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EMA/116531/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kayfanda

International non-proprietary name: Odevixibat

Procedure No. EMEA/H/C/006462/II/0001/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	17 Dec 2024	17 Dec 2024	☐
☐	CHMP Rapporteur Assessment Report	20 Jan 2025	23 Jan 2025	☐
☐	PRAC Rapporteur Assessment Report	27 Jan 2025	27 Jan 2025	☐
☐	PRAC members comments	31 Jan 2025	n/a	☐
☐	CHMP members comments	03 Feb 2025	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	04 Feb 2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	06 Feb 2025	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	11 Feb 2025	11 Feb 2025	☐
☐	Start of written procedure	11 Feb 2025	11 Feb 2025	☐
☐	RSI	13 Feb 2025	13 Feb 2025	☐
☐	Submission	18 Feb 2025	18 Feb 2025	☐
☐	CHMP Rapporteur Assessment Report	26 Feb 2025	26 Feb 2025	☐
☐	PRAC Rapporteur Assessment Report	26 Feb 2025	26 Feb 2025	☐
☐	PRAC members comments	03 Mar 2025	n/a	☐
☐	CHMP members comments	03 Mar 2025	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	06 Mar 2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	06 Mar 2025	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	11 Mar 2025	11 Mar 2025	☐
☐	Start of written procedure	11 Mar 2025	11 Mar 2025	☐
☒	Opinion	13 Mar 2025	13 Mar 2025	☐

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1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Ipsen Pharma submitted to the European Medicines Agency on 29 November 2024 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

A grouped application consisting of:
C.I.4: Update of sections 4.4, 4.8, and 5.1 of the SmPC based on results from Study A4250-015 listed as a category 3 study in the RMP; this is a Phase 3, multicentre, open-label extension study to evaluate the long-term safety and efficacy of odevixibat in patients with Alagille syndrome (ALGS). The Package Leaflet is updated accordingly. The RMP version 6.2 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the PI.

C.I.13: Submission of the 72 week report from study A4250-008. This is a Phase 3, multicentre, open-label extension study to investigate the long-term efficacy and safety of odevixibat in patients with Progressive Familial Intrahepatic Cholestasis (PFIC) Types 1 and 2 (PEDFIC 2).

The requested group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

GLP/GCP inspections

N/A

2. Overall conclusion and impact on the benefit/risk balance

The MAH submitted Study A4250-008, a long-term efficacy and safety of odevixibat in patients suffering from PFIC. The relevance for this study is less relevant for the Alagille indication, as only safety could be of value for this indication. This study did not reveal any relevant or unexpected adverse event. Therefore, this study is not further discussed in this assessment.

Further, the MAH proposed an update of sections 4.4, 4.8, and 5.1 of the SmPC based on results from Study A4250-015, which is an extension of pivotal Study A4250-012. This is a Phase 3, multicentre, open-label extension study to evaluate the long-term safety and efficacy of odevixibat in patients with ALGS.

The efficacy and safety study of odevixibat included patients with genetic confirmation of ALGS; patients with both the JAG1 and NOTCH2 mutations were enrolled. The baseline characteristics and medication history of the patients enrolled in the efficacy and safety studies were consistent with the clinical manifestations described in patients with ALGS. Patients were required to have moderate to severe pruritus at study entry based on a score of $\geqslant$ 2 on observer-reported information and baseline serum bile acids above the ULN.

For patients who had received odevixibat in Study A4250-012, further improvements (although limited) from baseline were observed to Weeks 69-72. For patients who had received placebo in A4250 012, improvements in scratching severity and bile acid levels occurred rapidly and were sustained to Weeks 69-72.

Based on observer-reported information, treatment with odevixibat also led to improved sleep and daytime tiredness in both patients who had previously received odevixibat and treatment-naïve patients who first received odevixibat in Study A4250-015. Further, cholesterol levels, global symptom relief, and QoL also showed improvements in both patients who had received odevixibat and those who had received placebo in Study A4250-012.

Consistent with current prescribing information, the safety profile of odevixibat is primarily characterised by Grade 1 or 2 gastrointestinal disturbances, primarily reports of diarrhoea. There were no deaths in the studies. Discontinuation due to TEAEs was uncommon, reported in 1 (2%) of the 52 patients due to blood bilirubin increased.

No unexpected AE were reported during of treatment with odevixibat in patients with ALGS. Based on review of post-marketing safety surveillance that includes estimated cumulative exposure in 737 patients, there is no evidence of any new significant safety issues with odevixibat when administered according to the recommendations given in the reference safety information and within the approved indications.

The safety profile emerging form the long-term extension is more or less in line with the adverse events profile and with comparable frequencies of AEs as observed in the initial placebo controlled studies.

The most common hepatic adverse reactions were increases in blood bilirubin, ALT, AST and GGT. Most of these excursions were mild in severity and non-serious, and increases were not indicative of drug-induced liver injury. Elevations in liver enzymes and bilirubin levels were observed due to the underlying hepatic pathophysiology of ALGS, hence the monitoring of liver function tests is recommended in section 4.4. of the SmPC. This information, in line with extension of Study A4250-012, was added to 4.8 of the SmPC.

In 4.4 of the SmPC the MAH changed the requirements for liver monitoring from 6 months after treatment to the whole time of treatment which is considered acceptable as it is more in line with clinical practise. Furthermore, hepatic related adverse events had been also reported after the first 6 weeks of treatment.

Due to the decreased release of bile acids into the intestine and risk of malabsorption, paediatric patients with ALGS with chronic cholestasis are at risk of fat-soluble vitamin deficiencies even with supplementation. Reductions in vitamin levels were observed during long-term treatment with odevixibat; the majority of these patients responded to appropriate vitamin supplementation. Overall, few patients had fat-soluble vitamin deficiencies that were refractory to supplementation. These events were mild in intensity and did not lead to treatment interruption or discontinuation of odevixibat. This information, in line with extension of Study A4250-012, was added to 4.8 of the SmPC.

In line with results from study A4250-015 the MAH updated the frequency table on adverse reactions in 4.8 of the SmPC listing also elevated liver parameters separately and adding hepatomegaly and Vitamin E deficiency with a frequency common. Vitamin D deficiency was added with a frequency very common with is also agreed based on the study results.

Furthermore, the applicant updated the efficacy information derived from the extension study as well as from pooled results in 5.1 of the SmPC which is acceptable:

A total of 44 (85%) of the 52 patients who received odevixibat across the Phase 3 studies completed the 72-week treatment period in ASSERT-EXT. Median duration of odevixibat treatment for the 52 patients across the pooled phase 3 studies was 99.79 weeks and ranged up to 2.5 years. Overall, 45 (87%) of the 52 patients had received > 72 weeks of odevixibat with 32 (64%) having received > 96 weeks of treatment. Continued treatment with odevixibat 120 mcg/kg/day in ASSERT-EXT led to further improvements in pruritus score with results for the pooled population at weeks 69-72 (n = 43) showing mean (SD) changes from baseline of -1.95 (0.838). For those 31 patients who received odevixibat in both Phase 3 studies and had data available for analysis, continued improvement was observed through weeks 93-96 with mean (SD) change from baseline of -2.18 (0.876). The reduction in serum bile acid levels was maintained at week 72, when mean change from baseline was -119.4 µmol/L (-48.8 µg/mL; n = 44). Among those 30 patients who received odevixibat in both Phase 3 studies and had data available for analysis at week 96, change from baseline in serum bile acid levels was -123.9 µmol/L (-50.6 µg/mL). Improvements in sleep parameters, serum cholesterol levels and xanthomas were maintained during long-term treatment.

The MAH also made editorial changes to the SmPC which are agreed.

The benefit-risk of odevixibat in the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

A grouped application consisting of:
C.I.4: Update of sections 4.4, 4.8, and 5.1 of the SmPC based on results from Study A4250-015 listed as a category 3 study in the RMP; this is a Phase 3, multicentre, open-label extension study to evaluate the long-term safety and efficacy of odevixibat in patients with ALGS. The Package Leaflet is updated accordingly. The RMP version 6.2 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the PI.

C.I.13: Submission of the 72 week report from study A4250-008. This is a Phase 3, multicentre, open-label extension study to investigate the long-term efficacy and safety of odevixibat in patients with Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC 2).

☒is recommended for approval

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion Kayfanda-H-C-006462-II-001/G.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Update of sections 4.4, 4.8, and 5.1 of the SmPC based on results from Study A4250-015. This is a Phase 3, multicentre, open-label extension study to evaluate the long-term safety and efficacy of odevixibat in patients with ALGS.

6. Clinical Efficacy aspects

6.1. Study A4250-015

The results in this section are for the primary Week 72 analysis of this study; at that time, all patients had received at least 72 weeks of odevixibat in Study A4250-015 or had discontinued prior to that time.

6.1.1. Methods – analysis of data submitted

6.1.1.1. Disposition, Demographics and Baseline Characteristics, and Exposure

Disposition data for presentation of results for Study A4250-012 were based on the patient's status at the end of the respective study; data for the pooled summary of the Phase 3 studies were based on status as of the data cutoff of 07FEB2024 for patients enrolled in Study A4250-015, or at the end of Study A4250-012 for patients who did not enrol in Study A4250-015.

The frequencies and percentages of patients with reported medical and surgical history findings, family history of ALGS, and prior and concomitant medications were tabulated. If a patient had taken more than one medication within the same ATC level or the same preferred term more than once, the patient was counted only once within the ATC level and/or preferred name. Prior medications were defined as any medications taken by the patient within 3 months prior to first intake of study drug; for patients who received placebo in Study A4250-012, any concomitant medications from Study A4250-012 taken within 3 months prior to the first dose of odevixibat in Study A4250-015 were included as prior medications for the pooled analyses.

6.1.1.1.1. Disposition

Overall, a total of 52 patients with ALGS received at least 1 dose of odevixibat across the Phase 3 studies and are included in the Safety Analysis Set; these 52 patients comprise:

35 patients who received odevixibat and completed treatment in Study A4250-012, 33 of whom rolled over and received treatment with odevixibat in Study A4250-015

17 patients who received placebo and completed treatment in Study A4250-012, all 17 of whom rolled over and received treatment with odevixibat in Study A4250-015

Overall, 44 of the 52 patients enrolled in Study A4250-012 completed the 72-week treatment with odevixibat in Study A4250-015. Eight patients discontinued treatment with odevixibat prior to that time, including 2 patients who completed Study A4250-012 but elected not to enrol in Study A4250-015, 2 patients withdrew consent, and 1 patient each due to AE (elevated bilirubin), lack of efficacy, switch to other medication; and liver transplantation.

In total, 40 of the 44 patients who completed Week 72 elected to enrol in the optional extension treatment period; 3 patients transitioned to commercial odevixibat and 1 patient opted not to continue treatment.

As of the data cutoff of 07FEB2024 for Study A4250-015, 36 of the 40 patients were ongoing on treatment with odevixibat in the optional extension treatment period. Three patients discontinued treatment in the optional extension period as they were transitioned to commercially available odevixibat, and 1 patient was referred for liver transplant.

6.1.1.1.2. Exposure

As detailed previously, Study A4250-012 was a 24-week study; eligible patients from this study could rollover to the 72-week extension Study A4250-015. For Study A4250-012, median duration of treatment was 24.0 weeks in both treatment groups (**Table 1**).

Across all odevixibat treatment in the Pooled Phase 3 group, median duration of exposure as of the data cutoff of 07FEB2024 was 99.79 weeks and ranged from 15.7 to 131.3 weeks. Overall, 45 (87%) of the 52 patients received odevixibat for > 72 weeks and 32 (62%) patients received odevixibat for > 96 weeks. Total patient-years of exposure to odevixibat as of the data cutoff date was 92.3 years in the Pooled Phase 3 group.

Table 1: Duration of Study Treatment (Safety Analysis Set)

EXPOSURE PARAMETER	STUDY A4250-012 (BY TREATMENT)		STUDIES A4250-012/ A4250-015 POOLED
	PLACEBO (N=17)	ODEVIXIBAT (N=35)	ODEVIXIBAT[A] (N=52)
Duration of exposure (weeks)			
n	17	35	52
Mean (SD)	24.26 (0.485)	23.94 (0.726)	92.61 (30.421)
Median	24.00	24.00	99.79
Minimum, maximum	23.7, 25.1	21.1, 26.0	15.7, 131.3
Total Patient-Years of Exposure	7.9	16.1	92.3
Duration category, n (%)			
≤ 24 weeks	9 (52.9)	22 (62.9)	4 (7.7)
> 24 - ≤ 36 weeks	8 (47.1)	13 (37.1)	1 (1.9)
> 36 - ≤ 48 weeks	NA	NA	2 (3.8)
> 48 - ≤ 52 weeks	NA	NA	0
> 52 - ≤ 72 weeks	NA	NA	0
> 72 weeks	NA	NA	45 (86.5)
> 96 weeks	NA	NA	32 (61.5)

NA: not applicable; SD: standard deviation.
[a] Includes data on active treatment for patients who received odevixibat at any time in Studies A4250-012 and/or A4250-015.
Data cutoff: 07FEB2024.
Source: ALGS ISS Table 14.1.7.

6.1.1.1.3. Demographics

In the Pooled Phase 3 group, median age of the 52 patients was 5.70 years and ranged from 1.0 to 15.5 years (Table 2). Most patients (39 of 52, 75%) were ≥ 2 to < 12 years of age; 7 (14%) were < 2 years of age and 6 (12%) were ≥ 12 to < 18 years old. Approximately half of the patients were male and half female (52% and 48%, respectively). Most patients were white (43, 83%) and not Hispanic or Latino (44, 85%). The majority of patients in the Pooled Phase 3 group were enrolled at sites in Europe (36, 69%); 11 (21%) were enrolled at sites in the US and 5 (10%) were enrolled at sites in the RoW.

Table 2: Demographic Characteristics (Safety Analysis Set, Integrated Data)

CATEGORY STATISTIC	STUDY A4250-012 (BY TREATMENT)		STUDIES A4250-012/ A4250-015 POOLED
	PLACEBO (N=17)	ODEVIXIBAT (N=35)	ODEVIXIBAT[A] (N=52)
Sex, n (%)			
Male	6 (35.3)	21 (60.0)	27 (51.9)
Female	11 (64.7)	14 (40.0)	25 (48.1)
Age (years)			
n	17	35	52
Mean (SD)	5.40 (4.411)	6.73 (3.780)	6.45 (3.975)
Age Category, n (%)			
< 10 years	13 (76.5)	29 (82.9)	42 (80.8)
≥ 10 to < 18 years	4 (23.5)	6 (17.1)	10 (19.2)
Age Category, n (%)			
< 2 years	5 (29.4)	3 (8.6)	7 (13.5)
≥ 2 to < 12 years	11 (64.7)	28 (80.0)	39 (75.0)
≥ 12 to < 18 years	1 (5.9)	4 (11.4)	6 (11.5)
Race, n (%)			
White	13 (76.5)	30 (85.7)	43 (82.7)
Black or African American	2 (11.8)	2 (5.7)	4 (7.7)
Asian	1 (5.9)	2 (5.7)	3 (5.8)
Other	1 (5.9)	1 (2.9)	2 (3.8)
Ethnicity, n (%)			
Hispanic or Latino	1 (5.9)	1 (2.9)	2 (3.8)
Not Hispanic or Latino	14 (82.4)	30 (85.7)	44 (84.6)
Unknown	2 (11.8)	4 (11.4)	6 (11.5)
Region, n (%)			
Europe	12 (70.6)	24 (68.6)	36 (69.2)
United States	4 (23.5)	7 (20.0)	11 (21.2)
Rest of World	1 (5.9)	4 (11.4)	5 (9.6)

SD: standard deviation.
[a] Includes data on active treatment for patients who received odevixibat at any time in Studies A4250-012 and/or A4250-015.
Data cutoff: 07FEB2024.
Source: ALGS ISS Table 14.1.2.

6.1.1.1.4. Baseline and Disease Characteristics

Median time since diagnosis of ALGS in the Pooled Phase 3 group was 4.60 years. In Study A4250-012, although the baseline disease characteristics were generally similar between the treatment groups, the median time since diagnosis was longer in the odevixibat group than in the placebo group (5.50 vs 2.70 years, respectively).

In the Pooled Phase 3 group, all patients had genetic confirmation of ALGS with most (48 of 52; 92%) having a mutation in JAG1; in 4 patients (8%), the NOTCH2 mutation was reported. Almost all patients (51, 98%) were receiving antipruritic medications at baseline, including UDCA (46, 89%).

Consistent with ALGS, all patients in the Pooled Phase 3 group had hepatic impairment at baseline based on both the Child-Pugh and NCI ODWG classifications. Overall, 51 (98%) patients had moderate hepatic impairment based on the Child-Pugh classification and 1 (2%) had severe impairment. Hepatic impairment classification based on the NCI ODWG indicated that 23 (44%) of the 52 patients had severe hepatic impairment; moderate impairment was reported for 15 (29%) and mild in 14 (27%).

Consistent with the underlying liver pathology in patients with ALGS, median levels of hepatic biochemical parameters were elevated at baseline, including ALT (152.0 U/L), AST (140.5 U/L), GGT (361.5 U/L) and total bilirubin (37.6 µmol/L; 2.20 mg/dL), as were levels of serum bile acids (217 µmol/L; 88.6 µg/mL). ALT and direct bilirubin levels were > 3 × ULN at baseline in 29 (56%) and 18 (35%) of the 52 patients. Median eGFR was 151.40 mL/min/1.73 m2 calculated by the modified Schwartz equation [Muhari-Stark 2018].

Cholesterol levels at baseline were also elevated across the 52 patients with a median level of 7.510 mmol/L (290.0 mg/dL) as were triglycerides with a median level of 1.660 mmol/L (146.9 mg/dL).

Patients with ALGS are known to have fat soluble vitamins (FSV) deficiency. At baseline, most of the 52 patients had vitamin A and E levels above the normal range. For vitamin D and INR, most patients had baseline levels within normal range, reflective of the vitamin supplementation the patients were receiving at baseline. The median baseline level of vitamin A was 1.954 µmol/L (0.560 mg/L), of vitamin E (as alpha tocopherol) was 22.87 µmol/L (9.85 mg/L), and of 25-hydroxyvitamin D was 60.0 nmol/L (24.0 ng/mL). Median INR at baseline, as a surrogate for vitamin K, was 1.00.

6.1.2. Efficacy Results

In the following section, efficacy data for the primary Week 72 analysis of Study A4250-015, representing up to 96 weeks of overall treatment with odevixibat for patients who completed active treatment in Study A4250-012, and up to 72 weeks for patients who received placebo in Study A4250-012, are summarised.

The estimand strategy for the primary analysis of all efficacy endpoints was to include all data collected except that following the ICEs of biliary diversion surgery and liver transplant. One patient, patient [redacted], underwent liver transplant prior to the primary Week 72 timepoint; for this patient, only data prior to the date of liver transplant were included in the efficacy analyses.

6.1.2.1. Changes from Baseline in Scratching Severity Score Based on the ObsRO

Patients who had received odevixibat during Study A4250-012 entered Study A4250-015 with improved pruritus symptoms compared with treatment-naïve patients, with mean (SD) baseline scratching scores of 1.19 (0.98) compared with 2.22 (0.986) for those who had received placebo.

For patients who had received odevixibat in Study A4250-012, continued treatment with odevixibat led to further improvement in scratching severity. Mean (SD) changes from Study A4250-015 baseline in scratching severity score for this group of patients were -0.41 (0.647) at Weeks 21-24 (n = 28) and -0.54 (0.822) at Weeks 69-72 (n = 28).

For patients who received placebo in Study A4250-012, improvement in pruritus symptoms was observed early following the start of treatment with odevixibat with continued improvement through Week 72. Mean (SD) change in scratching severity scores to Weeks 1-4 (n = 16) was -0.74 (0.458) and to Weeks 21-24 (n = 15) and Weeks 69-72 (n = 13) were -1.43 (0.881) and -1.66 (0.820), respectively.

Analyses for changes in monthly scratching scores also were conducted based on Study A4250-012 baseline for patients who received odevixibat in both Phase 3 studies (CSR A4250-015 Table 14.2.1.1.1 and Figure 14.2.1.1). At baseline of Study A4250-012, mean (SD) scratching score was 2.81 (0.535). Following 48 weeks of treatment with odevixibat across both studies (Study A4250-015 Weeks 21-24, n = 30), mean (SD) change in scratching score was -2.03 (0.828) and following 96 weeks (Study A4250-015 Weeks 69-72, n = 30), was -2.19 (0.887) indicating maintenance of the effect over long-term treatment.

Results for nighttime (AM scores) and daytime (PM scores) monthly scratching scores were consistent with those for the combined AM and PM scores. For nighttime scratching score, mean (SD) change from Study A4250-015 baseline to Weeks 69-72 was -0.56 (0.850), for patients who received odevixibat (n = 28) and -1.59 (0.821), for patients who received placebo (n = 12) in Study A4250-012. For daytime scratching severity scores, mean (SD) changes to Weeks 69-72 was -0.51 (0.821) for patients who received odevixibat (n = 28) and -1.64 (0.858) for patients who received placebo (n = 12) in Study A4250-012, respectively.

6.1.2.2. Changes from Baseline in Patient-Reported Itching Severity Based on the PRO

Although data were limited, results for changes from baseline in patient-reported itching severity were consistent with caregiver reports showing sustained improvements for patients who received odevixibat in Study A4250-012 and improvement from baseline after the start of odevixibat treatment for patients who were treatment-naïve.

6.1.2.3. Clinically Meaningful Improvement in Pruritus Through Week 72

Pruritus responder analyses based on ≥ 1.5- and ≥ 1.0-point drops in scratching severity scores were assessed from Study A4250-015 baseline for patients who had received placebo in Study A4250-012 and from Study A4250-012 baseline for patients who received odevixibat in Study A4250-012.

For those patients who received odevixibat in both studies, following 96 weeks of treatment (Study A4250-015 Weeks 69-72), 22 (73.3%) of 30 patients had a ≥ 1.5-point reduction in scratching severity score. Nearly all patients who received odevixibat in both studies had ≥ 1.0-point reduction following 96 weeks of treatment (28 of 30, 93.3%).

For those patients who received placebo in Study A4250-012, 7 (53.8%) of 13 patients had achieved a ≥ 1.5-point reduction in scratching score at Weeks 69-72. For the ≥ 1.0-point reduction, 10 (76.9%) of 13 patients had this level of improvement in scratching severity at Weeks 69-72.

6.1.2.4. Changes from Baseline Over Time in Serum Bile Acid Assessments

At Study A4250-015 baseline, patients who received 24 weeks of treatment with odevixibat in Study A4250-012 had lower mean (SD) serum bile acid levels (155.0 [105.54] µmol/L; 63.3 [43.11] µg/mL) compared with patients who received placebo (265.1 [160.02] µmol/L; 108.3 [65.37] µg/mL).

For patients who received odevixibat in Study A4250-012, further reductions in serum bile acid levels were observed with continued treatment. At Weeks 24 and 48, mean (SD) change from baseline in serum bile acid levels from their Study A4250-015 baseline were -32.7 (88.72) µmol/L (-13.4 [36.24] µg/mL) and -27.1 (72.99) µmol/L (-11.1 [29.82] µg/mL), respectively. At Week 72, mean (SD) change from baseline in serum bile acid levels was -36.0 (90.76) µmol/L (-14.7 [37.07)] µg/mL).

For patients who received placebo in Study A4250-012, a rapid reduction in serum bile acid levels was observed after the initiation of treatment with odevixibat. By Week 4 of treatment, the mean (SD) change in serum bile acids was -140.5 (92.66) µmol/L (-57.4 [37.85] µg/mL). At Week 24, mean (SD) change from baseline in serum bile acid levels was -123.6 (94.95) µmol/L (-50.5 [38.79] µg/mL) and at Week 48 was -145.8 (91.49) µmol/L (-59.6 [37.37] µg/mL). The reduction in serum bile acids was sustained at Week 72, with mean (SD) change from baseline of -138.6 (101.17) µmol/L (-56.6 [41.33] µg/mL).

Changes in serum bile acid levels were also assessed from Study A4250-012 baseline for patients who received odevixibat in both Phase 3 studies. At baseline of Study A4250-012, mean (SD) serum bile acid level was 243.9 (114.83) µmol/L (99.6 [46.91] µg/mL). After 48 weeks of treatment with odevixibat (Study A4250-015 Week 24), mean (SD) change in serum bile acids was -116.6 (104.82 µmol/L) (-47.6 [42.82] µg/mL) with maintenance of the effect through 96 weeks of treatment (Study A4250-015 Week 72) with a mean (SD) change of -123.9 (135.63) µmol/L (-50.6 [55.40] µg/mL).

6.1.2.5. Changes from Baseline in Sleep Parameters

For patients who received odevixibat during Study A4250-012, the improvements in sleep parameters observed in that study were sustained over time during long-term treatment in Study A4250-015. Mean (SD) changes from baseline to Weeks 69-72 for this group were -15.4% (30.77%) for percentage of days with help falling asleep; -12.9% (31.56%) for percentage of days with soothing; -5.8% (21.68%) for percentage of days sleeping with the caregiver; -0.13 (0.925) for mean daytime tiredness score; -8.3% (19.99%) for percentage of days seeing blood due to scratching, and -0.39 (0.892) for mean number of awakenings.

Among treatment-naïve patients who first received odevixibat in Study A4250-015, improvement from baseline in most sleep parameters occurred early in the course of treatment and was sustained over time. Mean (SD) changes from baseline to Weeks 1-4 were -10.4% (20.42%), -12.0% (19.93%), and -12.0% (24.01%) for the percentage of days with help falling asleep, with soothing, and sleeping with the caregiver, respectively, and -0.42 (0.581) for daytime tiredness score. Mean (SD) changes from baseline to Weeks 69-72 were -36.4% (44.26%) for percentage of days with help falling asleep; -42.5% (43.33%) for percentage of days with soothing; -36.2% (41.57%) for percentage of days sleeping with the caregiver; -1.28 (0.692) for mean daytime tiredness score; -30.9% (33.46%) for percentage of days seeing blood due to scratching, and -5.02 (9.860) for mean number of awakenings.

6.1.2.6. Global Impression of Symptoms and Change

Results for global symptom relief based on the GIS and GIC were consistent with the effects of odevixibat on the reduction in pruritus and improvement in sleep with a high proportion of patients

who had received odevixibat and those who had received placebo in Study A4250-012 reporting both pruritus and sleep were a little better, moderately better, or very much better through Week 72.

6.1.2.7. Quality of Life: Paediatric Quality of Life Inventory

Quality of life based on the PedsQL showed improvements through Week 72 in total score, family impact score, and all domain scores for patients who had received odevixibat and those who had received placebo in Study A4250-012.

6.1.2.8. Changes from Baseline Over Time in Cholesterol

At study entry, patients who received odevixibat in Study A4250-012 had improved cholesterol levels compared with treatment-naïve patients; the improvement in cholesterol levels in patients who had received odevixibat were maintained through Week 72 and were improved in those who had received placebo in Study A4250-012.

6.1.2.9. Changes from Baseline Over Time in the Clinician Xanthoma Scale

At Week 72, 44 of the 50 patients had baseline and at least 1 post-baseline assessment for xanthomas, including 38 patients with no xanthomas at baseline and 6 with xanthomas at baseline. None of 38 patients without xanthomas at baseline had xanthomas reported at Week 72. Of the 6 patients with xanthomas at baseline and an evaluation conducted at Week 72, 5 (83.3%) improved and 1 patient had worsening.

6.1.2.10. Changes from Baseline Over Time in Biomarkers

Mean autotaxin levels decreased (improved) over time on treatment through Week 72 in patients who had received odevixibat and those who had received placebo in Study A4250-012. For p-C4, mean levels increased (improved) over time on treatment in Study A4250-015 in patients who had received placebo and were relatively unchanged in patients who had received odevixibat, who entered the study with higher mean p-C4 levels compared with patients who had received placebo.

6.1.3. Safety results in patients with Alagille Syndrome

6.1.3.1. Population for Analysis

All analyses were based on the Safety Analysis Set, which includes all patients who received at least 1 dose of study drug. For presentation of data from Study A4250-012, analyses were based on actual treatment received at first dose, regardless of randomised treatment. All 52 patients in the study received treatment as randomised.

6.1.3.2. General Statistical Methods

Continuous variables were summarised using descriptive statistics, including the number of patients with non-missing values (n), mean, median, standard deviation (SD), minimum, and maximum. For categorical variables, summaries included counts of patients (frequencies) and percentages. Descriptive summaries of change from baseline in categorical variables were provided using shift tables, if applicable.

Medical history and AEs were up versioned (as needed) and coded to System Organ Class (SOC) and preferred term using Medical Dictionary for Regulatory Activities (MedDRA), Version 26.0. Prior and concomitant medications were up versioned (as needed) coded to Anatomic Therapeutic Chemical (ATC) classification and preferred drug name by using the World Health Organization Drug Dictionary version March 2023. For Study A4250-015, the MedDRA and WHODD versions (26.0 and March 2023 respectively) used were based on those used in the Week 72 analysis presented in the CSR for Study A4250-015. Adverse events and medical history presented in the CSR for Study A4250-012 were coded based on an earlier MedDRA Versions (25.0). For the integrated analyses, the AEs from these studies were recoded based on MedDRA Version 26.0 and medications were recoded to WHODD March 2023. The upcoding resulted in changes to assigned SOC and/or preferred terms of medical history in 3 cases and 1 AE in Study A4250-012.

For patients who received odevixibat in Study A4250-012, the baseline value of a parameter was defined as the last non-missing assessment of that parameter before first intake of active treatment. For patients who received placebo in Study A4250-012, the baseline value for presentation of data for Study A4250-012 was the last non-missing assessment before first intake of placebo; for patients randomised to placebo who subsequently enrolled in Study A4250-015, baseline for the pooled analyses of Studies A4250-012 and A4250-015 was reset based on the start of odevixibat in the extension study.

For any graphic displays, data for a given visit were only presented for a treatment group or for the pooled odevixibat group if there were ≥ 5 patients with data available for that visit.

Analysis visit windows for presentation of individual study results were based on the visits as defined in each study. For the summary of the pooled study results, the analysis visit windows at a given week were mapped from each of the Phase 3 studies to the total duration of treatment received with odevixibat in both Study A4250-012 and Study A4250-015. For example, for a patient who completed 24 weeks of odevixibat treatment in Study A4250-012, the Week 12 assessment conducted in Study A4250-015 for that patient would map to Week 36 in the pooled analyses. Details of the visit remapping are provided in Table 2 of the ISS SAP.

6.1.3.3. Adverse Events

In the Pooled Phase 3 group, 50 (96%) of 52 patients who received odevixibat in Studies A4250-012 and/or A4250-015 experienced at least 1 TEAE. In Study A4250-012, the overall incidence of TEAEs was similar in the odevixibat and placebo groups (74% and 71%, respectively).

Most TEAEs were Grade 1 or 2 in intensity. Grade 3 TEAEs were reported in 16 (31%) of the 52 patients in the Pooled Phase 3 group. The incidence of TEAEs of Grade 3 intensity during Study A4250-012 was similar in the odevixibat group (14%) and the placebo group (12%). There were no Grade 4 or 5 events in either Study A4250-012 or A4250-015.

The majority of TEAEs were reported as unrelated to study treatment by the Investigators. Drug-related TEAEs were reported in 19 (37%) patients in the Pooled Phase 3 group. In Study A4250-012, the incidence of drug-related AEs was 23% in the odevixibat group and 18% in the placebo group.

There were no deaths in the Phase 3 studies. Overall, treatmentemergent SAEs were reported in 13 (25%) of the 52 patients in the Pooled Phase 3 group. In Study A4250-012, the incidence of SAEs was similar in the odevixibat (14%) and placebo (12%) groups. One patient (patient [redacted]) had SAEs considered by the Investigator to be study drug-related during treatment with odevixibat in Study A4250-012. The patient experienced haematemesis and increased INR requiring hospitalisation.

One patient (patient [redacted]) discontinued treatment during Study A4250-015 because of a TEAE (blood bilirubin increased). Treatment-emergent AEs leading to interruption of study treatment were reported in 8 (15%) of the 52 patients in the Pooled Phase 3 group. Overall, 3 (6%) patients required a dose reduction due to a TEAE.

Table 3: Overall Summary of Treatment-emergent Adverse Events (Safety Analysis Set, Integrated Data)

	Study A4250-012 (By Treatment)		Studies A4250-012/ A4250-015 pooled
Patients with any:	**Placebo (N=17) n (%) / E**	**Odevixibat (N=35) n (%) / E**	**Odevixibat[a] (N=52) n (%) / E**
TEAEs	12 (70.6) / 42	26 (74.3) / 104	50 (96.2) / 465
Drug-Related TEAEs	3 (17.6) / 4	8 (22.9) / 17	19 (36.5) / 47
Severe (Grade ≥ 3) TEAEs	2 (11.8) / 3	5 (14.3) / 8	16 (30.8) / 35
Serious TEAEs	2 (11.8) / 5	5 (14.3) / 8	13 (25.0) / 23
Drug-Related Serious TEAEs	0	1 (2.9) / 2	1 (1.9) / 2
TEAEs Leading to Death	0	0	0
TEAEs Leading to Study Treatment Interruption	0	3 (8.6) / 4	8 (15.4) / 11
TEAEs Leading to Dose Reduction	0	1 (2.9) / 2	3 (5.8) / 6
TEAEs Leading to Study Treatment Discontinuation	0	0	1 (1.9) / 1

E = number of events; TEAE: treatment-emergent adverse event.
a Includes data on active treatment for patients who received odevixibat at any time in Studies A4250-012 and/or A4250-015.
Data cutoff: 07FEB2024.
Source: ALGS ISS Table 14.3.1.1.

6.1.3.4. Common Adverse Events

Common (≥ 10%) TEAEs reported in the Pooled Phase 3 group are presented in **Table 4**.

In the Pooled Phase 3 group, the most common types of events among patients who received odevixibat were in the Infections and Infestations SOC and Gastrointestinal disorders SOC. The most common TEAEs (occurring in ≥ 20% of patients) during treatment with odevixibat were diarrhoea (19 patients, 37%), nasopharyngitis (16 patients, 31%), pyrexia (15 patients, 29%), and COVID-19 infection (13 patients, 25%).

The median duration of exposure to odevixibat was 24.0 weeks in Study A4250-012 and 99.8 weeks in the Pooled Phase 3 group with the total patient years of exposure being 16.1 and 92.3, respectively. The EAIR for the overall incidence of TEAEs was 3.93 events per patient year (PPY) across all odevixibat treatment in the Pooled Phase 3 group and 3.93 for the odevixibat group during 24 weeks of treatment in Study A4250-012.

Table 4: Treatment-emergent Adverse Events (≥ 10% of Patients in the Pooled Population) by System Organ Class and Preferred Term (Safety Analysis Set, Integrated Data)

MedDRA SOC Preferred Term	Study A4250-012 (By Treatment)		Studies A4250-012/ A4250-015 pooled
	Placebo (N=17) n (%)	Odevixibat (N=35) n (%)	Odevixibat[a] (N=52) n (%)
Infections and infestations	**10 (58.8)**	**18 (51.4)**	**41 (78.8)**
Nasopharyngitis	1 (5.9)	2 (5.7)	16 (30.8)
COVID-19	4 (23.5)	5 (14.3)	13 (25.0)
Upper respiratory tract infection	2 (11.8)	3 (8.6)	9 (17.3)
Otitis media	0	1 (2.9)	8 (15.4)
Bronchitis	0	3 (8.6)	7 (13.5)
Ear infection	0	0	6 (11.5)
Influenza	1 (5.9)	0	6 (11.5)
Pharyngitis	0	1 (2.9)	6 (11.5)
Gastrointestinal disorders	**2 (11.8)**	**12 (34.3)**	**24 (46.2)**
Diarrhoea	1 (5.9)	10 (28.6)	19 (36.5)
Abdominal pain	1 (5.9)	4 (11.4)	7 (13.5)
General disorders and administration site conditions	**5 (29.4)**	**9 (25.7)**	**19 (36.5)**
Pyrexia	4 (23.5)	8 (22.9)	15 (28.8)
Respiratory, thoracic, and mediastinal disorders	**3 (17.6)**	**6 (17.1)**	**20 (38.5)**
Cough	1 (5.9)	3 (8.6)	9 (17.3)
Metabolism and nutrition disorders	**1 (5.9)**	**2 (5.7)**	**15 (28.8)**
Vitamin D deficiency	1 (5.9)	1 (2.9)	7 (13.5)

COVID-19: Corona Virus Disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; SOC: system organ class.

[a] Includes data on active treatment for patients who received odevixibat at any time in Studies A4250-012 and/or A4250-015.

Data cutoff: 07FEB2024.

Source: ALGS ISS Table 14.3.1.3.

6.1.3.4.1. Infections

The overall incidence of TEAEs in the Infections and Infestations SOC in the Pooled Phase 3 group was 79% (41 of 52 patients), with the most common types of infections being nasopharyngitis (16 patients; 31%), COVID-19 (13 patients; 25%), upper respiratory tract infection (9 patients; 17%), otitis media (8 patients; 15%), bronchitis (7 patients; 14%), and ear infection, influenza, and pharyngitis (each 6 patients; 12%). These types of infections are common in paediatric patients. All other infections occurred in < 10% of patients. Most infections among patients in the Pooled Phase 3 group were Grade 1 or 2 in intensity. Eight (15%) patients experienced a Grade 3 (severe) infection, including enterovirus infection, gastroenteritis, gastroenteritis rotavirus, influenza, otitis media, otitis media chronic, pneumonia, rhinovirus infection, and tonsillitis (each 1 patient: 2%. All infections were assessed by the Investigator as unrelated to study drug.

In 6 (12%) of the 52 patients in the Pooled Phase 3 group, an infection was reported as an SAE during treatment with odevixibat; all were assessed as unrelated to treatment with odevixibat. The SAEs in these 6 patients included tonsillitis and gastroenteritis in 1 patient (with the tonsillitis occurring during treatment in Study A4250-012 [patient [redacted]] and the gastroenteritis occurring in Study A4250-015 [patient [redacted]]), enterovirus and rhinovirus infection in patient [redacted] (Study A4250-015), gastroenteritis in patient [redacted] (Study A4250-015), pneumonia in patient [redacted] (Study A4250-012), and rhinovirus infection in patient [redacted] (Study A4250-012) (ALGS ISS

Table 14.3.1.8 and ALGS ISS Table 14.3.2.1). One patient (patient [redacted]) had SAEs of chronic otitis media and subcutaneous abscess during treatment with placebo in Study A4250-012.

In Study A4250-012, infections were reported with similar incidence in the 2 treatment groups (51% and 59% in the odevixibat and placebo groups, respectively). Furthermore, the profile of infections seen in the odevixibat group in Study A4250-012 was similar to that seen in the Pooled Phase 3 group.

Review of the EAIR for infections revealed an overall incidence of 1.32 events PPY across all odevixibat treatment in the Pooled Phase 3 group and 1.59 for the odevixibat group during 24 weeks of treatment in Study A4250-012.

6.1.3.4.2. Gastrointestinal Disorders

The overall incidence of TEAEs in the Gastrointestinal disorders SOC in the Pooled Phase 3 group was 46% (24 of 52 patients). The most commonly reported TEAE overall was diarrhoea, reported in 19 (37%) of the 52 patients. All reports of diarrhoea were Grade 1 or 2 in intensity and non-serious. None of the patients discontinued treatment with odevixibat due to diarrhoea. Abdominal pain events and vomiting were the only other gastrointestinal disorders reported in ≥ 5% of patients. Overall, 9 (17%) of the 52 patients had abdominal pain events, including reports of upper abdominal pain, and 3 (6%) patients had vomiting. The median number of episodes of abdominal pain and vomiting per patient was 1.0 with a median duration of 6.0 days for abdominal pain and 4.0 days for vomiting. Median time to onset of abdominal pain was 100.0 days and for vomiting was 3.0 days. Events of abdominal pain occurred concurrently with diarrhoea in 1 patient and vomiting in 1 patient.

Most gastrointestinal disorders among patients in the Pooled Phase 3 group were Grade 1 or 2 in intensity. Two (4%) patients experienced Grade 3 gastrointestinal disorders that were also reported as SAEs, including abdominal pain and constipation (patient [redacted]; Study A4250-012) and haematemesis (patient [redacted]; Study A4250012).

Drug-related gastrointestinal disorders were reported in 15 (29%) patients, most commonly reports of diarrhoea (9 patients; 17%). Other study drug-related gastrointestinal disorders occurred in 1 or 2 patients only, and included abdominal pain, upper abdominal pain, frequent bowel movements, nausea, and vomiting (each 2 patients; 4%) and faeces discoloured, haematemesis, and haematochezia (each 1 patient; 2%).

In Study A4250-012, gastrointestinal disorders were reported with higher incidence among patients who received odevixibat (34%) compared with patients who received placebo (12%). As was the case in the Pooled Phase 3 group, diarrhoea was the most common gastrointestinal TEAE, with this event reported at a higher incidence in patients who received odevixibat (29%) compared with patients who received placebo (6%).

Review of the EAIR for gastrointestinal disorders revealed an incidence of 0.46 events PPY across all odevixibat treatment in the Pooled Phase 3 group and 1.05 for the odevixibat group during 24 weeks of treatment in Study A4250-012, indicating no increase in the incidence rate of these events with long-term treatment.

6.1.3.4.3. Other TEAEs reported in ≥ 10% of patients

Other TEAEs reported in ≥ 10% of patients in the Pooled Phase 3 group included pyrexia (15 patients; 29%), cough (9 patients; 17%), and vitamin D deficiency (7 patients; 14%). The majority of events were Grade 1 or 2 in severity and non-serious.

6.1.3.5. Drug-related Adverse Events

In the Pooled Phase 3 group, drug-related TEAEs were reported in 19 (37%) of 52 patients during treatment with odevixibat. The most common study drug-related TEAE reported during treatment with odevixibat was diarrhoea, reported in 9 (17%) of the 52 patients. All other drug-related TEAEs were reported in 1 or 2 patients.

In Study A4250-012, the overall incidence of drug-related TEAEs was similar in the 2 treatment groups reported in 8 (23%) of the 35 patients who received odevixibat and 3 (18%) of 17 patients who received placebo. In this study, there was a higher incidence of drug-related TEAEs in the gastrointestinal disorders SOC in odevixibat-treated patients (20%) compared with placebo-treated patients (6%), primarily reports of diarrhoea.

6.1.3.6. Adverse Events of Grade 3 Intensity

In the Pooled Phase 3 group, 16 (31%) of the 52 patients experienced a TEAE of Grade 3 intensity. The incidence of Grade 3 TEAEs in Study A4250-012 was similar in the odevixibat group (5 patients, 14%) and the placebo group (2 patients, 12%).

Infections were the most common types of Grade 3 TEAEs, occurring in 8 (15%) of 52 patients in the Pooled Phase 3 group. All Grade 3 TEAEs by MedDRA preferred term were reported in 1 (2%) patient with the exception of GGT increased and adenoidal hypertrophy (each 2 patients, 4%).

6.1.3.7. Treatment-emergent Adverse Events of Interest

Patients with ALGS are known to have multiple comorbidities, including steatorrhea with diarrhoea, malabsorption leading to FSV deficiencies and coagulopathies, and hepatic impairment with deranged hepatic biochemical parameters (e.g. ALT, AST, total and direct bilirubin, ALP, GGT), clinical hepatitis, and exacerbation of cholestasis [Kamath 2018]. Based on this, tabulations were produced for specific AEs of interest, including clinically significant diarrhoea, new or worsening FSV deficiency refractory to clinically recommended vitamin supplementation, possible sequelae of FSV deficiency, and hepatic events (including liver decompensation events, liver-related events, and cases of potential DILI that underwent adjudication by the HSAC).

6.1.3.7.1. Diarrhoea Events

In the Pooled Phase 3 group, the incidence of diarrhoea events, including preferred terms of diarrhoea and faeces soft, was 37% (19 of 52 patients), with at least 1 diarrhoea event being considered by the Investigator to be study drug-related for 9 (17%) patients. All diarrhoea events were Grade 1 or 2 in intensity and non-serious. Two (4%) patients in the Pooled Phase 3 group required study treatment interruption for the management of diarrhoea. None of the patients discontinued due to diarrhoea events.

Review of the EAIR for diarrhoea did not indicate an increase in incidence rate with longer term exposure to odevixibat, with an incidence of 0.31 PPY across all odevixibat treatment in the Pooled Phase 3 group and 0.76 for the odevixibat group during 24 weeks of treatment in Study A4250-012.

6.1.3.7.2. Vitamins

Overall, 17 (33%) of the 52 patients in the Pooled Phase 3 group had TEAEs related to FSV deficiency, including vitamin D deficiency and blood 25-hydroxycholecalciferol decreased (8 patients, 15%), INR

increased and vitamin K deficiency (7 patients, 14%), vitamin E deficiency/decreased (6 patients, 12%), and vitamin A decreased and hypovitaminosis (1 patient each, 2%). For 1 patient, the TEAE of INR increased was Grade 3 in severity and reported as an SAE (Study A4250-012, patient [redacted]), with this event considered by the Investigator to be drug-related. All other TEAEs related to FSV deficiency were Grade 1 or 2 in severity and non-serious. No dose modifications or discontinuations of treatment were reported for vitamin deficiency TEAEs.

Review of the EAIR for FSV deficiency TEAEs revealed an overall incidence of 0.05 events PPY across all odevixibat treatment in the Pooled Phase 3 group and 0.06 for the odevixibat group during 24 weeks of treatment in Study A4250-012, indicating no overall increase in the incidence rate of these events during long-term treatment.

6.1.3.7.3. Hepatic TEAEs

None of the patients reported new or worsening portal hypertension or hepatic cirrhosis or had TEAEs of hepatic encephalopathy or variceal haemorrhage. As of the 07FEB2024 data cutoff date, 1 patient (patient [redacted]) had a non-serious Grade 1 TEAE of ascites during treatment in Study A4250-015; the event, which was categorised as a liver decompensation event by the investigator but did not meet protocol-defined criteria, was assessed as unrelated to treatment. This patient underwent liver transplant 5 days after the last dose of odevixibat with the ascites reported 4 days post-transplant.

Overall, 11 (21%) of the 52 patients in the Pooled Phase 3 group experienced liver-related TEAEs across the 4 SMQs. The most common TEAEs were INR increased (4 patients, 8%), ALT increased (3 patients, 6%), and AST increased, blood bilirubin increased, GGT increased, and hepatomegaly (2 patients each, 4%). Most liver-related events were Grade 1 or 2 in severity and non-serious. Grade 3 events were reported in 3 (6%) of the 52 patients and included patients [redacted] with Grade 3 bile acids increased and GGT increased; Patient [redacted] with Grade 3 ALT, AST and GGT increased; and patient [redacted] with Grade 3 INR; the latter event was also reported as an SAE. Two patients had treatment interruption due to liver-related events, including AST increased in patient [redacted] and hepatic enzyme increased in patient [redacted]. The latter patient underwent dose reduction due to a second report of hepatic enzyme; the reported AE remained ongoing as of the data cutoff (454 days after dose reduction). One patient, patient [redacted], was discontinued from treatment due to increased blood bilirubin.

In Study A4250-012, liver-related events were reported in 4 (11%) of 35 patients in the odevixibat group with a similar incidence in the placebo group (2 of 17 patients, 12%). Overall, the profile of these hepatic events in Study A4250-012 was consistent with that in the Pooled Phase 3 group.

Review of the EAIR for liver-related events did not indicate an increase in the incidence rate of these types of events during long-term treatment with odevixibat with 0.14 events PPY in the Pooled Phase 3 group and 0.26 events PPY during odevixibat treatment in Study A4250-012.

A review of clinical laboratory data for hepatic biochemical parameters was also conducted. Consistent with the patients' underlying disease, mean and median levels of hepatic biochemical parameters were elevated at Study A4250-012 baseline in both treatment groups and prior to the first dose of odevixibat for the Pooled Phase 3 group. In Study A4250-012, mean and median baseline ALT levels were higher in the odevixibat group (185.6 and 173 U/L, respectively) compared with the placebo group (149.1 and 114.0 U/L, respectively). Consistent with this, the percent of patients with baseline ALT >3 × ULN also was nearly 2-times higher in the odevixibat group compared with the placebo group (66% vs 35%).

For the Pooled Phase 3 group, median baseline levels of hepatic biochemical parameters were as follows: ALT (152.0 U/L), AST (140.5 U/L), GGT (361.5 U/L) and total bilirubin (37.60 µmol/L; 2.200 mg/dL) (ALGS ISS Table 14.1.3). More than half of the patients had baseline ALT levels > 3 × ULN (29 of 52 patients, 56%) and baseline total bilirubin levels > 2 × ULN (32 of 52, 62%) (ALGS ISS Table 14.3.5.6.4). It is clear from the data that ALT levels at baseline were highly variable across the 52 patients in the Pooled Phase 3 group ranging from 39 to 365 U/L as were levels of AST (range: 57 to 411 U/L) and GGT (46 to 2020 U/L).

An early increase in mean ALT with a relative plateau during long-term treatment observed after Week 48 with variability in the data after Week 84 was observed. Mean levels in ALT were greater than those observed with AST; results for GGT were highly variable. Mean and median changes from baseline in ALT at Week 48 were 77.5 U/L and 54.0 U/L, respectively, and were similar at Week 72 (74.6 U/L and 53.0 U/L, respectively). For AST, mean and median changes from baseline at Week 48 were 58.6 U/L and 54.0 U/L, respectively, and also were similar at Week 72 (54.6 U/L and 41.0 U/L, respectively). For all 3 transaminase parameters, the observed variability in mean and mean changes over time is consistent with fluctuating levels typical of patients with ALGS [Vandriel 2022]. For total bilirubin, mean and median changes from baseline varied around zero for most timepoints and at Week 48 were -1.78 µmol/L and -2.20 µmol/L, respectively and at Week 72 were -0.90 µmol/L and -1.25 µmol/L, respectively.

6.1.3.8. Deaths

No deaths were reported in Studies A4250-012 or A4250-015.

6.1.3.9. Serious Adverse Events

In the Pooled Phase 3 group, 13 (25%) of 52 patients experienced a treatment-emergent SAE. The incidence of treatment-emergent SAEs in Study A4250-012 was similar in the odevixibat group (5 patients, 14%) and in the placebo group (2 patients, 12%). The most commonly reported types of SAEs were infections, reported in 6 (12%) of the 52 patients in the pooled Phase 3 group. All treatment-emergent SAEs by preferred term were reported in only 1 patient each. None of these events led to discontinuation of treatment with odevixibat; 2 patients had treatment interrupted due to an SAE, including patient [redacted] for rhinovirus infection and patient [redacted] for rotavirus gastroenteritis.

For all but 1 patient, treatment-emergent SAEs were assessed as unrelated to study drug (ALGS ISS Table 14.3.1.10). Patient [redacted] experienced study drug-related SAEs of INR increased and haematemesis during treatment with odevixibat in Study A4250-012

6.1.3.10. Other Potentially Significant Adverse Events

6.1.3.10.1. Adverse Events Leading to Study Drug Dose Reduction

In the Pooled Phase 3 group, 2 (4%) of 52 patients reported TEAEs leading to permanent dose reduction from 120 to 40 µg/kg/day during treatment in Study A4250-015, including frequent bowel movements, nausea, and headache in patient [redacted] who had received placebo in Study A4250-012 and hepatic enzyme increased in patient [redacted] who had received odevixibat. Both patients completed the 72-week treatment period at a decreased dose of 40 µg/kg/day and, as of the data cutoff, treatment with odevixibat was ongoing in the optional extension period.

In addition to the patients with TEAEs leading to permanent dose reduction, temporary dose reduction was reported in 2 patients. In Study A4250-012, 1 patient (patient [redacted]) who received odevixibat had a temporary dose reduction from 120 to 40 µg/kg/day due to TEAEs of nausea and vomiting on Day 2; the odevixibat dose was increased to 120 µg/kg/day on Day 57. Patient [redacted] initiated treatment in Study A4250-015 at a dose of 40 µg/kg/day in error; the dose was increased to 120 µg/kg/day beginning on Day 3. Due to an event of diarrhoea, treatment was interrupted. On Day 29, the patient was rechallenged with a reduced odevixibat dose at 40 µg/kg/day, which was subsequently increased to 120 µg/kg/day on Day 169. For both patients, treatment was ongoing at 120 µg/kg/day as of the data cutoff with no recurrence of the TEAEs.

6.1.3.10.2. Adverse Events Leading to Study Drug Interruption

The only TEAE leading to study drug interruption for > 1 patient was diarrhoea (2 patients; 4%). Other TEAEs leading to dose interruption, each reported for 1 (2%) patient included abdominal pain, AST increased, dysuria, rotavirus gastroenteritis, influenza, hepatic enzyme increased, anaemia macrocytic, platelet count decreased, and rhinovirus infection. Treatment emergent AEs leading to study drug interruption that were considered by the Investigator to be study drug-related included 2 reports of hepatic enzyme increased and 1 report each of abdominal pain, diarrhoea, and AST increased. All but 1 patient who had odevixibat interrupted due to a TEAE resumed odevixibat at 120 µg/kg/day after resolution of the TEAE. The patient experiencing AST increased resumed odevixibat at a reduced dose (40 µg/kg/day).

In Study A4250-012, the incidence of TEAEs leading to interruption of study drug was 9% (3 patients) in the odevixibat group; none of the patients who received placebo had a TEAE leading to study drug interruption. All 3 patients who had odevixibat interrupted due to a TEAE resumed odevixibat at 120 µg/kg/day after resolution of the TEAE.

Most TEAEs leading to interruption of study drug were Grade 1 or 2 in severity. Grade 3 TEAEs leading to study drug interruption were reported in 4 patients and included rhinovirus infection, influenza, rotavirus gastroenteritis, and AST increased; the report of Grade 3 AST increased was considered possibly related to study drug.

6.1.3.10.3. Adverse Events Leading to Study Drug Discontinuation

One (2%) of the 52 patients in the Pooled Phase 3 group discontinued study drug because of a TEAE.

Patient [redacted], an [redacted]year-old [redacted] who received placebo in Study A4250-012, discontinued odevixibat during Study A4250-015 due to increased blood bilirubin that was assessed as Grade 2 in severity and considered possibly related to study treatment. The patient entered Study A4250-015 with elevated hepatic biochemical parameters with ALT, AST, and total bilirubin levels of 116 U/L (ULN: 45 U/L), 144 U/L (ULN: 48 U/L), and 75.4 µmol/L (ULN: 18.8 µmol/L), respectively. On Day 115 of Study A4250-015, local laboratory results showed an increase in total bilirubin to 123.12 µmol/L; ALT and AST were lower than baseline to 97 and 124 U/L, respectively. At the next study visit on Day 141, the elevation in total bilirubin was confirmed at the central laboratory at 139.9 µmol/L; ALT and AST were 104 and 148 U/L, respectively. Treatment with odevixibat was permanently discontinued at that time for the elevation in bilirubin; the patient had received [redacted] last dose the day prior on Day 140. At the follow-up assessment 27 days after the last dose of odevixibat, total bilirubin was further elevated at 177 µmol/L.

6.1.3.11. Post-Data Cutoff Safety Information

Following the 07FEB2024 data cutoff and finalisation of the CSR for Study A4250-015, changes were made to the safety data for patient [redacted] based on review. During treatment with odevixibat, on Study A4250-015 Day 110, this patient's bilirubin levels met criteria for suspected DILI (increase ≥4 mg/dL from baseline level) and the patient was recommended for liver transplantation. Based on the laboratory results, a corresponding AE of Grade 2 total bilirubin increased was added to the database by the investigator with an action of discontinuation from treatment. The case was sent for review and adjudication by the HSAC after the data cutoff date and the committee assessed the bilirubin elevation as unrelated to treatment with odevixibat. The patient subsequently underwent liver transplant (a secondary reason for treatment discontinuation) 5 days after discontinuation of odevixibat (total exposure 110 days).

6.2. Discussion

The efficacy and safety studies of odevixibat included patients with genetic confirmation of ALGS; patients with both the JAG1 and NOTCH2 mutations were enrolled. The baseline characteristics and medication history of the patients enrolled in the efficacy and safety studies were consistent with the clinical manifestations described in patients with ALGS. Males and females were represented equally. Most of the patients included in the pivotal trial were between 2 and 12 years of age with an age range from < 1 to 16 years. The protocol was designed to include patients ≥18 years of age; however, none were enrolled to the study during the 12-month recruitment period. This was likely a reflection of the natural history of ALGS, where approximately 60% to 76% of patients with ALGS have undergone liver transplantation by approximately 18 years of age [Kamath 2020; Vandriel 2022], making these patients ineligible for enrolment into the Phase 3 study. Patients were required to have moderate to severe pruritus at study entry based on a score of ≥ 2 on observer-reported information and baseline serum bile acids above the ULN.

For patients who had received odevixibat in Study A4250-012, further improvements (although limited) from baseline were observed to Weeks 69-72. For patients who had received placebo in A4250-012, improvements in scratching severity and bile acid levels occurred rapidly and were sustained to Weeks 69-72. Results for nighttime and daytime scratching severity scores based on caregiver reports were consistent with those reported for the AM and PM scores combined showing long-term and sustained improvement through Week 72. Review of patient-reported itching severity scores based on the PRO also showed improvements, although data were limited for this analysis.

Treatment with odevixibat also led to improved sleep and daytime tiredness for patients based on observer-reported information. For patients who had previously received odevixibat the improvements observed during study A4250-012 were sustained over time for each of the sleep parameters. Among treatment-naïve patients who first received odevixibat in Study A4250-015, improvements from baseline in sleep parameters occurred early in treatment and improved over time through Week 72. Further, cholesterol levels, global symptom relief, and QoL also showed improvements in both patients who had received odevixibat and those who had received placebo in Study A4250-012.

Consistent with current prescribing information, the safety profile of odevixibat is primarily characterised by Grade 1 or 2 gastrointestinal disturbances, primarily reports of diarrhoea. There were no deaths in the studies. The incidence of treatment-emergent SAEs was 25% with most reported as unrelated to treatment with odevixibat. One patient experienced SAEs that were considered treatment-related (INR increased and haematemesis). Discontinuation due to TEAEs was uncommon, reported in 1 (2%) of the 52 patients due to blood bilirubin increased.

No liver decompensation events were reported during the studies, nor did any patient report new or worsening portal hypertension, hepatic cirrhosis, hepatic encephalopathy, or variceal haemorrhage. Potentially clinically significant changes in transaminase levels (ALT > 3× baseline without concurrent elevation in total bilirubin > 2× baseline) were observed in 7 patients; 6 of the 7 patients remained on odevixibat as of the data cutoff and 1 had discontinued to undergo liver transplant.

Some patients experienced treatment-emergent shifts to low in vitamins D and E and some had clinically meaningful shifts in INR to > 1.5.

Based on review of post-marketing safety surveillance that includes estimated cumulative exposure in 737 patients, there is no evidence of any new significant safety issues with odevixibat when administered according to the recommendations given in the reference safety information and within the approved indications.

The totality of data collected did indicate a comparable safety profile with comparable frequencies of AE. No unexpected AE were reported during of treatment with odevixibat in patients with ALGS.

6.3. Conclusion

No unexpected adverse event was reported. The safety profile emerging form the long-term extension is more or less in line with the adverse events profile observed in the initial placebo controlled studies.

The benefit-risk of odevixibat in the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older remains positive.

7. PRAC advice

N/A

8. Risk management plan

The MAH submitted an updated RMP version 6.2 (data of final sign off 17 Oct 2024) with this application. The RMP was updated based on 72-week clinical data from Study A4250-015 and achieving the study milestone for completing this additional pharmacovigilance activity, which is a Category 3 trial. The main proposed RMP changes were the following:

- Part II: Module SIV - Populations Not Studied in Clinical Trials

Number of patients for the pooled phase III ALGS studies were updated for patients with hepatic/renal impairment.

- Part II: Module SVII - Identified and potential risks

Updated new data for important identified, potential risks and missing information from pooled phase III ALGS studies and Study A4250-015.

Characterisation of important identified and potential risks has been updated based on new data received from Study A4250-015.

- Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

Additional pharmacovigilance activities were updated to remove Study A4250-015.

- Part V: Risk minimisation measures (including evaluation of effectiveness of risk minimisation

activities)

Study A4250-015 was removed from additional pharmacovigilance activities.

- Part VI: Summary of the risk management plan

Based on the data from Study A4250-015, the important identified risk is updated to include hepatotoxicity and clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance.

Study A4250-015 was removed from additional pharmacovigilance activities and other studies in the post-authorisation development plan.

- Part VII: Annexes

Annex 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Study A4250-015 was updated as completed additional pharmacovigilance activity.

Annex 8 Summary of Changes to the RMP Over Time

Updated to reflect the above changes made based on the addition of new clinical trial data from Study A4250-015, presented in the Week 72 CSR.

8.1. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

9. Changes to the Product Information

As a result of this group of variations, sections 4.4, 4.8 and 5.1 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly. See separate SmPC assessment.

10. Request for supplementary information

10.1. Major objections

Clinical aspects

None

Request for a GCP Inspection

Not applicable

RMP aspects

None

10.2. Other concerns

Clinical aspects

SmPC

The Applicant is requested to update both SmPC and PL considering the Rapporteur's comments in separate product information document.

RMP aspects

None

11. Assessment of the responses to the request for supplementary information

11.1. Major objections

Clinical aspects

None

RMP aspects

None

11.2. Other concerns

Clinical aspects

Question 1
The Applicant is requested to update both SmPC and PL considering the Rapporteur's comments in separate product information document.

Summary of the MAH's response
The SmPC has been updated to address EMA's comments.

Further, the MAH would like to take the opportunity of this PI revision to align the SmPC 4.4 paragraph on monitoring patients with severe hepatic impairment with the wording in Bylvay's PI, as it is clearer.

In SmPC section 4.8 we would like to take the opportunity to remove the % linked to diarrhoea here.

Assessment of the MAH's response
The Applicant updated the product information as requested.

The additional text in SmPC section 4.4 on monitoring patients with severe hepatic impairment is considered acceptable, for now. However, the Applicant is requested to keep the text regarding hepatic impairment aligned with the Bylvay SmPC in case of any updates of this section in the Bylvay SmPC text that is currently being assessed.

The percentage linked to diarrhoea is in line with the Bylvay SmPC where it is mentioned as well. Therefore, it is not agreed to delete this percentage. The Applicant is requested not to delete the percentage or justify the deletion.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

RMP aspects

None

12. 2nd Request for supplementary information

12.1. Other concerns

Clinical aspects

SmPC

The Applicant is requested to update the SmPC section 4.8 considering the Rapporteur's comment in a separate product information document.

13. Assessment of the responses

The applicant addressed the outstanding SmPC comments without the need for a further RSI.