13 March 2025
EMA/116534/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bylvay

International non-proprietary name: Odevixibat

Procedure No. EMEA/H/C/004691/II/0022/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	19 Nov 2024	19 Nov 2024	☐
☐	CHMP Rapporteur Assessment Report	16 Dec 2024	16 Dec 2024	☐
☐	PRAC Rapporteur Assessment Report	20 Dec 2024	18 Dec 2024	☐
☐	PRAC members comments	03 Jan 2025	n/a	☐
☐	CHMP members comments	06 Jan 2025	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	07 Jan 2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	09 Jan 2025	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	14 Jan 2025	14 Jan 2025	☐
☐	Start of written procedure	14 Jan 2025	14 Jan 2025	☐
☐	RSI	16 Jan 2025	16 Jan 2025	☐
☐	Submission	12 Feb 2025	12 Feb 2025	☐
☐	CHMP Rapporteur Assessment Report	26 Feb 2025	26 Feb 2025	☐
☐	PRAC Rapporteur Assessment Report	28 Feb 2025	28 Feb 2025	☐
☐	PRAC members comments	03 Mar 2025	03 Mar 2025	☐
☐	CHMP members comments	03 Mar 2025	03 Mar 2025	☐
☐	Updated PRAC Rapporteur Assessment Report	04 Mar 2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	06 Mar 2025	06 Mar 2025	☐
☐	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 30 September 2024 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
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
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	None

A grouped application including two type II variations:
- Update of sections 4.2, 4.4, 4.8, and 5.1 of the SmPC based on the clinical study report for the completed 72 weeks of Study A4250-008; an open-label, phase III study to evaluate the long-term efficacy and safety of odevixibat in children with PFIC (category 3 study in the RMP; MEA 002).
The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and the Package Leaflet. An updated RMP version 6.1 is included in this submission.
- Submission of the clinical study report for Study A4250-J001; a Phase I PK study in healthy Japanese adult male patients.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0147/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0147/2022 was completed.

The PDCO issued an opinion on compliance for the PIP P/0147/2022.

GLP/GCP inspections

Not applicable

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

The applicant submitted a clinical study report for the completed safety and pharmacokinetics study in healthy Japanese adult subjects A4250-J001: a randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety and pharmacokinetics of repeated oral administration of A4250 in healthy Japanese adult subjects.

The number of subjects in the study was considered low (n=6 on active treatment and n=3 on placebo), but for the purpose of this study: to evaluate the safety, PK and PD in Japanese healthy adult subjects this is sufficient and in line with previous healthy volunteer studies. The sample

schedule for pharmacokinetic assessment of A4250 was considered adequate, the compound is expected to have low bioavailability, but on day 7 exposure is expected to be measurable between 1 and 8 hours after dosing, with a Tmax between 1 – 5 hours. The selection of biomarkers and sample schedule for pharmacodynamics was in line with previous studies in healthy adult volunteers (A4250-001) and is therefore adequate. Safety evaluation in this study was considered adequate, although with this low number of participants and short exposure duration the results are of limited value for extrapolation to the target population (paediatric population).

No unexpected, nor serious adverse events occurred. The study showed that also in Japanese adult subjects A4250 has very limited systemic exposure, is safe (in this small group of male Japanese adults) and shows a PD effect in the same directions as non-Japanese adults on similar dose.

The SmPC already contains the following information under 5.2 Special populations 'No clinically significant differences in the pharmacokinetics of odevixibat were observed based on age, sex or race.' This study did not lead to the necessity to adapt that statement.

The applicant also submitted a clinical study report for the completed 72 weeks of Study A4250-008: an open-label, phase III study to evaluate the long-term efficacy and safety of odevixibat in children with PFIC (category 3 study in the RMP; MEA 002).

Long-term treatment with odevixibat in patients with PFIC, including those with some of the rare PFIC subtypes, led to reductions in serum bile acid levels and pruritus for 96 weeks or longer. In patients naïve to odevixibat on entry into Study A4250-008, reductions in serum bile acid levels and pruritus symptoms occurred rapidly and were sustained during continued treatment. Results for secondary and exploratory endpoints were consistent with the reductions in serum bile acids and pruritus, showing continued improvement in growth parameters, improvements in sleep, and QoL measures. Patients who were treatment-naive were more likely than patients who had received odevixibat in Study A4250-005 to have undergone biliary diversion surgery or liver transplant during the study. The estimated surgery-free survival and native liver-survival rates at 4 years from the first dose of odevixibat were ≥ 76% and ≥ 77%, respectively, across the study groups.

Odevixibat was well tolerated for 96 weeks or longer, with most TEAEs being mild to moderate in severity and not dose limiting.

The applicant also further summarised results from two studies (mass balance study A4250-007, food effect study A4250-004). In summary, the mass balance study demonstrated no absorption of odevixibat at doses of 3 mg; the food effect study also confirmed that, following administration of 9.6 mg odevixibat, plasma concentrations and systemic exposure were very low, regardless of co-administration with food, supporting minimal systemic absorption from the GI tract. SmPC 5.2 already outlines that the impact of renal impairment is expected to be small due to low systemic exposure and odevixibat is not excreted in urine. With this variation it is proposed to include in SmPC 4.2 to specify that due to negligible renal excretion no dose adjustment is required for patients with mild to moderate renal impairment which is agreed with.

Also, the MAH proposed to add to the existing dosing advise on hepatic impairment in 4.2 of the SmPC the underlying rational (i.e. the minimal absorption of odevixibat) and that additional monitoring for adverse reactions may be warranted in these patients when odevixibat is administered. This is agreed.

Furthermore, the MAH proposed semantic edits to the warning in SmPC 4.2 on Diarrhoea and in accordance with risk mitigation strategies that applied in study A4250-008 which are agreed. The proposed addition under the warning on fat-soluble vitamin (FSV) absorption (i.e. that, if FSV deficiency is diagnosed, supplemental therapy should be prescribed) is considered standard clinical practise and is therefore agreed with too.

The applicant proposed for inclusion in 4.8 of the SmPC: "*Other reported adverse reactions were vomiting and stomach pain, mild to moderate increases in liver function tests, and decreases in Vitamin D and E levels*" and an update of the table on frequency of adverse reactions in PFIC patients in accordance with adverse event as reported in study A4250-008 with their respective frequencies which is agreed with.

Furthermore the MAH added a paragraph on the most common hepatic adverse reactions in 4.4. of the SmPC which reflects information in line with the incidents reported in study A4250-008 the paragraph was included into the existing warning to assess liver function tests for all patients prior to initiating odevixibat, with monitoring per standard clinical practice; this is agreed with.

Furthermore, and also in line with the results reported in study A4250-008 and the text in 4.4 of the SmPC the MAH added a paragraph in 4.8 of the SmPC that d*ue 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. Overall, few patients had fat-soluble vitamin deficiency that was refractory to supplementation. These events were mild in intensity and did not lead to discontinuation of odevixibat.* This is agreed with.

With regards to updated information proposed for 5.1 of the SmPC the applicant combined the results of Trial 1 (study A4250-005) and the extension thereof Trial 2 (Study A4250-008). The results are correct depicted and conscientious. Further the applicant included a pooled analysis of both studies. This is considered short and to the point. Further it can be considered practical information for the prescriber and patient. The proposed additions and changes are acceptable. Furthermore, the applicant completed their PIP (full compliance) and proposes the inclusion of a reference to study A4250-003 a Phase 2 dose-finding study in paediatric patients with cholestatic liver disease, including PFIC in 5.1. of the SmPC. This study was part of the PIP and the inclusion is agreed with.

Finally the MAH replaced on CHMP request where possible the trade name with the INN in the SmPC.

In light of the data submitted and the proposed and agreed changes to the SmPC, the benefit-risk balance of Bylvay 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.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
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	None

A grouped application including two type II variations:
- Update of sections 4.2, 4.4, 4.8, and 5.1 of the SmPC based on the clinical study report for the completed 72 weeks of Study A4250-008; an open-label, phase III study to evaluate the long-term efficacy and safety of odevixibat in children with PFIC (category 3 study in the RMP; MEA 002).
The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and the Package Leaflet. An updated RMP version 6.3 was

included in this submission.
- Submission of the clinical study report for Study A4250-J001; a Phase I PK study in healthy Japanese adult male patients.

☒is recommended for approval.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0147/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

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 Bylvay-H-C-004691-II-0022/G.

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

5. Introduction

The applicant submitted a grouped application including two type II variations:

- For the update of sections 4.2, 4.4, 4.8, and 5.1 of the SmPC based on the clinical study report for the completed 72 weeks of Study A4250-008; an open-label, phase III study to evaluate the long-term efficacy and safety of odevixibat in children with PFIC (category 3 study in the RMP; MEA 002).
  An updated RMP version 6.1 is included in this submission.
- Submission of the clinical study report for Study A4250-J001; a Phase I PK study in healthy Japanese adult male patients.

6. Clinical Pharmacology aspects

6.1. Methods – analysis of data submitted

The applicant submitted a clinical study report for the completed safety and pharmacokinetics study in healthy Japanese adult subjects A4250-J001; A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety and Pharmacokinetics of Repeated Oral Administration of A4250 in Healthy Japanese Adult Subjects.

6.1.1. Title of Study:

A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety and Pharmacokinetics of Repeated Oral Administration of A4250 in Healthy Japanese Adult Subjects (A4250-J001).

Table 1 Overview of the Clinical Study

Study number	A4250-J001
Clinical, Bioanalytical PK and Statistical Analysis	XXXXXXXXRedacted
Bioanalytical site	XXXXXXXXRedacted
PK / statistical analysis	CMIC CO., Ltd, 1-1-1 Shibaura, Minato-ku, Tokyo 105-0023, Japan
Study Sponsor	Jadeite Medicines Inc.
Principal investigator	XXXXXXXXRedacted
Biostatistician	XXXXXXXXRedacted
Protocol and ethics	Protocol version: not reported Ethics committee approval date: not reported Name IRB: not reported
Screening and informed consent	Screening was done between 02-21-Feb2024 for all subjects. Screening informed consent was signed on the day of screening, study informed consent was signed prior to the study start
Clinical study period	24 Aug 2022 to 2 Oct 2022
Bioanalytical analysis	Not reported
Statistical analysis	Not reported

Date of report	24-Apr-2023

The company declares that study A4250-J001 was conducted in compliance with Good Clinical Practices (GCP).

Assessor's comment:
Some documents have been deleted from the CSR, therefore it is not possible to check for ethics approval for this trial. The applicant is requested to provide the ethics committee approval letter(s) and also all appendices.

The bioanalytical validation or report have not been submitted. The applicant is requested to provide the bioanalytical method, validation and GLP statement.

6.1.2. Study design:

A randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety and pharmacokinetics of repeated oral administration of A4250 in healthy Japanese adult subjects.

Study Objectives

- To evaluate the safety and tolerability of multiple oral doses of A4250 administered to healthy Japanese adult subjects under fasting conditions
- To evaluate the PK and PD of multiple oral doses of A4250 in healthy Japanese adult subjects under fasting conditions

Nine subjects were included and randomized to active treatment (n=6, 3 mg A4250) or placebo (n=3). No calculations were performed to determine the sample size. The sample size of the study was instead selected because safety, tolerability, PK, and PD were evaluable when single doses of A4250 (0.1 mg, 0.3 mg, 1 mg, 3 mg, and 10 mg) were given to 6 subjects and placebo was given to 2 subjects in Part 1 of a Phase 1 study in non-Japanese subjects conducted outside Japan (Study A4250-001). It was thought that this sample size would allow comparisons of the data between Japanese and non-Japanese subjects.

Subjects took A4250 3 mg [1 No. 0 capsule (containing A4250 600 µg) and 2 No. 3 capsules (containing A4250 1200 µg)] or placebo, once daily for 7 consecutive days prior to breakfast (after fasting for at least 10 hours; water was allowed up to 2 hours prior to investigational product administration) with 200 to 240 mL of water.

Table 2 Product information

Treatment period	A4250/placebo	A4250 strength	Capsule used [a]	Number of dosage units per dose
Repeated once-daily use for 7 days	A4250 3 mg	600 µg	No. 0 capsule	1
		1200 µg	No. 3 capsule	2
	Placebo	N/A	No. 0 capsule	1
			No. 3 capsule	2

Test drug name:	A4250
Name of active ingredient:	Odevixibat (INN)
Structural formula:	(2S)-2-{[(2R)-2-(2-{[3,3-dibutyl-7-(methylsulfanyl)-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-1λ6,2,5-benzothiadiazepin-8-yl]oxy}acetamido)-2-(4-hydroxyphenyl)acetly]amino}butanoic acid
Molecular formula:	C37H48N4O8S2
Dosage form:	Capsule
Route of administration:	Oral
Batch Nos.	600 µg: 1319X, 1200 µg: 1416X
Storage conditions	Bottles containing odevixibat were stored at 15°C to 25°C. Albireo was to be immediately notified of any deviations from the recommended storage conditions, and the affected investigational product was not to be used until use was approved by Albireo.
Expiration date	600 µg: July 6, 2025, 1200 µg: May 10, 2025

The subjects were to eat the standard meals of the study site while admitted to the study site. The subjects were given lunch about 4 hours after and supper about 9 hours after receiving the investigational product and then a post-supper snack (if provided) after about 14 hours. The times when the meals were provided were entered in the source documents. On Day 1, the subjects were to fast for at least 10 hours before receiving the investigational product and until breakfast was provided within 15 minutes of taking the investigational product. The subjects were allowed to drink water up to 2 hours prior to investigational product administration.

Pharmacokinetics

Pharmacokinetic samples were taken for the analysis of A4250 in plasma on day 1 (first dose) prior to dosing, at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hours post dosing (prior to dosing on day 2) and on day 7 prior to dosing, at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hours post dosing.

Blood samples were collected using appropriate tubes specified by the analysis facility. The sampling tubes, details about processing samples, and where the samples were to be sent were specified in a separate Laboratory Manual.

Individual and mean concentration time curves were reported, the following pharmacokinetic parameters were reported for A4250 on Day 1 and Day 7:

PK parameter	Definition
T_{lag}	Time to the first quantifiable A4250 plasma concentration
T_{max}	Time to the maximum plasma concentration
C_{max}	Maximum plasma concentration
AUC(0-last)	Area under the plasma concentration-time curve from time zero to the last sampling time with quantifiable A4250
AUC(0-inf)	Area under the plasma concentration-time curve from time zero extrapolated to infinity
$AUC\%_{extrap}$	Percentage of area under the curve (AUC) extrapolated beyond last measured time point
AUC(0-tau)	Area under the plasma concentration-time curve within the dosing interval, following multiple dosing
R_A	Relative accumulation following multiple dosing (e.g., Day 7 AUC/Day 1 AUC, Day 7 C_{max}/Day 1 C_{max})
λ_z	Elimination rate constant
$T_{1/2}$	Elimination half-life
$T_{1/2el}$	Apparent elimination half-life

Pharmacodynamics

Plasma total bile acids and bile acid synthesis markers (7alfa-hydroxy-4-cholesten-3-one (C4), fibroblast growth factor-19 (FGF19)) were evaluated as biomarkers. Blood samples were collected on day 1 predose, 4 and 24 hours after dosing, and on day 7 prior to dosing, at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hours post dosing and also at follow-up day 14. Blood samples were collected using appropriate tubes specified by the analysis facility. The sampling tubes, details about processing samples, and where the samples were to be sent were specified in a separate Laboratory Manual.

Descriptive statistics of the plasma PD parameters (total bile acids, C4, and FGF19) 24 hours post-dose on Day 1 were calculated for each day of administration, and pairwise comparisons of active treatment with A4250 and placebo were performed using repeated measures ANOVA.

- The 24-hour post-dose values on Day 1 and 7 were compared, and the effects of repeated dosing were discussed.
- By-subject listings of PD parameters were prepared.

Safety

The safety evaluations included evaluations of adverse events, laboratory tests (predose daily, 24 hours after the last dose and at follow-up day 14), vital signs, and standard 12-lead electrocardiographic findings (daily predose and 1 hour after dosing and additionally at 4, 8 and 24 hour post dose on day 1 and day 7 and at follow-up on day 14. All clinical observations and laboratory test data collected from the first dose to study completion or subject discontinuation were compared with the Day -1 baseline data.

Adverse events were reported.

Assessor's comment:

The study design, dose of A4250 (3 mg) chosen is adequate. However, in the objectives it is stated that A4250 was given under fasting conditions. According to the CSR a breakfast was provided within 15 minutes after dosing. Therefore, this is not considered to be a study under fasting conditions. According to ICH guideline M13a 'Guideline on bioequivalence for immediate release solid oral dosage forms' on the PK sampling days in multiple-dose studies, no food should be allowed for at least 4

hours post-dose on each day of drug administration. The applicant is requested to comment on this statement and discuss the influence of food intake on the PK and PD parameters.

The number of subjects in the study is low (n=6 on active treatment and n=3 on placebo), but for the purpose of this study: to evaluate the safety, PK and PD in Japanese healthy adult subjects this is sufficient and in line with previous healthy volunteer studies.

The sample schedule for pharmacokinetic assessment of A4250 is adequate, the compound is expected to have low bioavailability, but on day 7 exposure is expected to be measurable between 1 and 8 hours after dosing, with a Tmax between 1 – 5 hours.

The selection of biomarkers and sample schedule for pharmacodynamics is in line with previous studies in healthy adult volunteers (A4250-001) and is therefore adequate.

Safety evaluation in this study is adequate, although with this low number of participants and short exposure duration the results are of limited value for extrapolation to the target population (paediatric population).

No information is provided regarding the bioanalysis method, most importantly the lower limit of quantification (LLOQ). The applicant is requested to provide the bioanalytical methods (both PK and PD analyses), validation (including stability of A4250 in whole blood and plasma), LLOQ and GLP statement.

Blood sample collection (which blood sampling tubes were used) and handling (for example storage conditions after collection, time between collection and centrifugation, storage conditions of plasma samples, shipment conditions to the bioanalysis lab) is not described in the CSR. The applicant is requested to provide information on the PK and PD blood sampling collection, handling and shipment.

6.2. Results

Population(s) studied

In total 9 healthy subjects were included in the trial, all subjects completed the trial, 6 were randomized to A4250 and 3 to placebo.

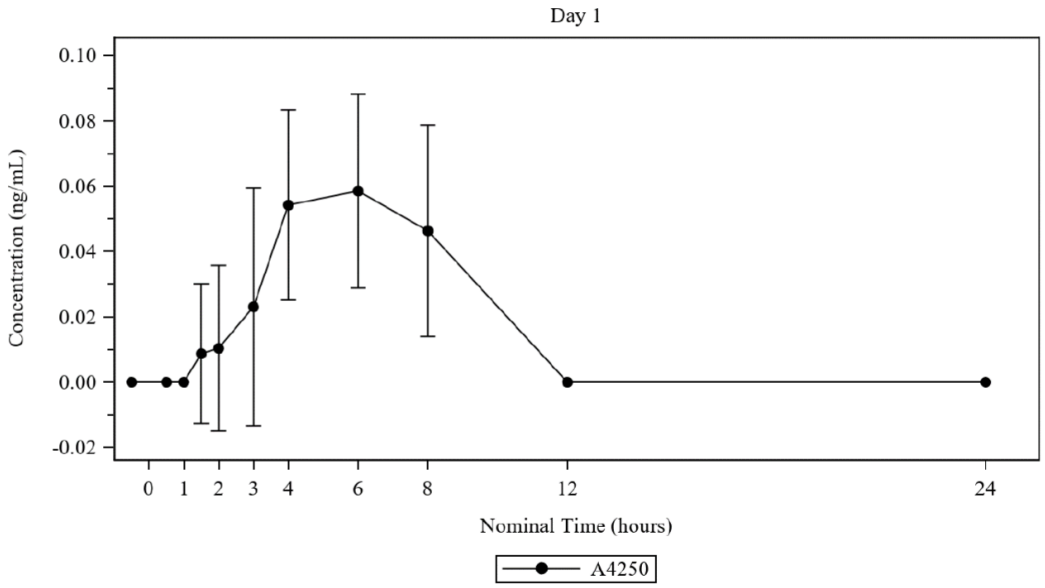
All subjects were of Japanese origin, 9 males, mean age was 26.3 years (range 20-38) in the A4250 group and 20.3 years (range 19-22) in the placebo group, mean BMI was 19.3 kg/m2 (range 18.0-22.8) in the A4250 group and 21.4 kg/m2 (range 18.1-24.3) in the placebo group. All were non-smoking.

There were no protocol deviations in the study.

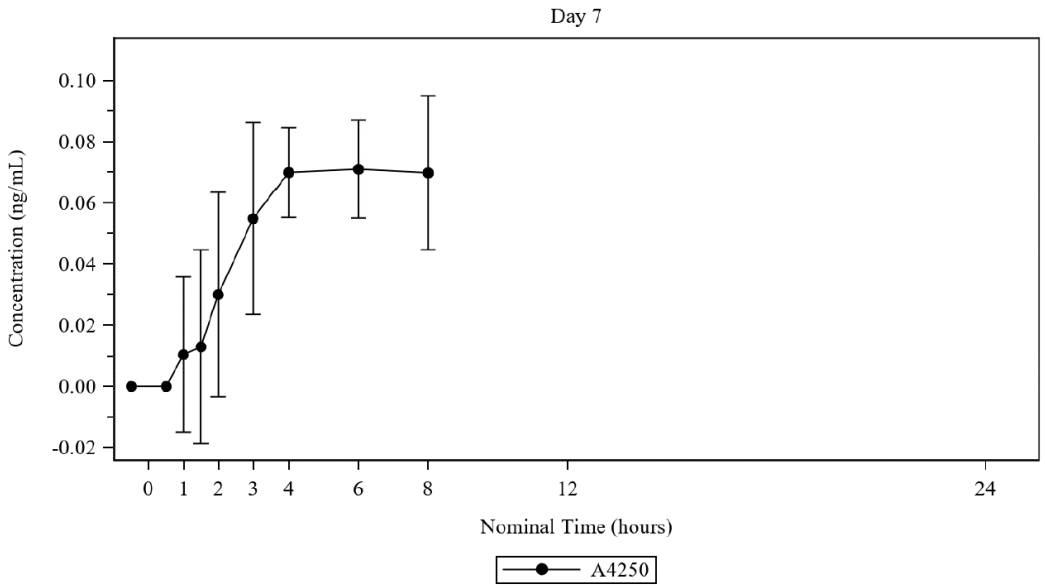
Pharmacokinetics

On Day 1, plasma drug concentrations were detected in 5 subjects from 1.5 to 8 hours postdose. On Day 7, plasma drug concentrations were detected in 6 subjects from 1 to 8 hours postdose.

Figure 1 Mean A4250 concentration time curves on day 1 and day 7 (A4250-J001)



*Values below the BLQ before Cmax were treated as 0. Values below the BLQ after the Cmax were treated as missing.



*Values below the BLQ before Cmax were treated as 0. Values below the BLQ after the Cmax were treated as missing.

Table 3 Summary of pharmacokinetic parameters (A4250-J001)

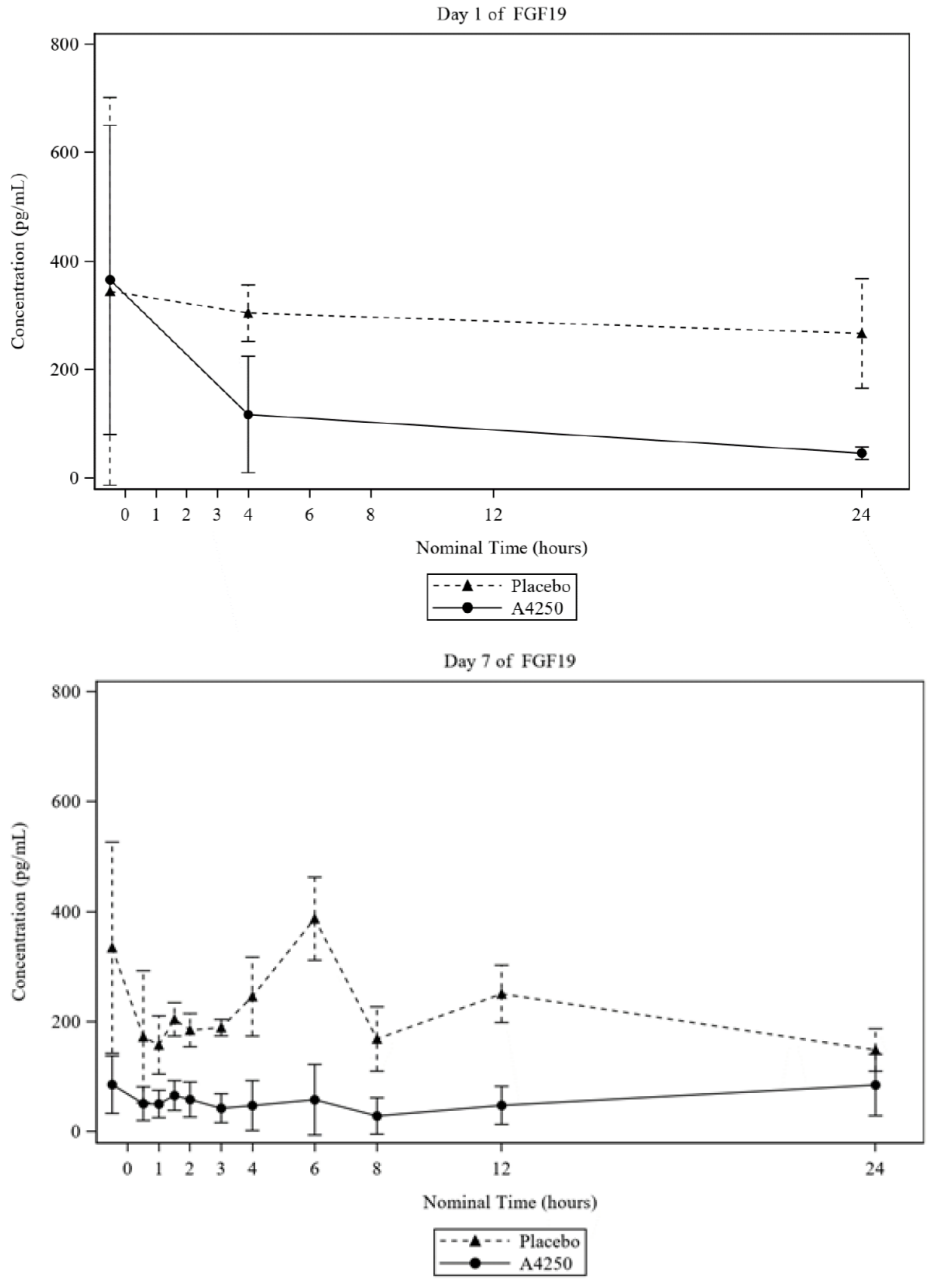
	n	Mean (S.D.)	CV (%)	Median	[Min , Max]	GM
A4250						
Day 1						
T_{lag}	5	2.900 (1.140)	39.3	3.000	[1.50 , 4.00]	2.702
T_{max}	6	5.000 (2.757)	55.1	6.000	[0.00 , 8.00]	5.860
C_{max}	6	0.06385 (0.03223)	50.5	0.07460	[0.00 , 0.0880]	0.07622
AUC (0-last)	5	0.29 (0.10)	35.0	0.27	[0.2 , 0.5]	0.27
AUC (0-inf)	0	- (-)	-	-	[- , -]	-
$AUC\%_{extrap}$	0	- (-)	-	-	[- , -]	-
AUC (0-24)	0	- (-)	-	-	[- , -]	-
λ_z	0	- (-)	-	-	[- , -]	-
$T_{1/2}$	0	- (-)	-	-	[- , -]	-
Day 7						
T_{max}	6	3.417 (1.625)	47.6	3.500	[1.50 , 6.00]	3.086
C_{max}	6	0.07080 (0.01465)	20.7	0.07095	[0.0516 , 0.0893]	0.06951
AUC (0-last)	6	0.23 (0.19)	83.6	0.24	[0.0 , 0.5]	0.12
AUC (0-tau)	2	0.96 (0.10)	10.5	0.96	[0.9 , 1.0]	0.96
R_{AAUC}	0	- (-)	-	-	[- , -]	-
R_{ACmax}	5	0.964 (0.224)	23.2	1.015	[0.64 , 1.20]	0.941
λ_z	2	0.0475 (0.0335)	70.5	0.0475	[0.024 , 0.071]	0.0412
$T_{1/2}$	2	19.41 (13.69)	70.5	19.41	[9.73 , 29.1]	16.83

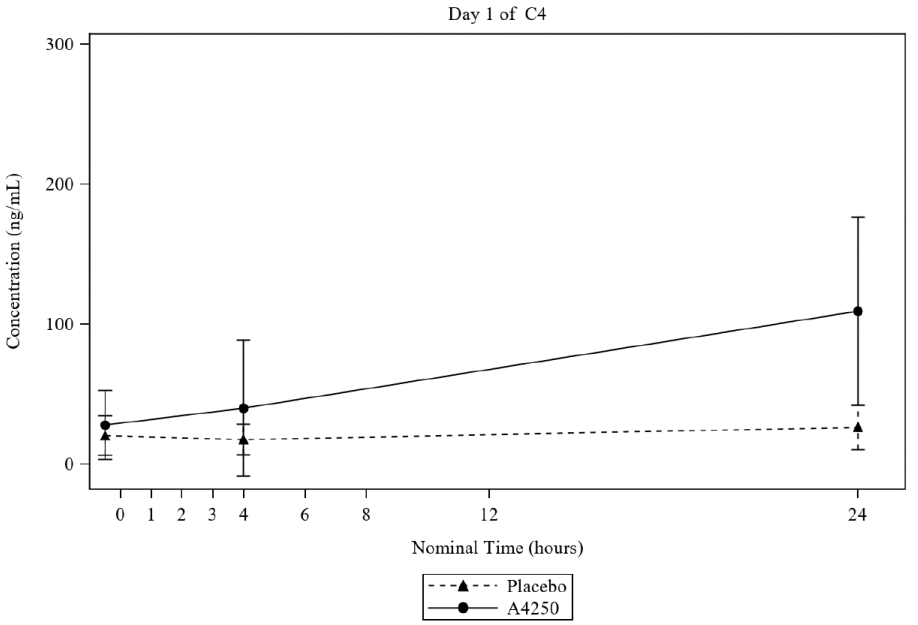
CV: coefficient of variation
GM: geometric mean

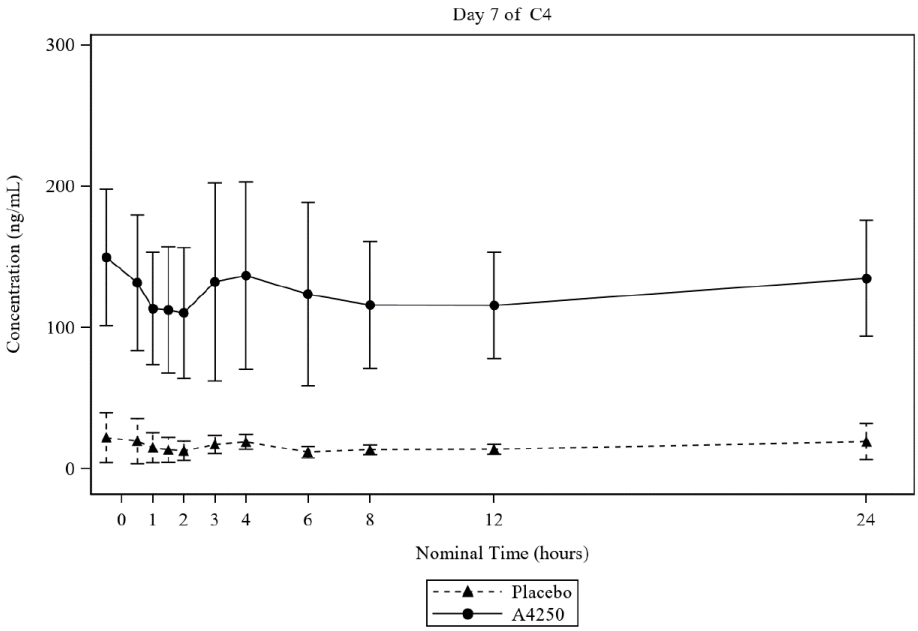
Pharmacodynamics

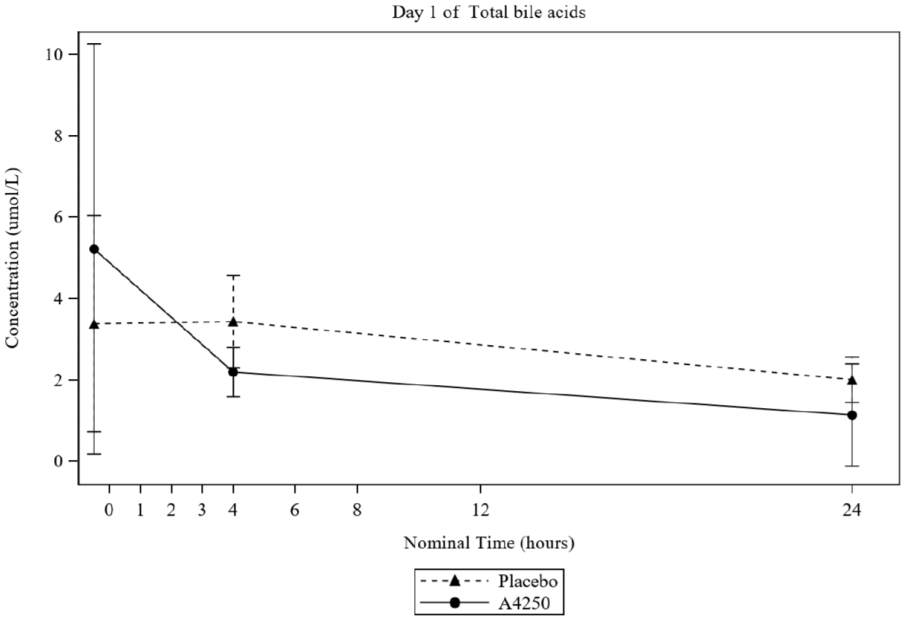
All subjects were included in the PD analysis.

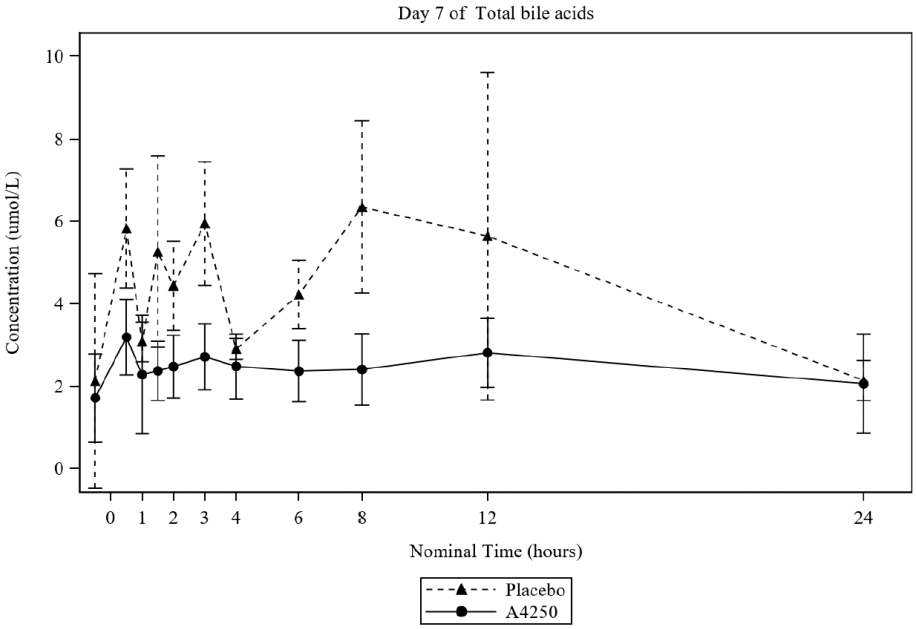
Figure 2 The results of the three biomarkers are depicted in the figures below.




Day 1 of C4
300
200
100
0
Concentration (ng/mL)
0 1 2 3 4 6 8 12 24
Nominal Time (hours)
Placebo
A4250


Day 7 of C4
300
200
100
0
Concentration (ng/mL)
0 1 2 3 4 6 8 12 24
Nominal Time (hours)
Placebo
A4250





The changes from baseline in plasma total bile acids and bile acid synthesis markers (C4 and FGF19) with a statistically significant inter-group difference were in C4 at 24 hours post-dose on Day 1 (inter-group difference in change: 75.49 h*ng/mL, p=0.0476) and pre-dose (120.20 h*ng/mL, p=0.0017), 4 hours post-dose (110.19 h*ng/mL, p=0.0076), and 24 hours post-dose (108.10 h*ng/mL, p=0.0031) on Day 7.

Comparing to the A4250-001 study: Following once daily repeated oral doses of 3 mg for 7 days, the changes from baseline in plasma total bile acids and bile acid synthesis markers (C4 and FGF19) with a statistically significant inter-group difference were in C4 on Day 1 at 4 hours post-dose (inter-group difference in change: 21.343 ng/mL, p=0.018) and at 24 hours post-dose (45.995 ng/mL, p=0.005) and on Day 7 at pre-dose (86.297 ng/mL, p=0.007), 4 hours post-dose (89.037 ng/mL, p=0.001), and 24 hours post-dose (94.283 ng/mL, p=0.001); and in FGF19 on Day 1 at 4 hours post-dose (-121.92 pg/mL, p=0.001) and 24 hours post-dose (-79.350 pg/mL, p=0.003) and on Day 7 at pre-dose (-118.68 pg/mL, p<0.001), 4 hours post-dose (-154.47 pg/mL, p<0.001), and 24-hours post-dose (-124.45 pg/mL, p<0.001).

Safety

No serious adverse events were reported.

All 6 subjects in the A4250 group reported adverse events, 1 subject in the placebo group reported adverse events. Adverse events were judged to be related to study drug, all were mild of intensity and resolved, all were gastro-intestinal adverse events (6 diarrhoea in the A4250 group; 1 soft faeces in the A4250 group and 1 soft faeces in the placebo group).

There were no clinically significant abnormalities that were classified as an adverse event.

In the study, no abnormality or abnormal change that was classified as an adverse event occurred in vital signs, physical findings, or other observations related to safety.

Assessor's comment:
No protocol deviations occurred, all subjects completed the trial, the CSR does not report whether samples were missing, or samples were reanalysed. The applicant is requested to provide information regarding missing samples or reanalysis of samples (PK and PD samples). (**PK, PD, OC, LoQ**)

Pharmacokinetics
Individual A4250 concentrations are missing (only available graphically), as well as individual PK parameters. The applicant is requested to provide individual A4250 concentrations and A4250 PK parameters.

As mentioned before, the LLOQ is very important to be reported, see earlier OC.

The comparison with the pharmacokinetic results of study A4250-001 is not reliable, as a different LLOQ was used (although not certain, as the LLOQ of the A4250-J001 study was not reported). The applicant is requested to mention this concern in the discussion and take this into consideration in the conclusion.

Table 11.4.1 shows geometric means, but the results cannot be correct, as they are 0.3 for the timepoints with no measurable concentrations. The applicant is requested to check all tables for missing units and errors.

Pharmacodynamics (PD)
Individual PD concentrations are missing, as well as individual PD parameters. The applicant is requested to provide individual PD concentrations and PD parameters. (**PD, OC, LoQ**)
For C4 AUCs seem to have been calculated, this was not mentioned in the methods section. The applicant is requested to be more specific about the pivotal PD parameter per biomarker and how they were assessed.

The comparison of the results with the A4250-001 study is very relevant. The applicant is requested to also compare the magnitude of the difference between the groups (A4250 versus placebo), as these seem to differ between the two studies (A4250-J001 shows a larger effect compared to A4250-001 on the same dose?).

Safety
No unexpected, nor serious adverse events occurred. However, Table 14.3.2-2 Serious Adverse Events Other than Death (SP) does contain all the adverse events that were reported. The applicant is requested to explain this.

Despite the inconsistencies the study does show that also in Japanese adult subjects A4250 has very limited systemic exposure, is safe (in this small group of male Japanese adults) and shows a PD effect in the same directions as non-Japanese adults on similar dose.

6.3. Discussion

The clinical overview includes the PK, PD and safety results of trial A4250-J001.

The study was mentioned in the clinical overview, the SmPC already contained the following information (before the submission of study A4250-J001): `paragraph 5.2 Special populations 'No clinically significant differences in the pharmacokinetics of odevixibat were observed based on age, sex or race.'

This study did not lead to the necessity to adapt that statement.

Assessor's comment

The clinical overview summary of the PD results of trial A4250-J001 is not consistent with the results in the CSR. The clinical overview suggests: 'The difference in changes from baseline in plasma total bile acids and bile acid synthesis markers (C4 and FGF19) were statistically significant for C4 at 24 hours post-dose on Day 1 and 24 hours post-dose on Day 7.' (page 27) the CSR reports: 'The changes from baseline in plasma total bile acids and bile acid synthesis markers (C4 and FGF19) with a statistically significant inter-group difference were in C4 at 24 hours post-dose on Day 1 (inter-group difference in change: 75.49 h*ng/mL, p=0.0476) and 4 hours post-dose (110.19 h*ng/mL, p=0.0076) and 24 hours post-dose (108.10 h*ng/mL, p=0.0031) on Day 7.' The applicant is requested to adapt the PD results of A4250-J001 in the clinical overview to be in line with the results of the trial.

7. Clinical Efficacy aspects

7.1. Methods – analysis of data submitted

The applicant submitted a clinical study report for the completed 72 weeks of Study A4250-008; an open-label, phase III study to evaluate the long-term efficacy and safety of odevixibat in children with PFIC (category 3 study in the RMP; MEA 002).

7.1.1. Title of Study:

An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of A4250 in Children with Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC 2).

7.1.2. Studied period (years):

Enrolment is complete; all patients completed the primary 72-week treatment period or discontinued prior to that time.

- Date first patient enrolled: 28SEP2018
- Date last patient completed Week 72: 15FEB2024
- Data cutoff date for ongoing optional extension period: 15FEB2024

7.1.3. Objectives:

Primary:

- Cohort 1: To demonstrate a sustained effect of odevixibat on serum bile acids and pruritus in children with progressive familial intrahepatic cholestasis (PFIC) Types 1 and 2.
- Cohort 2: To evaluate the effect of odevixibat on serum bile acids and pruritus in patients with PFIC who either (1) did not meet eligibility criteria for Study A4250-005 or (2) who did meet the eligibility criteria for Study A4250-005 after recruitment of Study A4250-005 had been completed.

Secondary:

- To evaluate the long-term safety and tolerability of repeated daily doses of odevixibat.
- To evaluate the effect of odevixibat on growth.
- To evaluate the effect of odevixibat on the need for biliary diversion and/or liver transplantation.
- To evaluate the effect of odevixibat on biochemical markers of cholestasis and liver disease.

7.1.4. Methodology:

Study A4250-008 is a Phase 3, multicentre, open-label extension study to investigate the long-term efficacy and safety of odevixibat in patients with PFIC. Two cohorts of patients were enrolled.

Cohort 1 includes paediatric patients with PFIC Types 1 and 2 who participated in the Phase 3, randomised, double-blind, placebo-controlled Study A4250-005. Cohort 2 includes patients of any age with any type of PFIC with elevated serum bile acids and cholestatic pruritus and who either did not meet eligibility criteria for Study A4250-005 or were eligible for enrolment after recruitment of Study A4250-005 was complete. Up to 40 patients post biliary-diversion surgery could participate in Cohort 2.

Prior to Amendment 6 of the protocol, the starting dose for all patients was 120 µg/kg/day; patients were to remain on this dose unless experiencing tolerability issues that required down titration to the 40 µg/kg once daily (QD). As of Amendment 6, the starting dose of odevixibat was 40 µg/kg/day; patients on this dose had the possibility to escalate to the 120 µg/kg/day dose after the first 12 weeks if there was no improvement in pruritus based on investigator judgement.

The study includes an 8-week screening period (Cohort 2 only), a 72-week treatment period, and a 4-week follow-up period. An optional extension period for continued treatment follows the 72-week treatment period; patients who enrol in the optional extension were not required to attend the follow-up visit.

All patients and/or their caregivers were provided an electronic diary (eDiary) at the first visit to record patient-reported (patients ≥ 8 years of age) and observer-reported (caregivers for all patients) outcome items from the Albireo patient-reported outcome (PRO) and observer-reported outcome (ObsRO) instruments for evaluation of itching, scratching, and sleep disturbance. Data were to be entered twice daily for the first 24 weeks of the study and then twice daily for the 21 days before each clinic visit thereafter. Clinic visits included physical examinations, including assessment of skin and vital signs; clinical laboratory assessments, including haematology, chemistry, international normalised ratio (INR), serum bile acid, plasma 7α-hydroxy-4-cholesten-3-one concentration (p-C4), autotaxin,

alpha-fetoprotein (AFP), vitamin A, vitamin E, 25-hydroxyvitamin D, urine pregnancy testing, and urinalysis; completion of the Pediatric Quality of Life Inventory (PedsQL), Global Impression of Change (GIC), and Global Impression of Symptoms (GIS); Fibroscan® (where available); abdominal ultrasound (liver and spleen); and review of concomitant medications and adverse events (AEs).

7.1.5. Number of patients (planned and analysed):

Planned: Approximately 120 patients total were planned, 60 patients per cohort.

Analysed: Overall, a total of 116 patients received at least 1 dose of odevixibat in Study A4250-008, including 56 patients in Cohort 1 and 60 patients in Cohort 2. All 116 patients were included in the full analysis set (FAS), the only analysis set for this study.

7.1.6. Diagnosis and Main Criteria for Inclusion:

Cohort 1: Patients who completed the 24-week treatment period of Study A4250-005 or (prior to Amendment 6 of the A4250-005 protocol) withdrew due to patient/caregiver judgment of intolerable symptoms after completing at least 12 weeks of treatment were eligible for enrolment in Cohort 1.

Key exclusion criteria included patients with decompensated liver disease, those who were noncompliant with treatment in Study A4250-005, or any other conditions or abnormalities that could compromise the safety of the patient.

Cohort 2: Male or female patients of any age and a body weight ≥ 5 kg with a genetically confirmed diagnosis of PFIC who did not meet the eligibility criteria for Study A4250-005 or were eligible for enrolment after recruitment in Study A4250-005 was complete were included in Cohort 2. Patients with PFIC, excluding those with episodic forms, were required to have an elevated serum bile acid concentration ≥ 100 µmol/L, taken as the average of 2 samples at least 7 days apart during screening; a history of significant pruritus; and a caregiver-reported average scratching score in the eDiary of ≥ 2 (on a 0 to 4 scale) in the 2 weeks prior to Visit 1. Patients with the episodic form of PFIC must have had an emerging flare characterised by clinically significant pruritus and elevated serum bile acid levels/cholestasis as judged by the investigator.

Key exclusion criteria included patients with pathologic variations of the ABCB11 gene that predict complete absence of the bile salt export pump (BSEP) protein, prior liver transplant or planned transplant within 6 months, alanine aminotransferase (ALT) or total bilirubin > 10 × upper limit of normal (ULN) at screening, decompensated liver disease, any uncontrolled, recalcitrant pruritic condition other than PFIC, or any other conditions or abnormalities that could compromise the safety of the patient or their ability to complete the study.

7.1.7. Test Product, Dose and Mode of Administration, Lot Number:

Odevixibat was administered orally, once daily at a dose of 120 µg/kg/day or 40 µg/kg/day (as of Protocol Amendment 6, patients entering Cohort 2 started treatment at 40 µg/kg/day with the possibility to dose escalate to 120 µg/kg/day after 12 weeks, if there was no improvement in pruritus based on investigator judgement); patients who were unable to tolerate the higher dose could reduce the dose to 40 µg/kg/day under specific conditions.

7.1.8. Duration of Treatment:

Duration of treatment was 72 weeks with an option to continue in an extension period that allowed patients to continue on study drug until commercial availability of odevixibat in their region/country.

7.2. Results

7.2.1. Disposition:

Of the 116 patients treated in this study, 37 had previously received odevixibat in Study A4250-005 and 79 were treatment-naïve, including 19 patients who had received placebo in Study A4250-005 and 60 patients in Cohort 2.

A total of 83 (72%) of the 116 patients completed the primary 72-week treatment period and 33 (28%) patients discontinued prior to that time. The primary reasons for discontinuation prior to Week 72 were AEs (9 patients, 8%) and withdrawal of consent/assent (8%). Among the 83 patients who completed 72 weeks of treatment, 74 entered the optional extension period; 7 of the 9 patients who did not enter the optional extension were placed on commercial product and for 2 patients the reason was not provided. As of the data cutoff date, 31 patients were ongoing on treatment with odevixibat in the optional extension and 43 had discontinued, including 33 patients who were transitioned to commercial product. One patient withdrew from treatment due to AE during the optional extension period.

7.2.2. Patient Characteristics at Study Entry:

Median age of the 116 patients was 3.70 years and ranged from 0.3 to 26.0 years; 55% of the patients were male and the majority were white (86%). All patients had a central diagnosis of PFIC; most had PFIC2 (65 patients, 56%); 36 (31%) patients had PFIC1, 7 (6%) had PFIC3, and 8 (7%) patients were classified as "other" PFIC type (including 2 patients each with PFIC4 and PFIC6 and 4 patients with episodic PFIC). Median time since diagnosis of PFIC was 2.1 years. At baseline, most patients (84%) were receiving ursodeoxycholic acid (UDCA) and/or rifampicin.

At Study A4250-008 baseline, mean serum bile acid levels were 137.77 µmol/L for patients who had received odevixibat in Study A4250-005 and were higher at 280.58 µmol/L for patients who had received placebo, and 220.93 µmol/L for patients in Cohort 2; when evaluated at Study A4250-005 baseline, mean serum bile acid levels for patients who had received odevixibat in that study were similar to the treatment-naïve patient groups at 248.11 µmol/L. Similarly, mean scratching scores at Study A4250-008 baseline based on the ObsRO were lower in Cohort 1 patients who received odevixibat in Study A4250-005 at 1.84, compared to 2.68 and 2.89, for Cohort 1 patients who had received placebo and Cohort 2 patients, respectively. When evaluated at Study A4250-005 baseline, mean scratching score for patients who had received odevixibat in that study was similar to the treatment-naïve patient groups at 2.89.

7.2.3. Efficacy Results:

For the primary endpoint for Europe and RoW, treatment with odevixibat led to sustained reductions in serum bile acid concentrations through Weeks 70/72 of Study A4250-008. For patients in Cohort 1 who had received odevixibat in Study A4250-005, mean (standard deviation [(SD]) change in serum bile acid concentration from Study A4250-005 baseline to Week 70/72 of Study A4250-008, i.e. after 96 weeks of treatment with odevixibat, was -139.84 (172.070) with a median percent change of -58% for those 28 patients with data available for analysis. For the 15 patients who had received placebo in Study A4250-005 and had data available, mean (SD) change from Study A4250-008 baseline to Week 70/72 was -104.00 (167.318) µmol/L and for the 43 patients in Cohort 2 was -57.97 (137.990) representing median percent changes to Week 70/72 of -18% and -25%, respectively.

For the US primary endpoint, treatment with odevixibat led to sustained improvements in pruritus based on the ObsRO instrument (AM and PM scores combined). For patients in Cohort 1 who received odevixibat in Study A4250-005 and entered the current study with improved scratching severity, a further improvement was observed during continued treatment in Study A4250-008. For this group of patients, the proportion of positive pruritus assessments at the patient level was 39% after 72 weeks of odevixibat treatment on Study A4250-008 for the 26 patients with data available for analysis. For treatment-naïve patients, the proportions of positive pruritus assessments at the patient level were 55% and 77%, respectively, for the 12 patients in Cohort 1 who had received placebo in Study A4250-005 and the 31 patients in Cohort 2 who had data available through 72 weeks of treatment with odevixibat on Study A4250-008.

Consistent with the US primary endpoint, changes from baseline in scratching severity score showed improvement following the initiation of treatment with odevixibat. For patients in Cohort 1 who had received odevixibat in Study A4250-005, mean (SD) change in scratching severity score from baseline of Study A4250-005 to Weeks 71-72 of Study A4250-008 (n=26), i.e. after 96 weeks of treatment with odevixibat was -1.88 (0.933). For patients who were treatment naïve at entry to Study A4250-008, mean decreases in scratching severity scores were observed by Weeks 1- 4 with mean (SD) changes from baseline of -0.52 (0.594) (n=19) and -0.87 (0.727) (n=53) in patients who had received placebo in Study A4250-005 and Cohort 2 patients, respectively, that improved to Weeks 71-72 with changes of -0.83 (0.942) (n=12) and -1.55 (1.477) (n=31), respectively.

Results for AM and PM scratching scores separately were consistent with the combined scores, indicating further improvement in both nighttime and daytime pruritus during long-term treatment for patients in Cohort 1 who had received odevixibat in Study A4250-005 and rapid improvement in treatment-naïve patients that was sustained over 72 weeks of odevixibat in Study A4250-008. As well, results for patient-reported itching were consistent with ObsRO results.

The proportion of patients who achieved a ≥ 1.0-point reduction in scratching severity score (AM and PM combined) determined to be a clinically meaningful threshold based on a psychometric analysis also confirmed the improvement in pruritus symptoms. When evaluated from baseline of Study A4250-005, 20 (83%) of 24 patients in Cohort 1 who received odevixibat in that study had achieved a ≥ 1-point reduction in scratching severity score at Weeks 68-72, i.e. after 96 weeks of treatment on odevixibat. For treatment-naïve patients, 7 (54%) of 13 patients and 20 (65%) of 31 patients in Cohort 1 who had received placebo in Study A4250-005 and in Cohort 2, respectively, had achieved a ≥ 1-point reduction in scratching severity score from baseline of Study A4250-008 to Weeks 68-72.

Review of the 11 patients with PFIC types other than PFIC1 and PFIC2 showed high rates of bile acid response (10 of the 11 patients) and pruritus response (9 of the 10) patients. As well, 2 of the 4 patients with the episodic form of PFIC who entered the study with pruritus and elevated bile acids also showed good response to treatment with odevixibat.

Nineteen (16%) of the 116 patients in this study underwent surgical intervention (including 3 patients who underwent biliary diversion surgery, 15 patients who underwent liver transplantation, and 1 patient who underwent both procedures). Eight of the 19 patients had their surgery after completing the primary 72-week treatment period. Patients who were treatment-naïve in Study A4250-008 were more likely to have undergone these surgical procedures with 14 (18%) of the 79 patients having biliary diversion surgery or liver transplant compared to 5 (14%) of 37 patients who had received odevixibat in Study A4250-005. Median time to surgery from start of odevixibat treatment was not reached in any study group with 84% of patients censored in the analysis. Based on the Kaplan-Meier analysis, the estimated proportions of patients without biliary diversion surgery or liver transplant at 4 years after the start of odevixibat treatment were 80%, 78%, and 76% in patients who had received odevixibat in Study A4250-005, patients who had received placebo in that study, and Cohort 2

patients, respectively; results for the estimated proportion without liver transplant at 4 years were 90%, 83%, and 77%, respectively.

Catch-up growth was noted over time in both study groups in Cohort 1 and in Cohort 2. For patients in Cohort 1 who had previously received odevixibat in Study A4250-005, mean (SD) changes from Study A4250-005 baseline to Week 70/72 of Study A4250-008 (n=28) in height z-score was 0.615 (0.7262) and in weight z-score was 0.557 (0.8869). For patients in Cohort 1 who had received placebo in Study A4250-005 (n=15), mean (SD) changes from Study A4250-008 baseline to Week 70/72 in height and weight z-scores were 0.547 (0.5047) and 0.429 (0.8793), respectively, and in Cohort 2 were 0.202 (0.6658) (n=39) and 0.339 (0.6557) (n=40), respectively.

Treatment with odevixibat also led to improved sleep for patients based on the ObsRO at Weeks 71-72, with reductions from baseline in all sleep parameters in all study groups.

In general, modest improvements were observed in ALT, AST, and total bilirubin during long-term treatment with odevixibat, although the results were highly variable as were the results for GGT. For patients in Cohort 1 who had received odevixibat in Study A4250-005, mean (SD) reductions from Study A4250-005 baseline to Week 70/72 of Study A4250-008, i.e. after 96 weeks of odevixibat treatment were observed for ALT (-66.72 [165.455] U/L; n=25), AST (-34.88 [58.445] U/L; n=25) and GGT (-1.08 [8.466] U/L; n=26). For total bilirubin, an increase from Study A4250-005 was observed at Week 70/72 (7.63 [74.669] µmol/L; n=25); however, mean reductions in total bilirubin were observed at assessments both prior to and after Week 70/72; at Weeks 88, 104, and 120, mean (SD) changes from Study A4250-005 baseline were -14.28 (40.896) µmol/L (n=27), -12.02 (42.127) µmol/L (n=24), and -13.83 (42.826) (n=21) µmol/L, respectively. For the treatment-naïve groups, mean reductions from baseline to Week 70/72 were observed in ALT (-12.79 [50.815] U/L; n=14

and -1.18 [64.850] U/L; n=39 for patients who had received placebo in Study A4250-005 and Cohort 2, respectively) and in total bilirubin (-10.56 [32.661] µmol/L; n=14 and -36.78 [164.421] µmol/L; n=40, respectively). Mean increases to Week 70/72 were observed in GGT in both groups:

0.33 (4.938) U/L in patients who had received placebo in Study A4250-005 (n=15) and 20.39 (64.966) U/L in Cohort 2 (n=38). Results for AST were variable across these 2 groups with a mean reduction observed in patients who received placebo, and a mean increase observed in Cohort 2 at Week 70/72. For all groups there were no appreciable mean changes from baseline to Week 72 in PELD, APRI, and FIB-4 scores. Mean MELD score decreased by approximately 2 points in Cohort 2 based on data from 9 patients.

Improvement to Week 72 in QoL as assessed by the PedsQL was observed in all study groups. Results for the GIC and GIS as completed by caregivers indicated improvements over time in both scratching and sleep in all study groups.

Consistent with the reduction in pruritus severity and serum bile acid levels, reductions in autotaxin levels and increases in p-C4 levels over time were seen in all study groups.

7.2.4. Safety Results:

Odevixibat was well tolerated for ≥ 96 weeks in patients with PFIC. Overall, 85 (73%) of the 116 patients had received ≥ 72 weeks of treatment with odevixibat in Study A4250-008 with 61 (53%) patients having received ≥ 96 weeks. Maximum duration of treatment was > 4.5 years.

No deaths were reported in this study. Treatment-emergent SAEs were reported in 35 (30%) of 116 patients overall, including 7 (19%) patients who had received odevixibat in Study A4250-005, 5 (26%) patients who had received placebo, and 23 (38%) patients in Cohort 2; as of the data cutoff date, only

2 of the SAEs (both diarrhoea) were considered by the investigator as related to study drug. The majority of patients with TEAEs were able to remain on study treatment. Discontinuation of odevixibat due to TEAEs was reported in 10 (9%) of the 116 patients, including 3 (16%) patients who received placebo in Study A4250-005 and 7 (12%) patients in Cohort 2. The most common TEAEs leading to treatment discontinuation were blood bilirubin increased (3 patients, 3%) and exacerbation of PFIC/disease progression and diarrhoea (2 patients each, 2%).

The most commonly reported TEAEs in this study (≥ 20%) were pyrexia (35 patients, 30%), upper respiratory tract infection (29 patients, 25%), blood bilirubin increased, and diarrhoea (28 patients each, 24%), cough (27 patients, 23%), and Coronavirus Disease 2019 (COVID-19) (22 patients, 19%). Overall, 45 (39%) of the 116 patients experienced TEAEs assessed as drug related by the investigator, including 17 (46%) and 8 (42%) patients who had received odevixibat and placebo in Study A4250-005, respectively, and 20 (33%) patients in Cohort 2. The most common drug-related TEAEs (≥ 5%) were diarrhoea (14 patients, 12%), blood bilirubin increased (12 patients, 10%), and ALT increased (7 patients, 6%).

Most TEAEs were mild to moderate in intensity. Events of severe intensity were reported in 20 (17%) patients, including 3 (8%) patients and 2 (11%) patients who received odevixibat and placebo in Study A4250-005, respectively, and 15 (25%) patients in Cohort 2.

Seven (6%) patients met the criteria for clinically significant diarrhoea, i.e. diarrhoea with duration ≥ 21 days without other aetiology; diarrhoea of severe intensity or reported as an SAE; or diarrhoea with concurrent dehydration requiring treatment with rehydration and/or other treatment intervention. Two of the 7 patients had received odevixibat in Study A4250-005 and 5 were in Cohort 2. Most were mild to moderate in intensity and nonserious; 1 patient discontinued treatment due to clinically significant diarrhoea. Only 1 of the patients required oral rehydration.

Four (3%) of the 116 patients, all in Cohort 2, experienced new or worsening fat-soluble vitamin deficiency refractory to clinically recommended vitamin supplementation. Three of the 4 patients had refractory vitamin D deficiency with 2 of these patients also having refractory vitamin E deficiency and 1 patient had refractory vitamin K deficiency (elevation in INR). The events in all 4 patients were mild in intensity and did not lead to treatment discontinuation. Potential sequalae of vitamin deficiency were investigated based on a broad search of TEAEs. The most commonly reported TEAEs in this category (≥ 5%) were INR increased (19 patients, 16%) and epistaxis (10 patients, 9%). Note that only 2 of the 19 patients with INR increased had concurrent bleeding events, including mild ear haemorrhage in 1 patient and mild epistaxis in 1 patient.

Overall, data from 63 (54%) of the 116 patients underwent review and adjudication by the DSMB during the study, including 26 (70%) and 12 (63%) patients who received odevixibat and placebo, respectively, in Study A4250-005 and 25 (42%) patients in Cohort 2. The majority of cases underwent review based on elevated hepatic biochemical parameters for possible DILI. None of the cases adjudicated were for possible liver decompensation events. Only 1 case, in a patient who had received placebo in Study A4250-005 who underwent adjudication for increased ALT and total bilirubin during Study A4250-008, was considered possibly related to odevixibat by the DSMB.

Review of haematology, coagulation, clinical chemistry, vital signs, and urinalysis data did not reveal any clinically meaningful changes from baseline.

7.3. Discussion

Long-term treatment with odevixibat in patients with PFIC, including those with some of the rare PFIC subtypes, led to reductions in serum bile acid levels and pruritus for 96 weeks or longer. In patients

naïve to odevixibat on entry into Study A4250-008, reductions in serum bile acid levels and pruritus symptoms occurred rapidly and were sustained during continued treatment. Results for secondary and exploratory endpoints were consistent with the reductions in serum bile acids and pruritus, showing continued improvement in growth parameters, improvements in sleep, and QoL measures. Patients who were treatment-naive were more likely than patients who had received odevixibat in Study A4250-005 to have undergone biliary diversion surgery or liver transplant during the study. The estimated surgery-free survival and native liver-survival rates at 4 years from the first dose of odevixibat were ≥ 76% and ≥ 77%, respectively, across the study groups.

Odevixibat was well tolerated for 96 weeks or longer, with most TEAEs being mild to moderate in severity and not dose limiting.

The benefit-risk balance of Bylvay, remains positive.

Some changes/additions to the SmPC are considered necessary (see SmPC assessment).

8. Risk management plan

The MAH submitted an updated RMP version with this application. The main proposed RMP changes were the following:

- Part I: Product Overview

Product overview updated to include ALGS under current indications, dosage, and approved procedure. Medicinal product to which this RMP refers is updated to 2.

- Part II: Module SIII: Clinical trial exposure

Updated clinical trial exposure data from Study A4250-008.

- Part II: Module SIV Populations not studied in clinical trials

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

- Part II: Module SV Post-authorisation experience

Post-authorisation exposure was updated on the basis of most recent PSUR data (DLP: 15 July 2024).

- Part II: Module SVII Identified and potential risks

Updated new data for important identified, potential risk and missing information from pooled phase III PFIC study and Study A4250-008.
Characterisation of important identified and potential risks has been updated based on new data received from Study A4250-008.

- Part III Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

Additional pharmacovigilance activities were updated to remove Study A4250-008.

- Part V Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Routine risk minimisation activities recommending specific clinical measures to address the risk interactions with fat-soluble drugs was updated to include SmPC sections 4.4 and 4.5.

Study A4250-008 was removed from additional pharmacovigilance activities.

- Part VI: Summary of the Risk Management Plan

The data from Study A4250-008 has been updated for the important identified risk: clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance.

Study A4250-008 was removed from additional pharmacovigilance activities and other studies in post-authorisation development plan.

- Part VII: Annexes

Annex 2 and Annex 3: Study A4250-008 was updated as completed.

The rationale for submitting RMP ver.6.1 is the completion of study A4250-008: An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of A4250 in Children with Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC 2). This study is category 3 study in the RMP. Based on the clinical study report for the completed 72 weeks of this study, the RMP was updated. Generally, the proposed changes are acceptable. However, some improvement is needed. The MAH removed sentence *"In the PFIC phase III clinical trials, no patients had hepatic events reported in the SMQ Drug Related Hepatic Disorders – Severe Events Only."* from two tables regarding the important potential risk - hepatotoxicity, i.e. Table 21. of Part II Module SVII.3.1 and Table of Part VI section II.B. This is accepted, however MAH is requested to propose an appropriate wording express the current evidence from the PFIC pooled phase III clinical studies. The MAH has submitted RMP ver. 6.3 in the frame of the RSI.

8.1. Overall conclusion on the RMP

☒ The changes to RMP ver. 6.3 is acceptable.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

9. Changes to the Product Information

As a result of this group of variations, sections 4.2, 4.4, 4.8, and 5.1 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Please refer to the SmPC assessment in a separate report for further assessment. The PI is agreed upon.

10. Request for supplementary information

10.1. Major objections

None

10.2. Other concerns

- The applicant is requested to provide the ethics committee approval letter(s) and also all appendices.

- The applicant is requested to provide the bioanalytical method, validation and GLP statement.
- The applicant is requested to comment on this statement and discuss the influence of food intake on the PK and PD parameters.
- The applicant is requested to provide the bioanalytical methods (both PK and PD analyses), validation (including stability of A4250 in whole blood and plasma), LLOQ and GLP statement.
- The applicant is requested to provide information on the PK and PD blood sampling collection, handling and shipment.
- The applicant is requested to provide information regarding missing samples or reanalysis of samples (PK and PD samples).
- The applicant is requested to provide individual A4250 concentrations and A4250 PK parameters.
- The applicant is requested to mention this concern in the discussion and take this into consideration in the conclusion.
- The applicant is requested to check and correct all tables for missing units and errors.
- The applicant is requested to provide individual PD concentrations and PD parameters.
- The applicant is requested to be more specific about the pivotal PD parameter per biomarker and how they were assessed.
- The applicant is requested to also compare the magnitude of the difference between the groups (A4250 versus placebo), as these seem to differ between the two studies (A4250-J001 shows a larger effect compared to A4250-001 on the same dose?).
- The applicant is requested to explain the information in Table 14.3.2-2.
- The applicant is requested to adapt the PD results of A4250-J001 in the clinical overview to be in line with the results of the trial.

See separate report for the SmPC assessment.

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

11.1. Major objections

Clinical aspects

Question X

Summary of the MAH's response

Assessment of the MAH's response

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

Question X

Summary of the MAH's response

Assessment of the MAH's response

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

11.2. Other concerns

Clinical aspects

Question 1

The applicant is requested to provide the ethics committee approval letter(s) and also all appendices.

Summary of the MAH's response

Ethics Committee approval letter for study A4250-J001 dated 29 July 2022 has been provided (Japanese and English versions).

In addition to the appendices provided at the end of A4250-J001 clinical study report, other appendices to A4250-J001 clinical study report are provided in Module 5.3.4.1 Study A4250-J001.

Assessment of the MAH's response

The applicant provided the ethics committee approval letter, which is dated prior to the start of the study. The first subject was screened 1 Feb 2024, which is more than 1 year after the approval date. The ethics committee approval letter did not contain an 'expiry date'.

Conclusion

This question was answered sufficiently.

Question 2

The applicant is requested to provide the bioanalytical method, validation and GLP statement (odevixibat, total bile acids, C4, and FGF19)

Summary of the MAH's response

The applicant refers to question 4.

Assessment of the Applicant's response

See question 4.

Question 3

The applicant is requested to comment on this statement (food was supposed to be given 4 hours post-dose per protocol and ICH, but CSR states that it was given 15 minutes post-dose) and discuss the influence of food intake on the PK and PD parameters.

Summary of the MAH's response

The applicant summarised results from several studies. In summary, the mass balance study demonstrated no absorption of odevixibat at doses of 3 mg; the food effect study also confirmed that, following administration of 9.6 mg odevixibat, plasma concentrations and systemic exposure were very low, regardless of co-administration with food, supporting minimal systemic absorption from the GI tract.

In conclusion, as absorption of odevixibat from the GI tract is minimal, and as there is a lack of correlation between systemic exposure and the effect of odevixibat on PD parameters, the lack of fasting conditions post-administration of odevixibat in study A4250-J001 is expected to have minimal impact on the pharmacokinetic profile and the pharmacodynamic effect.

Assessment of the MAH's response

The applicant agrees with the statement that the study A4250-J001 was not done under strict fasting conditions. However, the influence of food intake 15 minutes after dosing is expected to be minimal on both PK and PD.

Conclusion

This question was answered sufficiently.

Question 4

The applicant is requested to provide the bioanalytical methods (both PK and PD analyses), validation (including stability of A4250 in whole blood and plasma), LLOQ and GLP statement.

Summary of the MAH's response

The MAH confirms the following documents and source files have now been provided and are summarised in the table below.

Table 4

Analyte	Bioanalytical Method and LLOQ	Validation Report	GLP statement
Odevixibat	Liquid-liquid extraction followed by LC-MS/MS analysis. LLOQ: 0.05 ng/mL	- Validation report: QBR111522QB02 - Amendment No.1 to validation report: QBR111522QB02 - Long-term stability report: LGC333347QB40 - Partial validation report: LGC278335QB01 - Partial validation report: LGC308183QB21	A signed compliance statement was included in each report. The studies were conducted in accordance with the appropriate Standard Operating Procedures and in compliance with: The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No. 1031) and subsequent amendments & the principles of ICH Harmonised Tripartite Guidelines for GCP (May 1996). Additionally, the studies were conducted in laboratories that operate in compliance with: - The UK Good Laboratory Practice Regulations 1999 (Statutory Instrument No 3106) and subsequent amendments. - OECD Principles of Good Laboratory Practice (Paris 1998). - EC Commission Directive 2004/10/EC of February 2004.

Analyte	Bioanalytical Method and LLOQ	Validation Report	GLP statement
Total Bile Acids	Enzymatic and colorimetric LLOQ: 1.19 µmol/L	LGC320795QB10 Report fully signed version (v1.0) And for long term stability LGC320795QB10 Report fully signed version (v1.0)	The reports were conducted with the appropriate SOPs and in compliance with: -The Medicines for Human use Regulation 2004 -ICH Guidelines for Good Clinical Practise E6 (R2) -The UK Good Laboratory Practice Regulations 1999 -OECD Principles of Good Laboratory Practice (Paris 1998) -EC Commission Directive 2004/10/EC of February 2004
C4	LC-MS/MS LLOQ: 2.00 ng/mL	LGC322296QB10 final Analytical Project Report (v1.0)	
FGF19	ELISA LLOQ: 19.4 pg/mL.	-LGC320795QB11 FGF-19 -For stability report name is 116156QB04 FGF-19 Qualification data summary - For long term stability report name is LGC267155QB02 Processed Data_FGF-19 Long term stability	

Assessment of the MAH's response

PK blood samples were collected in lithium heparine tubes (for analysis of plasma A4250 and C4 levels). Centrifuged at room temperature within 60 minutes after blood collection, plasma was stored in amber vials within 60 minutes after collection at -20°C ±5°C C for A4250 until shipment and the C4 samples were stored at -70°C or below until shipment. Maximum time stored before analysis was less than 12 months.

For FGF-19 and bile acids K2EDTA samples were collected, centrifuged at room temperature, plasma was stored at -70°C or below within 60 minutes after collection.

A4250

Bioanalysis of A4250 was developed and performed by XXXXXXXXRedacted**.** A4250 in lithium heparine plasma was analysed by using LC-MS/MS. Samples were extracted using protein precipitation (changed to liquid-liquid extraction), with AZ 11639816-002 as internal standard.

The bioanalysis method was initially validated 25-Feb-2014, with one amendment dated 06-Sep-2017 correcting a typo in the conclusion. Partial validation to assess long term stability of A4250 in human plasma after 6 months and 12 months at -20°C and at least 14 days at -80°C, the calibration range was 0.05 ng/mL to 5.00 ng/mL (excluding calibration standard 50.0 ng/mL) and QClow, med and high (0.150 ng/mL, 1.5 ng/mL and 3.75 ng/mL).

The method was validated over a concentration range of 0.05 to 50.0 ng/mL for A4250.

Normal plasma, lipemic plasma, haemolysed plasma and whole blood were used for validation. The method was validated for selectivity, precision, accuracy, carry-over, matrix effect and dilution integrity (dilution factor 10). Carry-over was potentially problematic; it is recommended that control blank samples follow a samples profile to assess carryover. It was strongly recommended that conditioning

samples be run before every analytical run; especially during periods of sample analysis as this will help to stabilise the LC-MS/MS response and will increase the overall success rate.

Table 5 Validation information of A4250

Calibration range (ng/mL)	0.05 – 50.0 (9 calibration standards) A new calibration range (0.0500 - 5.00 ng/mL) was partially validated under analytical project LGC308183QB21.
Lower Limit of Quantification (ng/mL)	0.05
QC concentration (ng/mL)	0.05 (QCS LLOQ); 0.150 (QCS low); 3.00 (QCS med); 40.0 (QCS high) Adapted QCs: 0.05 (QCS LLOQ); 0.150 (QCS low); 1.15 (QCS med); 3.75 (QCS high)
Between – run accuracy	± 3.3% and ± 0.2% at LLOQ
Between – run precision	<11.9% and ≤ 15.4 at the LLOQ
Within – run accuracy	± 12.0% and ±15.0% at LLOQ
Within – run precision	≤ 11.0% and ≤11.5% at LLOQ

Short term stability in whole lithium heparine blood was confirmed up to 4 hours at room temperature. Short term stability in the biological matrix (lithium heparine plasma) was confirmed up to 24 hours at room temperature, both protected from light and normal laboratory lighting conditions. Freeze and thaw stability was confirmed up to 4 cycles at -20°C (protected from light). Long term stability in plasma was confirmed up to 12 months at -20°C and 14 days at -80°C.

C4

Bioanalysis of C4 was developed and perforemd by XXXXXXXXRedacted. C4 in lithium heparine plasma was analysed by using LC-MS/MS. Samples were extracted using protein precipitation, C4-d7 (7α-hydroxy-4-cholensten-3-one-d7) as internal standard.

The bioanalysis method was initially validated 08-Dec-2021.

Normal plasma, lipemic plasma, haemolysed plasma and whole blood were used for validation. The method was validated for selectivity, precision, accuracy, carry-over, matrix effect and dilution integrity (dilution factor 10).

Short term stability in whole lithium heparine blood was confirmed up to 1 hour and 50 minutes at room temperature. Short term stability in the biological matrix (lithium heparine plasma) was confirmed up to 26 hours and 50 minutes at room temperature. Freeze and thaw stability was confirmed up to 4 cycles at -20°C and -80°C. Long term stability in plasma was confirmed up to 123 days at -20°C and 103 days at -80°C.

Table 6 Validation information of C4

Calibration range (ng/mL)	2.00 – 500 (9 calibration standards)
Lower Limit of Quantification (ng/mL)	2.00
QC concentration (ng/mL)	2.00 (QC LLOQ); 4.9 (QC low); 29.4 (QC med); 388 (QC high)
Between – run accuracy	± 0.5 to ±2.3%
Between – run precision	2.3% to 6.3%
Within – run accuracy	± 4.9% and ± 6.0%
Within – run precision	≤ 2.2% and ≤ 6.3%

Total bile acids

Bioanalysis of total bile acids was evaluated and performed by XXXXXXXXRedacted. Total bile acids in K2EDTA plasma were analysed by using enzymatic colorimteroic assay kits (obtained from Randox Laboratories Ltd., 55 Diamond Road, Crumlin, Co. Antrim, United Kingdom).

The bioanalysis method was initially validated 10-Aug-2020.

The bioanalytical method has been qualified for the determination of total bile acids. The precision and accuracy of the method was found to be within the acceptable limits. The analytical range of the assay is defined as 1.19 – 38.9 µmol/L.

Parallelism for total bile acids was demonstrated up to 2-fold. Up to 24 hours stability at room temperature was confirmed, alongside 4 freeze-thaw cycle stability and 40 day long term stability. Storage temperature of plasma is -80°C.

The method is considered suitable for the exploratory and secondary determination of total bile acids in human plasma samples, although further test article assessments with the dosed drug may be required.

FGF-19

Bioanalysis of FGF-19 was evaluated and performed by XXXXXXXXRedacted. FGF-19 in K2EDTA plasma was analysed by using FGF-19 Quantikine ELISA kit (obtained from R&D Systems, 19 Barton Lane, Abingdon Science Park, Abingdon, United Kingdom).

The bioanalysis method was initially validated 30-Jul-2020.

The bioanalytical method has been re-qualified for the determination of FGF-19 in human plasma.

The precision and accuracy of the method was found to be within the acceptable limits. The analytical range of the assay is defined as 15.6 - 1000 pg/ml.

Parallelism was demonstrated up to 7-fold.

Up to 24 hours stability at room temperature was confirmed, alongside 4 freeze-thaw cycle stability and 195 day long term stability. Storage temperature of plasma is -80°C.

The method is considered suitable for the exploratory determination of FGF-19 in human plasma samples, although further test article assessments with the dosed drug may be required.

Within-study validation and analysis

A4250 Analytical project number LGC358370QB21, report dated 30-Aug-2023

Table 7 Information on analytical assay of A4250 (study A4250-J001)

Calibration range (ng/mL)	0.05 to 5.0
Lower Limit of Quantification (ng/mL)	0.05
QC concentration (ng/mL), 2 samples per level per run	0.150 (LQC); 1.50 (MQC); 3.75 (HQC)

The mean intra-assay precision and accuracy of the low, medium and high QC samples indicated that the method performed reliably during the analysis of clinical study samples.

The bioanalytical study took place from 26-Oct-2022 to 03-Nov-2022. The samples were stored at -20°C for a maximum of 43 days between the date of collection and the date of sample extraction.

A total of 198 were received and stored at -20°C. Samples were analysed in 7 batches, 3 batches (2 batches including the same samples) were rejected due to interference. Therefore, one batch of samples were thawed three times, which is acceptable. All samples were analysed blinded, all samples for one subject were analysed in the same run.

ISR was not performed under this analytical project as less than 20 samples had concentrations above QC Low.

No plasma samples were re-assayed.

On day 1 five out of 6 subjects (treated with A4250) had A4250 levels >LLOQ and on day 7 all six subjects had A4250 levels >LLOQ. All samples that were detectable showed concentrations A4250 <0.1 ng/mL.

Chromatograms of two subjects used in the PK analysis, including plasma blank, QC samples and calibration standards were submitted with the report.

C4 Analytical project number LGC358370QB20, report dated 30-Aug-2023

Table 8 Information on analytical assay of C4 (study A4250-J001)

Calibration range (ng/mL)	2.00 to 500
Lower Limit of Quantification (ng/mL)	2.00
QC concentration (ng/mL), 2 samples per level per run	4.78 (LQC); 28.7 (MQC); 387 (HQC)

The mean intra-assay precision and accuracy of the low, medium and high QC samples indicated that the method performed reliably during the analysis of clinical study samples.

The bioanalytical study took place from 01-Nov-2022 to 08-Nov-2022. The samples were stored at -80°C for a maximum of 44 days between the date of collection and the date of sample extraction, which is within the validated sample storage period of 103 days at -80°C.

A total of 270 human plasma samples (duplo) were received and stored at -80°C. In total 135 samples were analysed in 5 batches, 1 batch was rejected due to interference. 1 additional batch was included for ISR analysis.

Of the 22 samples selected for incurred sample reanalysis, 21 samples (95.5%) were within 20% of their mean value and ISR acceptance criteria were met.

Two plasma samples were re-assayed due to analytical errors.

Chromatograms of two subjects used in the PK analysis, including plasma blank, QC samples and calibration standards were submitted with the report.

FGF-19 Analytical project number LGC358373QB20, report dated 28-Jun-2024

Table 9 Information on analytical assay of FGF-19 (study A4250-J001)

Calibration range (pg/mL)	19.4 to 982 (original 15.6 to 1000)
Lower Limit of Quantification (pg/mL)	19.4
QC concentration (pg/mL), 3 samples per level per run	63.3 (LQC); 267 (MQC); 760 (HQC)

The mean intra-assay precision and accuracy of the low, medium and high QC samples indicated that the method performed reliably during the analysis of clinical study samples.

The bioanalytical study took place from 26-Oct-2022 to 03-Nov-2022. The samples were stored at -80°C for a maximum of 43 days between the date of collection and the date of sample extraction, which is within the validated sample storage period of 195 days at -80°C.

A total of 270 human plasma samples (duplo) were received and stored at -80°C. In total 135 samples were analysed in 6 runs, 1 run was rejected due to QC failure.

Three plasma samples were re-assayed due to one of the two replicates outside calibration range (n=2) or analyte concentration outside calibration range (n=1).

Bile acid Analytical project number LGC358379QB20, report dated 01-Jul-2024

Table 10 Information on analytical assay of bile acid (study A4250-J001)

Calibration range (µg/mL)	1.19 to 38.9 (original 0 to 44.5)
Lower Limit of Quantification (µg/mL)	1.19
QC concentration (µg/mL), 3 samples per level per run	4.21 (LQC); 17.7 (MQC); 25.5 (HQC)

The mean intra-assay precision and accuracy of the low, medium and high QC samples indicated that the method performed reliably during the analysis of clinical study samples.

The bioanalytical study took place from 26-Oct-2022 to 02-Nov-2022. The samples were stored at -80°C for a maximum of 42 days between the date of collection and the date of sample extraction, which is within the validated sample storage period of 362 days at -80°C.

A total of 270 human plasma samples (duplo) were received and stored at -80°C. In total 135 samples were analysed in 4 runs (all accepted).

No samples were repeated within this project.

Conclusion

This question was answered sufficiently, bioanalytical validation of the methods was sufficient as well as the study reports. Reanalysis of samples rarely occurred, and the reasons were valid.

Question 5

The applicant is requested to provide information on the PK and PD blood sampling collection, handling and shipment.

Summary of the MAH's response

The MAH confirms the PK and PD blood sampling collection, handling and shipment conditions for study A4250-J001 described in the laboratory manual for the study and stated below were in line with the validated conditions for A4250, C4, FGF19 and bile acids.

Blood collection and handling for C4 and A4250:

4 mL of blood were collected in lithium heparin tube. Within 60 minutes after collection, blood was mixed and centrifuged at 1700 g for 10 minutes at room temperature. Then 0.4 mL of plasma were transferred into 4 amber vials and stored at -20°C (±5℃) for A4250 or -70°C or below for C4 until shipment.

Blood collection and handling for FGF-19 and Bile acids:

6 mL of blood were collected in K2EDTA tube. Within 60 minutes after collection, blood was mixed and centrifuged at 1700 g for 10 minutes. Then 0.5 mL of plasma for FGF-19 or 0.6 mL for bile acids were transferred into 4 polypropylene vials and stored at -70°C or below until shipment.

Primary and Backup vials were shipped separately to Drug Development Solutions in dry ice for A4250, C4, FGF-19 and bile acids vial. A temperature logger was included in each shipment.

Assessment of the MAH's response

Sample handling has been described by the applicant and the laboratory manual was submitted and reviewed. The sample handling was done in line with the validated conditions for all compounds analysed.

Conclusion

This question was answered sufficiently.

Question 6

The applicant is requested to provide information regarding missing samples or reanalysis of samples (PK and PD samples).

Summary of the MAH's response

The MAH has summarised the information (regarding missing samples or reanalysis of either PK or PD samples) which was described in each dedicated analytical project reports for each analyte in the

Table 11

Analyte	Missing samples	Reanalysis of Samples	Source data
Odevixibat	No missing samples. 198 samples were received as planned in the clinical protocol (9 subjects, 22 timepoints/subject) and 198 samples were analysed for A4250 concentration determination.	No sample analysis was repeated.	Source: a4250-j001-csr-appendices_LGC358370QB21 Final Analytical Project Report (v1.0); section 9.1 and section 9.2.
Bile Acids	No missing samples	No sample reanalysis	Paragraph 12.3 and Table 6 of report a4250-j001-csr-appendices_LGC358379QB20 Final Report
C4	No missing samples	2 samples because of analytical error	Paragraph 9.2 and Table 10 and 11 of report LGC358370QB20 Final Analytical Report
FGF-19	No missing samples	3 samples because at least one of replicate outside of calibration range	Paragraph 12.4 and Table 7 and 8 of report a4250-j001-csr-appendices_LGC358373QB20 Final Report

Assessment of the MAH's response

The applicant has provided the requested information. No samples were missing and only a few samples were re-analysed with valid reasons.

Conclusion

This question was answered sufficiently.

Question 7

The applicant is requested to provide individual A4250 concentrations and A4250 PK parameters.

Summary of the MAH's response

The MAH confirms that the information requested has now been provided and can be found in the following locations:

• Individual A4250 concentrations are available in Table 16.2.6-1 of the A4250-J001 Clinical Study Report and in Table 9 of the a4250-j001-csrappendices_LGC358370QB21 Final Analytical Project Report (v1.0).

• Individual A4250 PK parameters are available in Table 16.2.6-2 of the A4250-J001 Clinical Study Report.

Assessment of the MAH's response

The provided data were reviewed. All pre-dose samples were below LLOQ, and most samples overall were below LLOQ. PK parameters Tmax of 0h and Cmax of 0 ng/mL were reported for one subject without concentrations >LLOQ on day 1, it concerns J001-020 Day 1. This is not correct; these concentrations should have been set to missing. These concentrations were also included in the summary statistics, which is also incorrect (and did lead to minimum Tmax of 0h and minimum Cmax of 0 ng/mL in Table 11.4-2 in the CSR).

Conclusion

This question was answered sufficiently; however, it did raise another concern. Despite the errors, this will not change the conclusion of the study, and it is therefore acceptable not to correct the errors in this stage.

Question 8

(The comparison with the pharmacokinetic results of study A4250-001 is not reliable, as a different LLOQ was used (although not certain, as the LLOQ of the A4250-J001 study was not reported). The applicant is requested to mention this concern in the discussion and take this into consideration in the conclusion.

Summary of the MAH's response

The MAH can confirm that the bioanalytical method for study A4250-J001 (analytical report No. LGC358370QB21) had the same conditions as study A4250-001 (analytical report No. QBR111522QB03), regarding extraction method, LC-MS/MS settings and the Lower Limit of Quantification (LLOQ) of 0.05 ng/mL. All clinical samples from both studies were analysed using validated conditions, which enables the reliable comparison of results between A4250-J001 and A4250-001.

Assessment of the MAH's response

The LLOQ has now been shared and is 0.05 ng/mL, the reason for the assumption that the LLOQ was not identical for both trials, was the fact that for A4250-J001 the ½ LLOQ level was used for descriptive statistics, see also question 9. This approach is acceptable but was not according to the predefined statistical analysis plan.

Conclusion

This question was answered sufficiently.

Question 9

(Table 11.4.1 shows geometric means, but the results cannot be correct, as they are 0.03 ng/mL for the timepoints with no measurable concentrations.) The applicant is requested to check and correct all tables for missing units and errors.

Summary of the MAH's response

The MAH can confirm that the calculations of geometric means in Table 11.4.1 of the A4250-J001 CSR are correct. As done in the comparator study A4250-001, values below the limit of quantification (BLQ) were set to the midpoint between the lower limit of quantification (LLOQ) and zero. Hence, the geometric means for timepoints with no measurable concentrations were calculated by dividing the LLOQ of 0.05 ng/mL by 2 (0.025 ng/mL) and rounded to 2 decimal points (0.03 ng/mL).

The MAH also acknowledges that the approach to the calculation of the geometric means is not reflected in the Statistical Analysis Plan (SAP) of Study A4250-J001, which stated that any PK or PD values BLQ after the start of administration of odevixibat would be handled as missing. Whilst the approach of

handling BLQ values used for the geometric means on Table 11.4-1 is not reflected in the SAP, the applicant believes that overall, the approach is acceptable since it makes the geometric means from Study A4250-J001 directly comparable with Study A4250-001. Given that absorption of odevixibat from the GI tract is minimal, resulting in very low systemic concentrations at all timepoints measured, the sponsor considers that the impact of the calculation method used for geometric means of odevixibat on the conclusions of the study to be negligible.

Assessment of the MAH's response

The applicant explained that values below LLOQ were set to ½ LLOQ, which is a valid method. This was done only for the calculation of the geometric means. As already indicated by the applicant: not according to the SAP. As the impact of this approach is minimal this is acceptable.

Conclusion

This question was answered sufficiently.

Question 10

The applicant is requested to provide individual PD concentrations and PD parameters.

Summary of the MAH's response

The MAH can confirm that the individual concentrations and parameters can be found in the following locations:

- Individual values for PD parameters can be seen in Table 16.2.6-3/4, page 622 of the CSR.
- Bile Acids individual concentrations are in Table 6 of report a4250-j001-csrappendices_LGC358379QB20 Final Report (v1.0)
- C4 individual concentrations are in Table 10 of report a4250-j001-csrappendices_LGC358370QB20 Final Analytical Report (v1.0)
- FGF-19 individual concentrations are in Table 7 of report a4250-j001-csrappendices_LGC358373QB20 Final Report (v1.0)

Assessment of the MAH's response

The applicant provided the individual PD concentrations and AUC0-12h on day 7. These data are reflected in the summary table 14.2-2 of the CSR, and also the conclusion regarding pharmacodynamics.

Conclusion

This question was answered sufficiently.

Question 11

The applicant is requested to be more specific about the pivotal PD parameter per biomarker and how they were assessed.

Summary of the MAH's response

The applicant can confirm that the pivotal PD parameters in study A4250-J001 were the same for all 3 biomarkers (FGF-19, C4 and Total bile acids).

• Table 11.4.3: for both groups A4250 and placebo, the adjusted arithmetic means for change from baseline were calculated at Day 1 for 4h and 24 h after IMP administration, and at Day 7 for pre-dose and 4 and 24 h after IMP administration. The difference (A4250-Placebo) was calculated at each

timepoint. Significant difference (P values) between treated groups was observed only for C4 24 h after the first administration and for the 3 time points at day 7.

- Table 14.2.3: the Adjusted arithmetic means were compared in the A4250 group between Day 7 and Day 1. A significant difference was observed only for C4 showing highest increase 4 h after IMP at Day 7 compared to Day 1.
- Section 11.4.2: time course with AUC calculation for the 3 biomarkers showed the same conclusions with a statistically significance inter-group difference in change only for C4 at 24 h post dose on Day 1 and at pre-dose, 4 h and 24 h post-dose on Day 7.

Assessment of the MAH's response

The applicant provided the statistical analysis plan with the detailed description of the planned analysis for both PK and PD parameters. For PD parameters, next to descriptive statistics and charts ANOVA analysis was to be performed for group comparisons of changes in plasma concentration from pre-administration on Day 1 for the PD evaluation items at each analysis point. Also, within-group comparisons of changes in plasma concentration from pre-administration on Day 1 for the PD evaluation items before and after repeated administration. The measurement days are Day 1 and Day 7, and the analysis is conducted at 4 hours and 24 hours.

Overall Summary and Conclusion

This question was answered sufficiently.

Question 12

The applicant is requested to also compare the magnitude of the difference between the groups (A4250 versus placebo), as these seem to differ between the two studies (A4250-J001 shows a larger effect compared to A4250-001 on the same dose?).

Summary of the MAH's response

The applicant has compared the difference of change between A4250 and placebo between studies A4250-001 and A4250-J001 where a dose level of 3 mg of A4250 was used in both studies.

Table 12 presents the magnitude of difference of change between groups (Difference of mean change (A4250 – Placebo) for FGF-19 and C4 for studies A4250-001 and A4250-J001

Table 1. Magnitude of difference of change between groups (Difference of mean change (A4250 – Placebo) for FGF-19 and C4 for studies A4250-001 and A4250-J001

	Study A4250-001			Study A4250-J001		
Mean change at Day1		**4h**	**24h**		**4h**	**24h**
FGF-19 Difference of mean change (pg/mL) with Placebo		-121.92	-79.35		-208.33	-241.76
C4 Difference of mean change (ng/mL) with Placebo		2.58	72.99		14.91	75.49
Mean change at Day7	**Pre dose**	**4h**	**24h**	**Pre dose**	**4h**	**24h**
FGF-19 Difference of mean change (pg/mL) with Placebo	-118.68	-154.47	-124.97	-270.18	-219.26	-84.86
C4 Difference of mean change (ng/mL) with Placebo	86.3	89.04	94.28	120.21	110.19	108.2

Source data: table 11.4.3 for study A4250-J001 and the difference of mean change calculated from table 19 for study A4250-001

Table 13 below summarised total bile acid mean change between studies.

Table 2. Magnitude of difference of change between 4250 and Placebo for total bile acids for studies A4250-001 and A4250-J001

	Study A4250-001			Study A4250-J001		
Acid Mean change at Day1		**4h**	**24h**		**4h**	**24h**
Total Bile Difference of mean change (ng/mL) with Placebo		-1501.23	-757.72			
Total Bile Difference of mean change (µmol/L) with Placebo		-3.67	-1.85		-3.07	-2.71
Mean change at Day7	**Pre dose**	**4h**	**24h**	**Pre dose**	**4h**	**24h**
Total Bile Acid Difference of mean change (ng/mL) with Placebo	-620.73	-691.43	-1353.1			
Total Bile Acid Difference of mean change (µmol/L) with Placebo	-1.52	-1.69	-3.31	-2.25	-2.25	-1.91

Calculated from source data table 11.4.3 for study A4250-J001 and table 19 in study A4250-001 (converted from ng/mL to µmol/L)

As can be seen from the data presented in Table 10 and Table 11, the magnitude of difference between groups (A4250 – Placebo) for all 3 biomarkers (FGF-19, C4 and total bile acids) is comparable between both studies.

Assessment of the MAH's response

The applicant provided the overview of comparison of the PD parameters between the study A4250-001 and A4250-J001 and concludes that the magnitude of differences between the A4250 and placebo groups are similar for both studies.

For most parameters this is indeed the case, however, for FGF-19 the difference of mean change with placebo is 3 times larger for the A4250-J001 study at 24hours on Day 1 and less pronounced at 24h on day 7. This will not change the overall conclusion of this study and is therefore not further pursued.

Conclusion

This question was answered sufficiently.

Question 13

(No unexpected, nor serious adverse events occurred. However, Table 14.3.2-2 Serious Adverse Events Other than Death (SP) does contain all the adverse events that were reported.) The applicant is requested to explain the information in Table 14.3.2-2.

Summary of the MAH's response

The applicant confirms Table 14.3.2-2 has been completed by mistake and should have been empty. A signed erratum page will be provided in the closing sequence for this procedure.

Assessment of the MAH's response

The applicant confirms the mistake.

Conclusion

This question was answered sufficiently.

Question 14

The applicant is requested to adapt the PD results of A4250-J001 in the clinical overview to be in line with the results of the trial.

Summary of the MAH's response

The PD results of A4250-J001 are already included in Module 2.5 on page 27, and the provided information is accurate in respect to the study results and the responses provided in the present document.

Assessment of the MAH's response

The applicant is of the opinion that the data have been described sufficiently in module 2.5. And this is accepted.

Conclusion

This question was answered sufficiently.

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

Question 15

The MAH has removed sentences: "In the PFIC phase III clinical trials, no patients had hepatic events reported in the SMQ Drug Related Hepatic Disorders – Severe Events Only." from two tables regarding the important potential risk - hepatotoxicity, i.e. Table 21. of Part II Module SVII.3.1 and Table of Part VI section II.B. This is accepted; however, MAH is requested to propose an appropriate wording express the current evidence from the PFIC pooled phase III clinical studies.

Summary of the MAH's response

This is acknowledged. The MAH is providing an alternative wording which reflects the current evidence from the PFIC pooled Phase III data on important potential risk of hepatotoxicity based on the SMQ Drug Related Hepatic Disorders – comprehensive search (narrow and broad): "Overall, 52% of patients in the Pooled Phase 3 group had TEAEs in the SMQ of Drug related Hepatic Disorders – comprehensive search (narrow and broad). The most common TEAEs reported in this SMQ were blood bilirubin increased, INR increased, ALT increased, AST increased, hepatomegaly and jaundice. The majority of TEAEs were mild to moderate in intensity. Eight patients (0.66%) reported severe events from this SMQ, three of which serious and considered by the investigator to be unrelated to study drug. In PFIC clinical trials, Drug Safety Monitoring Board (DSMB) was conducting an independent, adjudication of hepatic events. Overall, 69 (57%) of the 121 patients in the Pooled Phase 3 groups had an event that underwent adjudication by the DSMB. Based on review of 69 cases by the DSMB, all but one case (increased ALT and total bilirubin) was adjudicated as unrelated to study treatment."

The same wording has been updated in Table 21. of Part II Module SVII.3.1 and Table of Part VI section II.B., in the attached EU RMP v6.3 (Bylvay EU-RMP v6.3_15 July 2024_PAR).

Additionally, the MAH has another ongoing procedure (procedure number EMEA-H-C-006462 sequence 0006) as part of the ALGS 72-week Phase III data and for the EU RMP v6.2. Considering Question 16.1 of the EMA post-authorisation procedural advice for users of the centralised procedure (updated 17 December 2024), the MAH is taking the opportunity of this submission to attach the colour coded combined "working document" of the EU RMP v6.1 (data consequential to PFIC procedure is marked in yellow) and EU RMP v6.2 (data consequential for ALGS procedure is marked in blue). In this "working

document" of the EU RMP, the above-mentioned wording included in EU RMP v6.3 has been reflected in both tables (green).

Assessment of the MAH's response

The MAH is providing an alternative wording which reflects the current evidence from the PFIC pooled Phase III data on important potential risk of hepatotoxicity based on the SMQ Drug Related Hepatic Disorders – comprehensive search (narrow and broad). Issue resolved.

Question X

Summary of the MAH's response

Assessment of the MAH's response

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