibat is missed, the patient should take the forgotten dose as soon as possible without exceeding one dose per day.

### *Special populations*

#### Renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment.

There are no available clinical data for the use of odevixibat patients with moderate or severe renal impairment or end-stage renal disease (ESRD) requiring haemodialysis (see section 5.2).

#### Hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment (see sections 5.1 and 5.2).

No data are available for PFIC patients with severe hepatic impairment (Child Pugh C). Additional monitoring for adverse reactions may be warranted in these patients when odevixibat is administered (see section 4.4).

#### Paediatric population

The safety and efficacy of odevixibat in children aged less than 6 months has not been established. No data are available.

#### Method of administration

Bylvay<sub>is</sub> is for oral use. To be taken with or without food in the morning (see section 5.2).

The larger 200 mcg and 600 mcg capsules are intended to be opened and sprinkled on food but may be swallowed whole.

The smaller 400 mcg and 1,200 mcg capsules are intended to be swallowed whole but may be opened and sprinkled on food.

If the capsule is to be swallowed whole, the patient should be instructed to take it with a glass of water in the morning.

For capsules to be opened, the patient should be instructed to:

- place a small quantity (30 mL/2 tablespoons) of soft food (yoghurt, apple sauce, oatmeal porridge, banana puree, carrot puree, chocolate-flavoured pudding or rice pudding) in a bowl. The food should be at or below room temperature.
- hold the capsule horizontally at both ends, twist in opposite directions and pull apart to empty the pellets into the bowl of soft food. The capsule should be gently tapped to ensure that all pellets will come out.
- repeat the previous step if the dose requires more than one capsule.
- gently mix the pellets with a spoon into the soft food.
- administer the entire dose immediately after mixing. Do not store the mixture for future use.
- drink a glass of water following the dose.
- dispose all empty capsule shells.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

The mechanism of action of odevixibat requires that the enterohepatic circulation of bile acids and bile salt transport into biliary canaliculi is preserved. Conditions, medications or surgical procedures that impair either gastrointestinal motility, or enterohepatic circulation of bile acids, including bile salt transport to biliary canaliculi have the potential to reduce the efficacy of odevixibat. For this reason, e.g. patients with PFIC2 who have a complete absence or lack of function of Bile Salt Export Pump (BSEP) protein (i.e. patients with BSEP3 subtype of PFIC2) will not respond to odevixibat.

There are limited or no clinical data with odevixibat in PFIC subtypes other than 1 and 2.

Patients with severe hepatic impairment (Child-Pugh C) have not been studied (see section 5.2). Periodic liver function tests should be considered for patients with severe hepatic impairment.

Diarrhoea has been reported as a common adverse reaction when taking odevixibat. Diarrhoea may lead to dehydration. Patients should be monitored regularly to ensure adequate hydration during episodes of diarrhoea (see section 4.8).

In clinical trials, increased levels in liver function tests were observed in some patients receiving odevixibat. Assessment of liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase and total bilirubin) is recommended for all patients prior to initiating Bylvay, with monitoring per standard clinical practice.

For patients with liver function test elevations, more frequent monitoring should be considered.

Assessment of fat-soluble vitamin levels (Vitamins A, D, E) and international normalised ratio (INR) are recommended for all patients prior to initiating Bylvay, with monitoring per standard clinical practice.

Treatment with odevixibat may impact the absorption of fat-soluble medicinal products, including lipophilic oral contraceptives (see sections 4.5 and 4.6).

#### **4.5 Interaction with other medicinal products and other forms of interaction**

##### Transporter-mediated interactions

Odevixibat is a substrate for the efflux transporter P-glycoprotein (P-gp). In adult healthy subjects, co-administration of the strong P-gp inhibitor itraconazole increased the plasma exposure of a single dose of odevixibat 7,200 mcg by approximately 50-60%. This increase is not considered clinically relevant. No other potentially relevant transporter-mediated interactions were identified *in vitro* (see section 5.2).

##### Cytochrome P450-mediated interactions

*In vitro*, odevixibat did not induce CYP enzymes (see section 5.2).

In *in vitro* studies, odevixibat was shown to be an inhibitor of CYP3A4/5 (see section 5.2).

In adult healthy subjects, concomitant use of odevixibat decreased the area under the curve (AUC) of oral midazolam (a CYP3A4 substrate) by 30% and 1-OH-midazolam exposure by less than 20%, which is not considered clinically relevant.

No interaction studies have been conducted with UDCA and rifampicin.

No interaction studies have been conducted with oral hormonal contraceptives or other lipophilic medicinal products. It cannot be excluded that the absorption of oral contraceptives is affected by concomitant use of odevixibat.

In clinical trials, decreased levels of fat-soluble vitamins were observed in some patients receiving odevixibat. Levels of fat-soluble vitamins should be monitored (see section 4.4).

##### Paediatric population

No interaction studies have been performed in paediatric patients. No differences are expected between the adult and paediatric populations.

## 4.6 Fertility, pregnancy and lactation

### Women of childbearing potential

Women of childbearing potential should use an effective method of contraception when treated with Bylvay. Since the uptake of lipophilic oral contraceptives may be affected by odeixibat, a barrier contraceptive method should be used (see section 4.4).

### Pregnancy

There are no or limited data from the use of odeixibat in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). Bylvay is not recommended during pregnancy and in women of childbearing potential not using contraception.

### Breast-feeding

It is unknown whether odeixibat or its metabolites are excreted in human milk. There is insufficient information on the excretion of odeixibat in animal milk (see section 5.3).

A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Bylvay therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

### Fertility

No fertility data are available in humans. Animal studies do not indicate any direct or indirect effects on fertility or reproduction (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Bylvay has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

### Summary of the safety profile

The most commonly reported adverse reaction was diarrhoea reported in (7%) of patients.

### Tabulated list of adverse reactions

The table lists adverse reactions identified in clinical trials in patients with PFIC aged between 4 months to 25 years of age (median 3 years 7 months).

Adverse reactions are ranked according to system organ class, using the following convention: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ ), rare ( $\geq 1/10\ 000$  to  $< 1/1\ 000$ ), very rare ( $< 1/10\ 000$ ) and not known (cannot be estimated from the available data).

**Table 3: Frequency of adverse reactions in PFIC patients**

MedDRA system organ class	Common
Gastrointestinal disorders	diarrhoea, abdominal pain <sup>a</sup> , diarrhoea haemorrhagic, faeces soft
Hepatobiliary disorders	hepatomegaly

<sup>a</sup>Includes abdominal pain upper

### Description of selected adverse reactions

### *Gastrointestinal adverse reactions*

Gastrointestinal adverse reactions occurred at a frequency of 11% in patients treated with Bylvay. Adverse reactions of diarrhoea, abdominal pain and faeces soft were of short duration with most events  $\leq 5$  days in duration; median time to first onset was 16 days. All reports were mild to moderate in severity and non-serious. Two patients experienced an adverse reaction of clinically significant diarrhoea defined as diarrhoea that persisted for 21 or more days without any other aetiology, was severe in intensity, required hospitalisation or was considered an important medical event, or presented with concurrent dehydration requiring treatment with oral or intravenous rehydration and/or other treatment intervention (see section 4.4). Treatment interruption was reported for diarrhoea in 4% of patients and discontinuation of Bylvay due to diarrhoea was reported in 1%.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

## **4.9 Overdose**

An overdose may result in symptoms resulting from an exaggeration of the known pharmacodynamic effects of the medicinal product, mainly diarrhoea and gastrointestinal effects.

The maximum dose administered to healthy subjects in clinical trials was odeixibat 10,000 mcg as a single dose, without any adverse consequences.

In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Bile and liver therapy, other drugs for bile therapy, ATC code: A05AX05

#### Mechanism of action

Odeixibat is a reversible, potent, selective inhibitor of the ileal bile acid transporter (IBAT).

#### Pharmacodynamic effects

Odeixibat 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. The extent of reduction of serum bile acids does not correlate with systemic PK.

#### Clinical efficacy

The efficacy of Bylvay in patients with PFIC was evaluated in two phase 3 trials. Trial 1 was a 24-week, randomised, double-blind, placebo-controlled trial conducted in 62 patients with a confirmed diagnosis of PFIC Type 1 or Type 2. Patients were randomised 1:1:1 to placebo, or 40 or 120 mcg/kg/day odeixibat and stratified by PFIC Type (1 or 2) and age (6 months to 5 years, 6 to 12 years, and 13 to  $\leq 18$  years). Patients with pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein and those with ALT  $> 10 \times$  ULN or bilirubin  $> 10 \times$  ULN were excluded. 13% of the patients had prior biliary diversion surgery. Patients completing Trial 1 were eligible to enrol in Trial 2, a 72-week open-label extension trial. The primary endpoint in Trial 1 was

the proportion of patients with at least a 70% reduction in fasting serum bile acid levels or who achieved a level  $\leq 70 \mu\text{mol/L}$  at week 24.

The proportion of positive pruritus assessments at the patient level over the 24-week treatment period based on an observer-reported outcome (ObsRO) instrument was a secondary endpoint. A positive pruritus assessment was a score of  $\leq 1$  or at least 1-point improvement from baseline. Pruritus assessments were conducted in the morning and evening using a 5-point scale (0-4). Additional secondary endpoints included changes from baseline to end of treatment in growth, sleep parameters (per ObsRO) and ALT.

Median (range) age of patients in Trial 1 was 3.2 (0.5 to 15.9) years; 50% were male and 84% were white. 27% of patients had PFIC Type 1 and 73% had PFIC Type 2. At baseline, 81% of patients were treated with UDCA, 66% with rifampicin, and 89% with UDCA and/or rifampicin. Baseline hepatic impairment per Child-Pugh classification was mild in 66% and moderate in 34% of patients. Baseline mean (SD) eGFR was 164 (30.6) mL/min/1.73 m<sup>2</sup>. Baseline mean (SD) ALT, AST and bilirubin levels were 99 (116.8) U/L, 101 (69.8) U/L, and 3.2 (3.57) mg/dL, respectively. Baseline mean (SD) pruritus score (range: 0-4) and serum bile acids levels were similar in odevixibat-treated patients (2.9 [0.089] and 252.1 [103.0]  $\mu\text{mol/L}$ , respectively) and placebo-treated patients (3.0 [0.143] and 247.5 [101.1]  $\mu\text{mol/L}$ , respectively).

Table 4 presents the results of the comparison of the key efficacy results in Trial 1 between odevixibat and placebo. These data are displayed graphically over the 24-week treatment period in Figure 1 (serum bile acids) and Figure 2 (scratching scores).

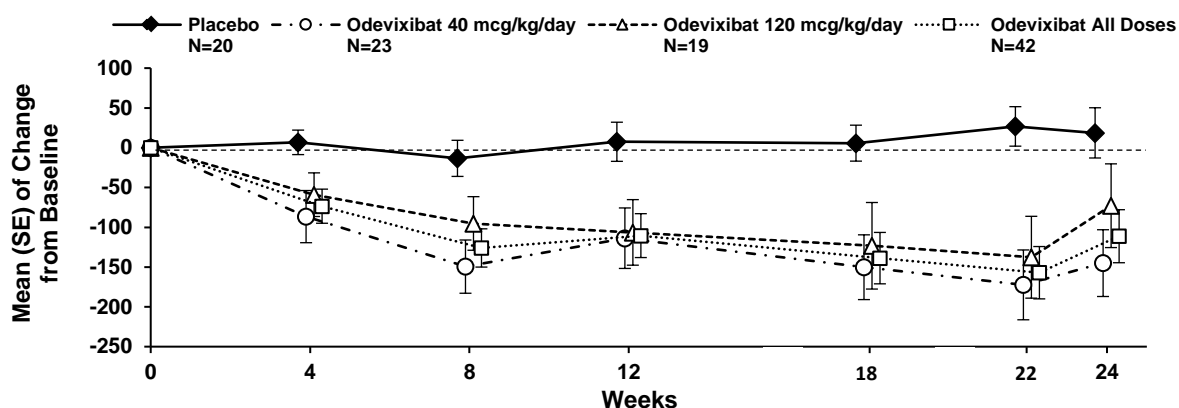
**Table 4: Comparison of key efficacy results for odevixibat vs. placebo over the 24-week treatment period in patients with PFIC in trial 1**

Efficacy endpoint	Placebo (N=20)	Odevixibat		
		40 mcg/kg/day (N=23)	120 mcg/kg/day (N=19)	Total (N=42)
<b>Proportion of patients with reduction in serum bile acids at end of treatment</b>				
n (%) (95% CI)	0 (0.00, 16.84)	10 (43.5) (23.19, 65.51)	4 (21.1) (6.05, 45.57)	14 (33.3) (19.57, 49.55)
Difference in proportion vs. placebo (95% CI)		0.44 (0.22, 0.66)	0.21 (0.02, 0.46)	0.33 (0.09, 0.50)
One-sided p-value <sup>a</sup>		0.0015	0.0174	0.0015
<b>Proportion of positive pruritus assessments over the treatment period</b>				
Proportion	28.74	58.31	47.69	53.51
Difference in proportion (SE) vs. placebo (95% CI) <sup>b</sup>		28.23 (9.18) (9.83, 46.64)	21.71 (9.89) (1.87, 41.54)	24.97 (8.24) (8.45, 41.49)

<sup>a</sup>Based on Cochran Mantel Haenszel test stratified by PFIC Type. P-values for the dose groups are adjusted for multiplicity.

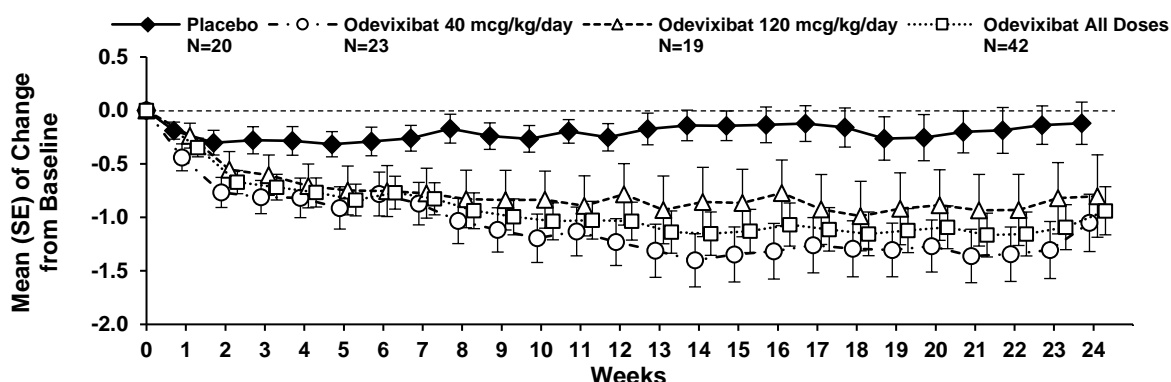
<sup>b</sup>Based on least squares means from an analysis of covariance model with daytime and night-time baseline pruritus scores as covariates and treatment group and stratification factors (PFIC Type and age category) as fixed effects.

**Figure 1: Mean ( $\pm$ SE) change from baseline in serum bile acid concentration ( $\mu\text{mol/L}$ ) over time**



Number of Patients							
Placebo	20	20	18	17	16	12	11
40 mcg/kg/day	23	21	21	20	15	14	17
120 mcg/kg/day	19	19	16	16	11	11	15
All doses	42	40	37	36	26	25	32

**Figure 2: Mean ( $\pm$ SE) change from baseline in pruritus (scratching) severity score over time**



Number of Patients																											
Placebo	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	18	18	17	17	17	16	15	15	15	15	13	12
40 mcg/kg/day	23	23	23	23	23	23	23	22	22	23	23	23	23	23	19	19	19	19	20	19	18	19	19	19	19	19	17
120 mcg/kg/day	19	19	19	19	19	19	19	19	19	18	18	18	18	18	16	16	16	16	16	16	16	16	16	16	16	15	14
All doses	42	42	42	42	42	42	42	41	41	41	41	41	41	41	35	35	35	35	36	35	34	35	35	35	35	34	31

In line with the results for reduction of pruritus (scratching), odevixibat reduced the percentage of days the patient required soothing, and patients less often required help falling asleep and had fewer days needing to sleep with a caregiver. Treatment with odevixibat also led to improvements from baseline in liver function test results (Table 5). The effect of odevixibat on growth parameters over 24 weeks is also presented.



**Table 5: Comparison of efficacy results for growth and hepatic biochemical parameters for odevixibat vs. placebo over the 24-week treatment period in patients with PFIC in trial 1**

Efficacy endpoint	Placebo (N=20)	Odevixibat		
		40 mcg/kg/day (N=23)	120 mcg/kg/day (N=19)	Total (N=42)
<b>Alanine aminotransferase (U/L) (mean [SE])</b>				
Baseline	76.9 (12.57)	127.7 (34.57)	89.1 (19.95)	110.2 (20.96)
Change to Week 24	3.7 (4.95)	-27.9 (17.97)	-25.3 (22.47)	-26.7 (13.98)
Mean difference vs. placebo (95% CI) <sup>a</sup>		-14.8 (16.63) (-48.3, 18.7)	-14.9 (17.25) (-49.6, 19.9)	-14.8 (15.05) (-45.1, 15.4)
<b>Aspartate aminotransferase (U/L) (mean [SE])</b>				
Baseline	90.2 (11.59)	114.2 (17.24)	96.0 (16.13)	106.0 (11.87)
Change to Week 24	4.7 (5.84)	-36.7 (12.21)	-27.0 (19.42)	-32.1 (11.02)
<b>Total bilirubin (µmol/L) (mean [SE])</b>				
Baseline	53.3 (12.97)	52.2 (10.13)	57.0 (18.05)	54.4 (9.75)
Change to Week 24	-9.6 (15.16)	-23.7 (9.23)	-19.3 (13.62)	-21.7 (7.92)
<b>Height z-scores (mean [SE])</b>				
Baseline	-2.26 (0.34)	-1.45 (0.27)	-2.09 (0.37)	-1.74 (0.23)
Change to Week 24	-0.16 (0.10)	0.05 (0.11)	0.00 (0.16)	0.03 (0.09)
Mean difference vs. placebo (95% CI) <sup>a</sup>		0.32 (0.16) (0.00, 0.65)	0.15 (0.17) (-0.18, 0.48)	0.24 (0.14) (-0.05, 0.53)
<b>Weight z-scores (mean [SE])</b>				
Baseline	-1.52 (0.32)	-0.74 (0.27)	-1.19 (0.35)	-0.94 (0.21)
Change to Week 24	0.10 (0.10)	0.29 (0.11)	0.15 (0.12)	0.22 (0.08)
Mean difference vs. placebo (95% CI) <sup>a</sup>		0.28 (0.14) (-0.01, 0.57)	0.08 (0.15) (-0.22, 0.37)	0.18 (0.13) (-0.08, 0.44)

<sup>a</sup>Based on least squares means from a mixed model for repeated measures (MMRM) with baseline value as a covariate, and treatment group, visit, treatment-by-visit interaction, treatment-by-baseline interaction and stratification factors (PFIC type and age category) as fixed effects.

Trial 2 is an interim cut of data from an ongoing 72-week open-label extension trial in PFIC patients treated with Bylvy 120 mcg/kg/day. The 79 patients (PFIC1 [22%], PFIC2 [51%], PFIC3 [5%] or PFIC6 [1%]) treated with 120 mcg/kg/day for up to 48 weeks experienced a durable effect on serum bile acids reduction, improvement in pruritus score, ALT, AST and total bilirubin. Across the 79 patients, 45 had assessments on or after 48 weeks of treatment with odevixibat, including 13, 30, 1 and 1 patients with PFIC1, PFIC2, PFIC3, and PFIC6, respectively; 9, 21, 4, and 0 patients, respectively, had not reached 48 weeks of treatment and were ongoing at the data cut-off. Overall, 7 patients with PFIC2 had discontinued prior to 48 weeks of treatment with odevixibat. Improvements in z-scores for height and weight indicate an enhanced growth velocity and the potential for catch-up growth in actively growing children.

## 5.2 Pharmacokinetic properties

### Absorption

Odevixibat is minimally absorbed following oral administration; absolute bioavailability data in humans are not available, and estimated relative bioavailability is < 1%. Peak odevixibat plasma concentration ( $C_{max}$ ) is reached within 1 to 5 hours. Simulated  $C_{max}$  values in a paediatric PFIC patient population for the 40 and 120 mcg/kg/day doses are 0.211 ng/mL and 0.623 ng/mL, respectively, and AUC values were 2.26 ng × h/mL and 5.99 ng × h/mL, respectively. There is minimal accumulation of odevixibat following once-daily dosing.

### *Effect of food*

Systemic exposure of odevixibat does not predict efficacy. Therefore, no dose adjustment for food effects is considered necessary. Concomitant administration of a high-fat meal (800 - 1,000 calories

with approximately 50% of total caloric content of the meal from fat) resulted in decreases of approximately 72% and 62% in  $C_{max}$  and  $AUC_{0-24}$ , respectively, compared to administration under fasted conditions. When odevixibat was sprinkled on apple sauce, decreases of approximately 39% and 36% in  $C_{max}$  and  $AUC_{0-24}$ , respectively, were observed compared to administration under fasted conditions. Taking into account the lack of PK/PD relationship and need for sprinkling the odevixibat capsule contents on food for younger children, odevixibat can be administered with food.

### Distribution

Odevixibat is more than 99% bound to human plasma proteins. The mean body weight adjusted apparent volumes of distribution (V/F) in paediatric patients for the 40 and 120 mcg/kg/day dose regimens are 40.3 and 43.7 L/kg, respectively.

### Biotransformation

Odevixibat is minimally metabolised in humans.

### Elimination

Following administration of a single oral dose of 3,000 mcg of radiolabeled odevixibat in healthy adults, the average percent recovery of the administered dose was 82.9% in faeces; less than 0.002% was recovered in the urine. More than 97% of faecal radioactivity was determined to be unchanged odevixibat.

The mean body weight normalised apparent total clearances CL/F in paediatric patients for the 40 and 120 mcg/kg/day dose regimens are 26.4 and 23.0 L/kg/h, respectively, and the mean half-life is approximately 2.5 hours.

### Linearity/non-linearity

The  $C_{max}$  and  $AUC_{0-t}$  increase with increasing doses in a dose-proportional manner; however due to the high interindividual variability of approximately 40%, it is not possible to estimate the dose proportionality accurately.

### *Pharmacokinetic/pharmacodynamic relationship(s)*

Consistent with the mechanism and site of action of odevixibat in the gastrointestinal tract no relationship between systemic exposure and clinical effects is observed. Also, no dose-response relationship could be established for the investigated dose range 10-200 mcg/kg/day and the PD parameters C4 and FGF19.

### Special populations

No clinically significant differences in the pharmacokinetics of odevixibat were observed based on age, sex or race.

### *Hepatic impairment*

The majority of patients with PFIC presented with some degree of hepatic impairment because of the disease. Hepatic metabolism of odevixibat is not a major component of the elimination of odevixibat. Analysis of data from a placebo-controlled study in patients with PFIC Types 1 and 2 did not demonstrate a clinically important impact of mildly impaired hepatic function (Child Pugh A) on the pharmacokinetics of odevixibat. Although, body weight adjusted CL/F values were lower and body weight adjusted V/F values were larger in paediatric patients with PFIC with Child Pugh B compared to healthy subjects, the safety profile was comparable between the patient groups. Patients with severe hepatic impairment (Child-Pugh C) have not been studied.

### *Renal impairment*

There are no clinical data in patients with renal impairment, but the impact of renal impairment is expected to be small due to low systemic exposure and odevixibat is not excreted in urine.

### In vitro studies

In *in vitro* studies, odevixibat did not inhibit CYPs 1A2, 2B6, 2C8, 2C9, 2C19 or 2D6 at clinically relevant concentrations, but was shown to be an inhibitor of CYP3A4/5.

Odevixibat does not inhibit the transporters P-gp, breast cancer resistance protein (BCRP), organic anion transporter (OATP1B1, OATP1B3, OAT1, OAT3), organic cation transporter (OCT2), multidrug and toxin extrusion transporter (MATE1 or MATE2-K).

Odevixibat is not a BCRP substrate.

## **5.3 Preclinical safety data**

Adverse reactions not observed in clinical trials, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

### Reproductive and developmental toxicity

In pregnant New Zealand White rabbits, early delivery/abortion was observed in two rabbits receiving odevixibat during the period of foetal organogenesis at an exposure multiple of  $\geq 2.3$  of the anticipated clinical exposure (based on total plasma odevixibat AUC<sub>0-24</sub>). Reductions in maternal body weight and food consumption were noted in all dose groups (transient at the exposure multiple 1.1 of the anticipated dose).

Starting from the exposure multiple of 1.1 of the clinical human exposure (based on total plasma odevixibat AUC<sub>0-24</sub>), 7 foetuses (1.3% of all foetuses from odevixibat exposed does) in all dose groups were found to have cardiovascular defects (i.e. ventricular diverticulum, small ventricle and dilated aortic arch). No such malformations were observed when odevixibat was administered to pregnant rats. Because of the findings in rabbits, an effect of odevixibat on cardiovascular development cannot be excluded.

Odevixibat had no effect on the reproductive performance, fertility, embryo-foetal development, or prenatal/postnatal development studies in rats at the exposure multiple of 133 of the anticipated clinical exposure (based on total plasma odevixibat AUC<sub>0-24</sub>), including juveniles (exposure multiple of 63 of the anticipated human exposure).

There is insufficient information on the excretion of odevixibat in animal milk.

The presence of odevixibat in breast milk was not measured in animal studies. Exposure was demonstrated in the pups of lactating dams in the pre- and post-natal developmental toxicity study with rats (3.2-52.1% of the odevixibat plasma concentration of the lactating dams). It is therefore possible that odevixibat is present in breast milk.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule content

Microcrystalline cellulose (MCC) spheres 700  
Hypromellose 3mPa.s

#### Capsule shell

*Bylvay 200 mcg and 600 mcg hard capsules*

Hypromellose

Titanium dioxide

Yellow iron oxide (E172)

*Bylvay 400 mcg and 1,200 mcg hard capsules*

Hypromellose

Titanium dioxide

Yellow iron oxide (E172)

Red iron oxide (E172)

#### Printing ink

Shellac glaze in ethanol

Black iron oxide

N-butyl alcohol

Isopropyl alcohol

Propylene glycol

Ammonia hydroxide 28%

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

The expiry date of the product is indicated on the packaging materials

### **6.4 Special precautions for storage**

Do not store above 25 °C. Store in the original package in order to protect from light.

### **6.5 Nature and contents of container**

High-density polyethylene (HDPE) bottle with a tamper evident, child resistant polypropylene closure.

Pack size: 30 hard capsules

### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MANUFACTURER**

Albireo AB

Arvid Wallgrens backe 20

413 46 Göteborg

Sweden

## **8. LICENSE HOLDER**

Medison Pharma Ltd.  
10 Hashiloach St.,  
POB 7090 Petach Tikva  
Israel

## **9. REGISTRATION NUMBERS**

Bylvay 200 micrograms hard capsules: 171-41-37197-99  
Bylvay 400 micrograms hard capsules: 171-42-37198-99  
Bylvay 600 micrograms hard capsules: 171-43-37199-99  
Bylvay 1,200 micrograms hard capsules: 171-44-37200-99

Approved in January 2023

Bylvay 200 mcg, 400 mcg, 600 mcg, 1200 mcg-SPC-1222-V2