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 odevixibat sesquihydrate equivalent to 200 micrograms odevixibat

Bylvay 400 mcg hard capsules

Each hard capsule contains odevixibat sesquihydrate equivalent to 400 micrograms odevixibat

Bylvay 600 mcg hard capsules

Each hard capsule contains odevixibat sesquihydrate equivalent to 600 micrograms odevixibat

Bylvay 1,200 mcg hard capsules

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

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

Progressive Familial Intrahepatic Cholestasis (PFIC)
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).

Alagille Syndrome (ALGS)
Bylvay is indicated for the treatment of cholestatic pruritus in patients 12 months of age and older with ALGS.

4.2 Posology and method of administration

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

Posology

Recommended Dosage for Progressive Familial Intrahepatic Cholestasis (PFIC) in Patients Aged 6 Months or Older

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	**1**	or	N/A
7.5 to < 12.5	**2**	or	1
12.5 to < 17.5	**3**	or	N/A
17.5 to < 25.5	**4**	or	2
25.5 to < 35.5	6	or	**3**
35.5 to < 45.5	8	or	**4**
45.5 to < 55.5	10	or	**5**
≥ 55.5	12	or	**6**

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	**1**	or	N/A
7.5 to < 12.5	**2**	or	1
12.5 to < 17.5	**3**	or	N/A
17.5 to < 25.5	**4**	or	2
25.5 to < 35.5	6	or	**3**

35.5 to < 45.5	8	or	**4**
45.5 to < 55.5	10	or	**5**
≥ 55.5	12	or	**6**

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.

Recommended Dosage for Alagille Syndrome (ALGS) in Patients Aged 12 Months and Older

- The recommended dosage of BYLVAY is 120 mcg/kg taken orally once daily in the morning with or without a meal. Table 3 below shows the recommended once daily dosage by body weight.

Table 3. Recommended Dosage for ALGS in Patients aged 12 months and older (120 mcg/kg/day)

Body Weight (kg)	Once Daily Dosage (mcg)
7.4 and below	600
7.5 to 12.4	1,200
12.5 to 17.4	1,800
17.5 to 25.4	2,400
25.5 to 35.4	3,600
35.5 to 45.4	4,800
45.5 to 55.4	6,000
55.5 and above	7,200

Dosage Modification for Management of Adverse Reactions

Tolerability for Alagille Syndrome (ALGS)

Dose reduction to 40 mcg/kg/day may be considered if tolerability issues occur in the absence of other causes. Once tolerability issues stabilize, increase to 120 mcg/kg/day.

Liver Test Abnormalities

Establish the baseline pattern of variability of liver tests prior to starting BYLVAY, so that potential signs of liver injury can be identified. Monitor liver tests (e.g., ALT [alanine aminotransferase], AST [aspartate aminotransferase], TB [total bilirubin], DB [direct bilirubin] and International Normalized Ratio [INR]) during treatment with BYLVAY. Interrupt BYLVAY if new onset liver test abnormalities occur or symptoms consistent with clinical hepatitis are observed [see section 4.4].

Once the liver test abnormalities either return to baseline values or stabilize at a new baseline value, consider restarting BYLVAY at the recommended dosage [see section 4.2]. Consider discontinuing BYLVAY permanently if liver test abnormalities recur.

Discontinue BYLVAY permanently if a patient experiences a hepatic decompensation event (e.g., variceal haemorrhage, ascites, hepatic encephalopathy).

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 for the treatment of PFIC in children aged less than 6 months has not been established. No data are available.

The safety and effectiveness of BYLVAY have been established in paediatric patients 12 months to 17 years of age for the treatment of pruritus in ALGS. Use of BYLVAY in this age group is supported by evidence from one randomized, double-blind, placebo-controlled trial conducted in 52 patients with a confirmed diagnosis of ALGS (Trial 3) and one open-label extension trial in ALGS patients (Trial 4) [see sections 4.8 and 5.1].

The safety and effectiveness of BYLVAY for the treatment of pruritus in ALGS in paediatric patients less than 12 months of age have not been established.

Method of administration

Bylvay 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

Enterohepatic circulation
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 clinical data with odevixibat in PFIC subtypes other than 1 and 2.

Diarrhoea
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). Treatment interruption or discontinuation may be required for persistent diarrhoea.

Liver monitoring
Elevations in liver enzymes and bilirubin levels have been observed in patients treated with odevixibat. Assessment of liver function tests is recommended for all patients prior to initiating odevixibat, with monitoring per standard clinical practice. For patients with liver function test elevations and severe hepatic impairment (Child-Pugh C), more frequent monitoring is to be considered.

Fat-soluble vitamin absorption
Assessment of fat-soluble vitamin (FSV) levels (Vitamins A, D, E) and international normalised ratio (INR) are recommended for all patients prior to initiating odevixibat, with monitoring per standard clinical practice. If FSV deficiency is diagnosed, supplemental therapy should be prescribed.

Patients enrolled in the ALGS trial had abnormal liver tests at baseline. In Trial 3 in ALGS patients, treatment-emergent elevations or worsening in liver tests relative to baseline values were observed during the trial. Most abnormalities included elevation in ALT or AST. One patient interrupted treatment for 40 days; none of the patients in Trial 3 permanently discontinued treatment due to liver test abnormalities.

In Trial 3, diarrhoea in ALGS patients was reported in 1 placebo-treated patient (6%) and in 10 (29%) BYLVAY-treated patients [see section 4.8]. No patients interrupted or permanently discontinued BYLVAY due to diarrhoea.

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.

In an interaction study with a lipophilic combination oral contraceptive containing ethinyl estradiol (EE) (0.03 mg) and levonorgestrel (LVN) (0.15 mg) conducted in adult healthy females, concomitant use of odevixibat had no impact on the AUC of LVN and decreased the AUC of EE by 17%, which is not considered clinically relevant. Interaction studies with other lipophilic medicinal products have not been performed, therefore, an effect on the absorption of other fat-soluble medicinal products cannot be excluded.

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).

In Trial 3, new or worsening of existing Fat-Soluble Vitamin (FSV) deficiency was reported in 3 (17.6%) placebo-treated patients and 3 (8.6%) BYLVAY-treated patients.

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 odevixibat..

Pregnancy

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

Breast-feeding

It is unknown whether odevixibat or its metabolites are excreted in human milk. There is insufficient information on the excretion of odevixibat 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 odevixibat 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

Odevixibat 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 (32.2%). Other reported adverse reactions were mild to moderate increases in blood bilirubin (24.8%), ALT (14%) and AST (9.1%), vomiting (16.5%), stomach pain (11.6%), and decreases in Vitamin D (11%) and E levels (5%).

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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 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	Frequency	Adverse drug reaction
Gastrointestinal disorders	Very common	diarrhoea[a], vomiting abdominal pain[b],
Hepatobiliary disorders	Very common	blood bilirubin increased, ALT increased
	Common	hepatomegaly AST increased
Metabolism and nutrition disorders	Very common	vitamin D deficiency
	Common	vitamin E deficiency

[a] Based on the combined frequency of diarrhoea, diarrhoea haemorrhagic and faeces soft
[b] Includes abdominal pain upper and abdominal pain lower
ALT = alanine aminotransferase
AST = aspartate aminotransferase

Description of selected adverse reactions

PHIC Clinical Studies

Gastrointestinal adverse reactions
In clinical trials, diarrhoea was the most common gastrointestinal adverse drug reaction. Adverse reactions of diarrhoea, diarrhoea haemorrhagic and soft faeces were of short duration with most events ≤ 5 days in duration. Most cases of diarrhoea were mild to moderate in intensity and non-serious. Dose reduction, treatment interruption and discontinuation due to diarrhoea was reported with few patients requiring intravenous or oral hydration due to diarrhoea (see section 4.4).
Other commonly reported gastrointestinal disorders were vomiting and abdominal pain (including upper and lower abdominal pain), all non-serious, mild to moderate and in general not requiring dose adaption.
Hepatobiliary disorders
The most common hepatic adverse reactions were increases in blood bilirubin, AST and ALT. The majority of these were mild to moderate in severity. Treatment interruption due to increases in liver function tests were noted in patients with PFIC treated with odevixibat. Most excursions in ALT, AST,

and bilirubin values were also due to the underlying disease, as well as to intermittent concomitant viral or infectious illnesses, which are common at the age of the patients, hence, monitoring of liver function tests is recommended (see section 4.4).

Metabolism and nutrition disorders
Due to decreased release of bile acids into the intestine and malabsorption, patients with PFIC are at risk for fat-soluble vitamin deficiency (see section 4.4). Reductions in vitamin levels were observed during long-term treatment with odevixibat; the majority of these patients responded to appropriate vitamin supplementation. These events were mild in intensity and did not lead to discontinuation of odevixibat.

ALGS Clinical Studies
Trial 3 is a randomized, double-blind, placebo-controlled, 24-week study of a single dose level of BYLVAY (120 mcg/kg) administered once daily [see section 5.1]. Fifty-two patients were randomized (2:1) to receive one of the following:

- BYLVAY 120 mcg/kg/day (n=35), or
- Placebo (n=17).

Table 5 summarizes the frequency of adverse reactions in patients with ALGS, reported in ≥5% and at a rate greater than placebo in patients treated with BYLVAY in Trial 3. No patients discontinued study treatment due to an adverse reaction. The most common adverse reactions observed in Trial 3 included diarrhoea, abdominal pain, hematoma, and decreased weight.

Table 5. Common Adverse Reactions[a] from a Clinical Study of BYLVAY in Patients with Alagille Syndrome (Trial 3)

Adverse Reaction	Placebo N=17 n (%)	BYLVAY 120 mcg/kg/day N=35 n (%)
Diarrhoea	1 (6%)	10 (29%)
Abdominal Pain	1 (6%)	5 (14%)
Hematoma	0	3 (9%)
Weight decreased	0	2 (6%)

[a] Adverse reactions that occurred in ≥5% of BYLVAY-treated patients

Trial 4 is a 72-week, open-label extension study in 49 paediatric patients with ALGS aged 1 to 15 years. BYLVAY 120 mcg/kg/day was administered once daily. Treatment-emergent adverse reactions were similar to those observed in Trial 3. The most common reason for BYLVAY treatment interruption was gastrointestinal disorders, including diarrhoea and abdominal pain.

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 odevixibat 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

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

Pharmacodynamic effects

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

Trial 3 is a 24-week, randomized, double-blind, placebo-controlled trial conducted in 52 patients with a confirmed diagnosis of ALGS who were administered treatment with BYLVAY 120 mcg/kg once daily. At baseline, serum bile acids were variable ranging from 93 to 510 mcmol/L. Serum bile acid concentrations were reduced from baseline as early as Week 4 of odevixibat treatment and the reduction was generally maintained during treatment over 24 weeks.

Clinical efficacy

PFIC

The efficacy of Bylvay in patients with PFIC was evaluated in two phase 3 trials and in a Phase 2 dose-finding study (A4250-003) in paediatric patients with cholestatic liver disease, including PFIC. Trial 1 (Study A4250-005) 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 odevixibat and stratified by PFIC Type (1 or 2) and age (6 months to 5 years, 6 to 12 years, and 13 to ≤ 18 years). Patients with pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein and those with ALT > 10 × ULN or bilirubin > 10 × ULN were excluded. 13% of the patients had prior biliary diversion surgery. Patients completing Trial 1 were eligible to enrol in Trial 2 (Study A4250-008), a 72-week open-label extension trial. In total, 116 patients were enrolled in Study A4250-008, including 37 patients who received odevixibat in Study A4250-005 and 79 patients who were treatment naïve. Results were analysed for Study A4250-005 and pooled for Studies A4250-005 and A4250-008, representing 96 weeks of treatment for patients that completed treatment with odevixibat in both trials. The primary endpoint in Trial 1 and Trial 2 was the proportion of patients with at least a 70% reduction in fasting serum bile acid levels or who achieved a level ≤ 70 µmol/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 ≤ 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 m². 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] µmol/L, respectively) and placebo-treated patients (3.0 [0.143] and 247.5 [101.1] µmol/L, respectively). Demographic and baseline characteristics of the pooled phase 3 population were generally consistent with the Study A4250-005 population. 36 (30%) of patients had PFIC Type 1, 70 (58%) had PFIC Type 2, 7 (6%) had PFIC Type 3, 4 (3%) had the episodic form of PFIC, and 2 (2%) each had PFIC Type 4 and PFIC Type 6.

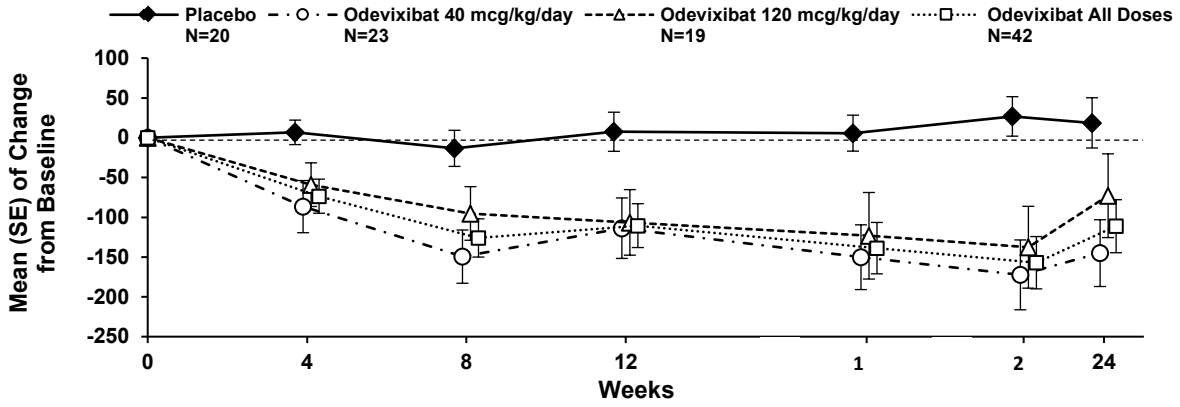
Table 6 presents the results of the comparison of the key efficacy results in Trial 1 between odevixibat and placebo. These data are displayed graphically over the 24-week treatment period in Figure 1 (serum bile acids) and Figure 2 (scratching scores).

Table 6: 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)
Proportion of patients with reduction in serum bile acids at end of treatment (responders[a])				
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[b]		0.0015	0.0174	0.0015
Proportion of positive pruritus assessments over the treatment period				
Proportion	28.74	58.31	47.69	53.51
Difference in proportion (SE) vs. placebo (95% CI)[b]		28.23 (9.18) (9.83, 46.64)	21.71 (9.89) (1.87, 41.54)	24.97 (8.24) (8.45, 41.49)

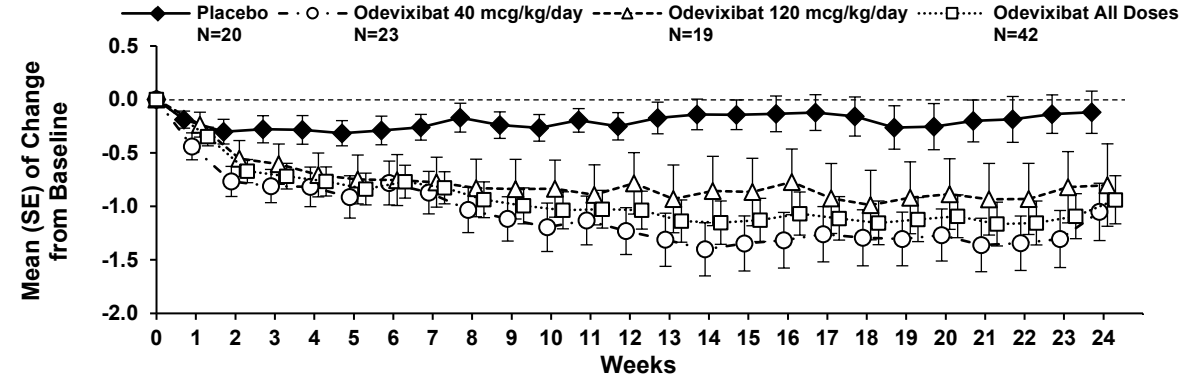
[a]Responders were defined as at least a 70% reduction in serum bile acids concentration from baseline or reaching a level ≤ 70 µmol/L.
[b]Based on Cochran Mantel Haenszel test stratified by PFIC Type. P-values for the dose groups are adjusted for multiplicity.
[c]Based on least squares means from an 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 (±SE) change from baseline in serum bile acid concentration (µmol/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 (±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	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	19	19	19	19	20	19	18	19	19	19	19	17
120 mcg/kg/day	19	19	19	19	19	19	19	19	19	18	18	18	18	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	35	35	35	35	36	35	34	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 7). The effect of odevixibat on growth parameters over 24 weeks is also presented.

Table 7: 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)
Alanine aminotransferase (U/L) (mean [SE])				
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)[a]		-14.8 (16.63) (-48.3, 18.7)	-14.9 (17.25) (-49.6, 19.9)	-14.8 (15.05) (-45.1, 15.4)
Aspartate aminotransferase (U/L) (mean [SE])				
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)
Total bilirubin (µmol/L) (mean [SE])				
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)
Height z-scores (mean [SE])				
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)[a]		0.32 (0.16) (0.00, 0.65)	0.15 (0.17) (-0.18, 0.48)	0.24 (0.14) (-0.05, 0.53)
Weight z-scores (mean [SE])				
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)[a]		0.28 (0.14) (-0.01, 0.57)	0.08 (0.15) (-0.22, 0.37)	0.18 (0.13) (-0.08, 0.44)

[a]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.

In the pooled phase 3 analysis, median duration of exposure across the 121 patients having received at least one dose of odevixibat was 102.0 weeks. 87 (72%) of the 121 patients received ≥72 weeks of treatment with odevixibat.

At week 24, 36% of patients were serum bile acids responders (N=112); this effect was sustained at week 72 when 44% were serum bile acids responders (N=85). Pruritus scores improved in a consistent fashion by 63.5% at week 24 (N=102) and 72.3%, at week 72 (N=76).
The rate of serum bile acid responders at week 72 for patients with PFIC1 was 25% (7 of 28 patients), 49% (22 of 45) for PFIC2 and 67% (8 of 12) for patients with other types of PFIC. Positive pruritus assessments at the patient level over 72 weeks was similar in patients with PFIC1 (n=24) and PFIC2 (n=43), with response rates of 69% and 70%, respectively. In the subgroup of patients with other types of PFIC (PFIC3, PFIC4, PFIC6 and episodic PFIC, n=9) 91% were responders.

Mean (SD) changes from baseline at week 72 in ALT, AST, and total bilirubin in the pooled phase 3 group were -25.88 (119.18) U/L (n=78), -9.38 (69.279) U/L (N=79), and -25.65 (120.708) µmol/L (1.50 mg/dL) (n=79), respectively. Results for GGT were variable. Consistent and substantial improvement in growth was observed during longer term treatment with odevixibat. Mean height and weight z-scores improved to -1.26 and -0.75 at week 72, respectively, representing mean (SD) changes of 0.44 (0.705) (n=76) and 0.42 (0.762) (n=77), respectively.

ALGS
The efficacy of BYLVAY was evaluated in Trial 3 (NCT04674761), a 24-week, randomized, double-blind, placebo-controlled trial. Trial 3 was conducted in 52 paediatric patients, aged 6 months to 15

years, with a confirmed diagnosis of ALGS and presence of pruritus at baseline. Patients who had decompensated liver disease, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT was greater than 10-times the upper limit of normal (ULN) at screening, whose total bilirubin was greater than 15-times the ULN at screening, or who had received a liver transplant were excluded from Trial 3.

Patients were randomized to placebo (n=17) or 120 mcg/kg (n=35). Study drug was administered once daily with a meal in the morning. In patients weighing less than 19.5 kg or patients who could not swallow the whole capsule, study drug was sprinkled on soft food and then administered orally.

Median age (range) of the patients in Trial 3 was 6.1 (1.7 to 15.5) years in the BYLVAY group and 4.2 (0.5 to 14.3) years in the placebo group; 5 patients were older than 12 years of age. Of the 52 patients, 52% were male and 83% were white; 92% of patients had the JAG1 mutation and 8% had the NOTCH2 mutation. The mean (standard deviation [SD]) scratching score in the 2 weeks prior to baseline was 2.9 (0.6). Baseline mean (SD) eGFR was 159 (51.4) mL/min/1.73 m^2. Baseline median (range) ALT, AST, and total bilirubin were 152 (39-403) U/L, 135 (57-427) U/L, and 2.0 (0.4-11.4) mg/dL, respectively.

Given the patients' young ages, a single-item observer-reported outcome (ObsRO) was used to measure patients' scratching severity as observed by their caregiver twice daily (once in the morning and once in the evening). Scratching severity was assessed on a 5-point ordinal response scale, with scores ranging from 0 (no scratching) to 4 (worst possible scratching). Patients were included in Trial 3 if the average scratching score was greater than or equal to 2 (medium scratching) in the 14 days prior to baseline.

Table 8 presents the results of the comparison between BYLVAY and placebo on the change from baseline in average scratching score based on ObsRO assessments to Month 6 (Weeks 21 to 24). The average scratching score for each patient for each month post-baseline was calculated by: (Step 1) averaging the morning scores and averaging the evening scores within a week; (Step 2) averaging the morning and evening weekly scores to yield a single weekly score; and finally (Step 3) averaging the 4 weekly scores within the month. The baseline average scratching score for each patient was calculated by averaging the weekly scores obtained in Step 2 across the 2 weeks prior to randomization and initiation of blinded treatment. Patients treated with BYLVAY demonstrated greater improvement in pruritus compared with placebo. Figure 2 displays the means (95% confidence interval) of patients' average scratching scores in each treatment group for each month.

Table 8: Efficacy Results in Patients with ALGS in Trial 3

	Placebo (n=17)	**BYLVAY 120 mcg/kg/day (n=35)**
Baseline Average Scratching Score		
Mean (SD)	3.0 (0.6)	2.8 (0.5)
Change from Baseline in Average Scratching Score to Month 6 (Weeks 21 to 24)[a]		
Mean (SE)	-0.8 (0.2)	-1.7 (0.2)
Mean Difference vs Placebo (95% CI) p-value	-0.9 (-1.4, -0.3) 0.002	

[a] Based on least square means from a mixed-effect model for repeated measures (MMRM) for change from baseline to each month accounting for baseline average scratching score, baseline age stratification (<10, ≥10 years), baseline direct bilirubin, treatment group, time (in months), and treatment-by-time interaction.

Figure 2: Mean* of the Average Scratching Scores for Each Month in Trial 3

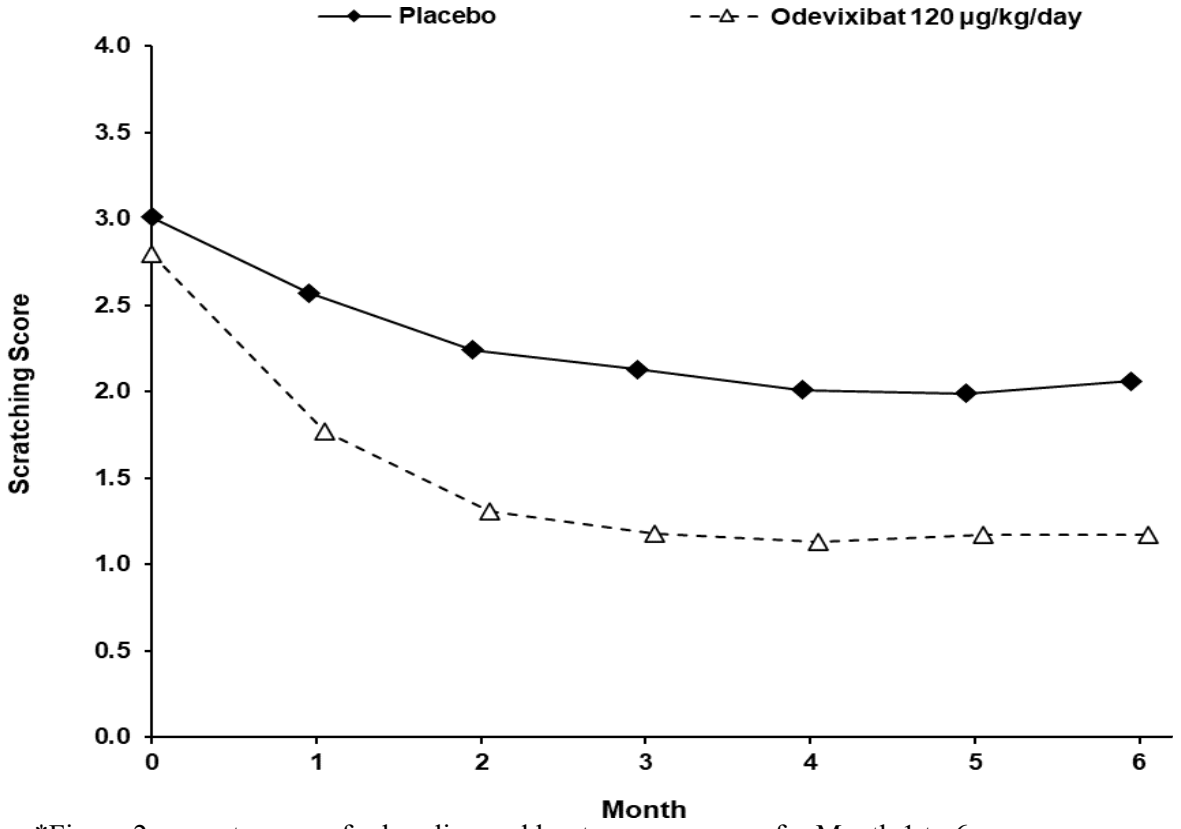


*Figure 2 presents means for baseline and least squares means for Month 1 to 6
Least squares means are based on a mixed model repeated measure (MMRM) analysis accounting for baseline average scratching score, baseline age stratification (<10, ≥10 years), baseline direct bilirubin, treatment group, time (in months), and treatment-by-time interaction.

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.

Paediatric patients
In paediatric patients with ALGS who received BYLVAY 120 mcg/kg once daily with food in the morning, the measurable odevixibat concentrations ranged from 0.05 to 3.4 ng/mL.

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 ≥ 2.3 of the anticipated clinical exposure (based on total plasma odevixibat AUC_{0-24}). 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_{0-24}), 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_{0-24}), 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.

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

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