Report on the Deliberation Results

March 7, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Livmarli Oral Solution 10 mg/mL
Non-proprietary Name	Maralixibat Chloride (JAN*)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	June 27, 2024

Results of Deliberation

In its meeting held on March 6, 2025, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 10 years. The drug substance is classified as a poisonous drug. The drug product is not classified as a poisonous drug or a powerful drug.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

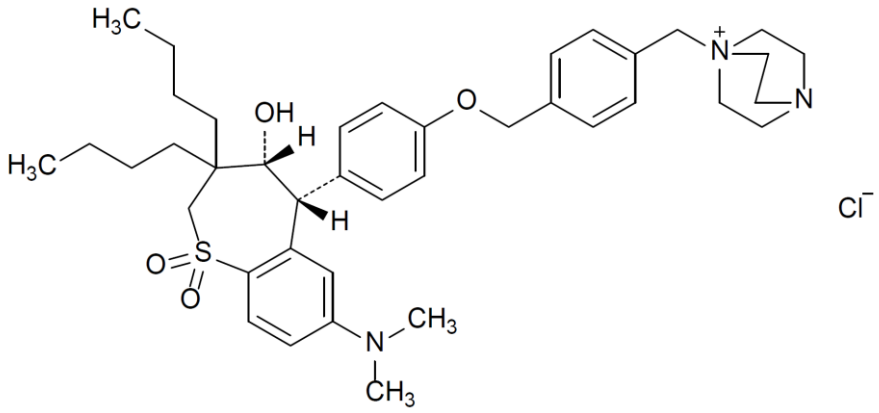
Review Report

February 25, 2025
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Livmarli Oral Solution 10 mg/mL
Non-proprietary Name	Maralixibat Chloride
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	June 27, 2024
Dosage Form/Strength	Oral solution containing 10 mg of maralixibat chloride (9.5 mg of maralixibat) per mL
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{40}H_{56}ClN_3O_4S$

Molecular weight: 710.41

Chemical name: 1-{[4-({4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxo-2,3,4,5-tetrahydro-1*H*-1λ^6-benzothiepin-5-yl]phenoxy}methyl)phenyl]methyl}-1,4-diazabicyclo[2.2.2]octan-1-ium chloride

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 550 of 2022 [*R4 yaku*] and No. 551 of 2022 [*R4 yaku*]; PSEHB/PED Notification No. 1216-1 dated December 16, 2022, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of cholestatic pruritus in patients with Alagille syndrome and progressive familial intrahepatic cholestasis, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following condition. The product is not classified as a biological product or a specified biological product. The drug substance is classified as a poisonous drug. The drug product is not classified as a poisonous drug or a powerful drug.

Indications

Cholestatic pruritus in patients with the following diseases:

○ Alagille syndrome

○ Progressive familial intrahepatic cholestasis

Dosage and Administration

Alagille syndrome

The usual dosage is 200 μg/kg of maralixibat chloride orally administered once daily before a meal. After 1 week of the treatment, the dose should be increased to 400 μg/kg administered once daily.

Progressive familial intrahepatic cholestasis

The usual dosage is 300 μg/kg of maralixibat chloride orally administered once daily before a meal. After 1 week of the treatment, the dose should be increased to 300 μg/kg administered twice daily. After another week of the treatment, the dose should be further increased to 600 μg/kg administered twice daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

January 24, 2025

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Livmarli Oral Solution 10 mg/mL
Non-proprietary Name	Maralixibat Chloride
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	June 27, 2024
Dosage Form/Strength	Oral solution containing 10 mg of maralixibat chloride (9.5 mg of maralixibat) per mL

Proposed Indications

○ Alagille syndrome

○ Progressive familial intrahepatic cholestasis (PFIC)

Proposed Dosage and Administration

Alagille syndrome

The usual initial dosage is 200 μg/kg of maralixibat chloride orally administered once daily. After 1 week of the treatment, the dose should be increased to 400 μg/kg administered once daily.

Progressive familial intrahepatic cholestasis (PFIC)

The usual initial dosage is 300 μg/kg of maralixibat chloride orally administered once daily. After 1 week of the treatment, the dose should be increased to 300 μg/kg administered twice daily. After another week of the treatment, the dose should be further increased to 600 μg/kg administered twice daily.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Alagille syndrome (ALGS) is intrahepatic cholestasis inherited in an autosomal dominant manner and caused by *JAGGED1* or *NOTCH2* mutations. ALGS manifests as cardiovascular malformations, vertebral anomalies, eye anomalies, and characteristic facies in addition to the cholestasis. Jaundice that starts in infancy is one of the major symptoms, and in approximately one third of the affected patients, jaundice progresses to hepatic cirrhosis because of severe cholestasis. Severe pruritus associated with chronic cholestasis can lead to sleep disorders and impaired quality of life (QOL) (*J Pediatr Gastroenterol Nutr.* 2018;67:148-56, *Japanese Journal of Pediatric Medicine.* 2011;43:1073-6). At present, no drugs indicated for the treatment of ALGS are approved in Japan. Currently used symptomatic drug therapies include oral ursodeoxycholic acid and bile acid adsorbent, supplementation with fat-soluble vitamins and essential fatty acids, and for pruritus, oral antihistamines and phenobarbital, but their effects are all limited (*Japanese Journal of Pediatric Medicine.* 2011;43:1073-6). Liver transplant is required for treatment of hepatic cirrhosis in patients with ALGS. According to published literature, however, 24% of patients reached adulthood without undergoing liver transplant (Japan Intractable Diseases Information Center, https://www.nanbyou.or.jp/entry/4845 [last accessed on January 24, 2025]), and the proportion of such patients ranged from approximately 24% to 41% overseas (*Liver Int.* 2020;40:1812-22, *J Hepatol.* 2020;73:S554-5). Although the 10-year survival rate after liver transplant in Japan is relatively as good as ≥80% (*J. New Rem. & Clin.* 2018;67:1572-6), liver transplant may be precluded due to accompanying cardiovascular malformation or other causes in some of the patients, posing challenges to address.

Progressive familial intrahepatic cholestasis (PFIC) is intrahepatic cholestasis inherited in an autosomal recessive manner and is classified into multiple subtypes according to the disease-causing gene mutation, which differ in symptoms and clinical courses. Most of reported cases in Japan are classified into either the PFIC1 type caused by mutations in the *ATP8B1* gene that encodes familial intrahepatic cholestasis 1 (FIC1) protein or the PFIC2 type caused by mutations in the *ABCB11* gene that encodes bile salt export pump (BSEP) protein. Both of the two PFIC subtypes develop in infancy, and the cholestasis causes severe pruritus accompanied by sleep disorders and impaired QOL, and finally progresses to liver failure. Although cases of subtypes other than the PFIC1 and PFIC2 types are highly limited in Japan, these subtypes also cause cholestasis as with the PFIC1 and PFIC2 types (*Japanese Journal of Pediatrics.* 2020;73:772-6). At present, no drugs indicated for the treatment of PFIC are approved in Japan. Currently usually used symptomatic drug therapies include ursodeoxycholic acid and bile acid adsorbent as well as, for pruritus, antihistamines and phenobarbital, but their effects are all limited. When the liver lesion is progressive, liver transplant is considered, but patients with PFIC1 are known to experience intractable diarrhea and pancreatitis even after liver transplant (*Japanese Journal of Pediatric Medicine.* 2011;43:1077-81). Patients with PFIC2 who underwent liver transplant have a generally favorable outcome, but post-transplant recurrence of cholestasis has been reported, posing challenges such as difficulty in reducing doses of immunosuppressive agents (*Japanese Journal of Pediatrics.* 2020;73:772-6).

Maralixibat chloride (hereinafter referred to as maralixibat), the active ingredient of Livmarli, is an inhibitor against the ileal bile acid transporter (IBAT), a transmembrane protein, discovered by G.D. Seale & Co. (the US). By inhibiting absorption of bile acids from the intestine, maralixibat reduces bile

acids in enterohepatic circulation, increases excretion of bile acids into feces, and consequently decreases serum bile acid (sBA) concentrations. Maralixibat is therefore expected to be used as a drug for the treatment of ALGS and PFIC.

The applicant has submitted an application for marketing approval of maralixibat based on results from clinical studies in patients with ALGS and patients with PFIC in and outside Japan, which demonstrate the efficacy and safety of maralixibat. Outside Japan, maralixibat has been approved for the indications of the treatment of ALGS and PFIC in 41 and 31 countries or regions, respectively, including the European countries and the US, as of November 2024.

Maralixibat was designated as an orphan drug with the intended indications of the treatment of "alagille syndrome" and "progressive familial intrahepatic cholestasis" on December 16, 2022 (Orphan Drug Designation No. 550 of 2022 [*R4 yaku*] and No. 551 of 2022 [*R4 yaku*]).

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance occurs as a white to light yellow solid. The determined general properties of the drug substance include description, thermogravimetric property, differential scanning calorimetric property, partition coefficient, dissociation constant (pKa), crystalline polymorphism, hygroscopicity, and solubility. The drug substance occurs in 2 crystal forms (Form I and Form II), but only Form [redacted] ([redacted]) is produced by the commercial manufacturing process. The drug substance has been demonstrated to be stable at room temperature.

The chemical structure of the drug substance has been elucidated by elemental analysis, infrared absorption spectroscopy (IR), ultraviolet-visible spectroscopy (UV-VIS), nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR), mass spectrometry, X-ray powder diffractometry, single crystal X-ray crystallography, and optical rotation determination. The drug substance has 2 asymmetric carbons in the benzothiepin ring of its chemical structure, and the asymmetric carbons are (*4R*, *5R*)-configurated.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted] and [redacted] as starting materials. [redacted] ([redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]) has been defined as a critical step. [redacted] and the crude drug substance are controlled as critical intermediates.

Based on the following investigations, the quality control strategy has been established (Table 1).

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) based on quality risk assessment and design of experiments method

Table 1. Outline of control strategy of drug substance

CQA	Control method
Content	[redacted]
Description	[redacted]
Identification	[redacted]
Crystal form	[redacted]
Related substances	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Residual solvents	[redacted]
Water content	[redacted]
Residue on ignition	[redacted]
[redacted]	[redacted]

2.1.3 Control of drug substance

The proposed specifications for the drug substance include the content, description, identification (chloride, IR, high performance liquid chromatography [HPLC] [retention time]), purity (related substances [HPLC], genotoxic impurities [gas chromatography (GC) or HPLC], and residual solvents [GC]), water content, residue on ignition, crystal forms (X-ray powder diffractometry), optical purity (HPLC), and assay (HPLC).

2.1.4 Stability of drug substance

Table 2 shows the main stability studies conducted with the drug substance. The results have shown that the drug substance is stable. Photostability testing has shown that the drug substance is unstable to light.

Table 2. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 pilot batches 2 commercial batches	25°C	60% RH	Double-layer bags made of linear low-density polyethylene and low-density polyethylene or double-layer bags made of low-density polyethylene + a container made of high-density polyethylene	36 months
Accelerated		40°C	75% RH		6 months

Based on the above, a retest period of 36 months has been proposed for the drug substance when stored in the double-layer bags made of linear low-density polyethylene and low-density polyethylene or double-layer bags made of low-density polyethylene, which is placed in a container made of high-density polyethylene to protect from light, at room temperature. Long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an oral solution containing 10 mg of maralixibat chloride (9.5 mg of maralixibat free base) per mL. The drug product contains the following excipients: propylene glycol, disodium edetate hydrate, sucralose, flavor, and purified water.

2.2.2 Manufacturing process

The drug product is manufactured through a process consisting of drug solution preparation, filling, stoppering, packaging/labeling/storage, and testing. [redacted] and [redacted] have been defined as critical

steps, and process control items and process control values are specified in the steps of [redacted], [redacted], and [redacted].

Based on the following investigations, the quality control strategy has been established (Table 3).

- Identification of CQAs
- Identification of CPPs based on quality risk assessment

Table 3. Outline of control strategy of drug product

CQA	Control method
Content	[redacted]
Description	[redacted]
Identification	[redacted]
Purity (degradation products)	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Extractable volume	[redacted]
Microbial limit	[redacted]

2.2.3 Control of drug product

The proposed specifications for the drug product include the content, description, identification (HPLC [retention time], UV-VIS), pH, purity (degradation products [HPLC]), propylene glycol content (HPLC), disodium edetate hydrate content (HPLC), extractable volume, microbial limit, and assay (HPLC).

2.2.4 Stability of drug product

Table 4 shows the main stability studies conducted with the drug product. Long-term testing showed trends toward increases with time in [redacted], multiple [redacted] and [redacted] as well as a trend toward [redacted] in [redacted] potentially attributable to [redacted]. In the 36-month study, [redacted] in 3 [redacted] batches exceeded the acceptance limit ([redacted]%) for the stability study. Accelerated testing showed a trend toward an increase with time in the amount of a degradation product (Impurity A) and a trend toward [redacted] in [redacted]. Photostability testing showed that the drug product filled in a transparent glass vial was unstable to light but the drug product filled in a brown polyethylene terephthalate bottle was stable to light.

Table 4. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	[redacted]a) 3 batches	25°C	60% RH	Brown polyethylene terephthalate bottle + low-density polyethylene bottle adaptor + cap with a low-density polyethylene liner	36 months
Accelerated	[redacted] 1 batch	40°C	75% RH		6 months

a) Manufactured through a process before a change of [redacted] for manufacture at [redacted].

Based on the above, a shelf life of 30 months has been proposed for the drug product when stored in a brown polyethylene terephthalate bottle stoppered with a low-density polyethylene bottle adaptor and a cap with a low-density polyethylene liner at room temperature. In-use stability study[1)] has shown that the drug product is stable for up to 130 days.

1) During storage of 1 commercial scale batch of the drug product at 30°C, 0.05 mL of the solution per session was withdrawn twice daily (separated by at least [redacted] hours) using a dispenser for oral administration.

2.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA has concluded that quality of the drug substance and drug product is appropriately controlled.

2.R.1 Stability of drug product

The applicant's explanation about appropriateness of the evaluation of the stability study:

The stability of the to-be-marketed formulation was evaluated based on the stability study results from 3 [redacted] batches out of a total of 4 primary stability batches, which were manufactured through a process before a change of [redacted] for manufacture at [redacted].

The measurement results on [redacted] fell within the specification range but tended to be high, and thus [redacted] was fine-tuned for manufacture at [redacted]. The [redacted] concentration of the drug substance was changed from [redacted] w/w% to [redacted] w/w%, and changes to the amounts of [redacted] and [redacted] were minor and thus had no impact on [redacted] of [redacted] and each [redacted] in [redacted] process. The manufacturing process and container and closure system were comparable between the pre- and post-[redacted] change drug products, and the [redacted] attributes of the pre- and post-[redacted] change drug products ([redacted], [redacted], [redacted], and [redacted]) were almost the same. In addition, batch analysis results on the pre-[redacted] change drug product (3 [redacted] batches out of the primary stability batches) and that on the post-[redacted] change drug product (1 primary stability batch manufactured at [redacted] and [redacted] batches for [redacted]) as well as stability study results obtained to date[2)] show similar trends. Based on the above, the pre- and post-[redacted] change drug products are comparable in terms of the process and quality. The applicant thus considered it appropriate to use the stability study results including the results for the 3 [redacted] batches to evaluate the stability of the to-be-marketed formulation.

PMDA's view:

The 3 [redacted] batches manufactured through the process before the change of [redacted] for manufacture at [redacted] are not qualified as the primary stability batches defined in the "Revision of the Guidelines on Stability Testing of New Drug Substances and Products" (PFSB/ELD Notification No. 0603001 dated June 3, 2003). However, in view of the following points, it is acceptable for the applicant to use the stability study results including the results for the 3 [redacted] batches to evaluate the stability of the to-be-marketed formulation and thereby propose the shelf life of 30 months for the to-be-marketed formulation when stored at room temperature:

- Other than the primary stability batches, stability study results were obtained from [redacted] batches[2)] of the post-[redacted] change drug product for [redacted] which yielded results consistent with those of the 1 [redacted] batch used as primary stability batches in the long-term testing and accelerated testing. The results of the [redacted] batch, which provided results in the long-term testing for up to [redacted] months, fell within the acceptance criterion ([redacted]%) for the stability study.
- Although stability study results on the post-[redacted] change drug product obtained to date are limited in terms of the number of batches and storage period, the [redacted] concentrations before and after the change of [redacted] differ by [redacted] w/w% for [redacted] and by up to [redacted] w/w% for [redacted]. The

[2)] The storage period of the long-term testing of [redacted] batches for [redacted] was [redacted] months ([redacted] batches), [redacted] months ([redacted] batches), [redacted] months ([redacted] batches), and [redacted] months ([redacted] batches).

manufacturing process and container and closure system were comparable between the pre- and post-[redacted] change drug products, and the [redacted] attributes of the pre- and post-[redacted] change drug products remained almost the same. Batch analysis results on the pre- and post-[redacted] change drug products were also similar except for results on [redacted] of the pre-[redacted] change drug product, which was high but within the specification range.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

In primary pharmacodynamic studies, the effects of maralixibat on IBAT as well as those in normal animals and animal models were investigated. In secondary pharmacodynamic studies, the off-target effect of maralixibat and its binding to cholestyramine were investigated. In safety pharmacology studies, the effects on the cardiovascular, central nervous, and respiratory systems were investigated. The doses and concentrations of maralixibat are expressed as free base.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* study

3.1.1.1 Effect of maralixibat on IBAT (CTD reference data 4.2.1.1-2 and 4.2.1.1-3)

To investigate the selectivity and mode of inhibition of maralixibat, H-14 cell line stably expressing recombinant human IBAT, which was derived from baby hamster kidney cells (BHK cells),[3)] was used. Maralixibat inhibited intracellular uptake of taurocholic acid in a concentration-dependent manner with the 50% inhibitory concentration (IC_{50}) of 0.28 nmol/L. The effect on intracellular uptake of alanine, which is mediated by a sodium-dependent cotransport system like IBAT, was investigated, and the IC_{50} of maralixibat against alanine transport was 127,500 times higher than that against bile acid transport.

An investigation using maralixibat and taurocholic acid at various concentrations revealed that maralixibat inhibited intracellular uptake of taurocholic acid in a competitive and reversible manner with the apparent inhibition constant of 0.13 nmol/L and the IC_{50} of 0.2 nmol/L.

3.1.2 *In vivo* studies

3.1.2.1 Effect of maralixibat in normal rats (CTD reference data 4.2.1.1-5)

Maralixibat at 0 (vehicle[4)]), 0.0006, 0.002, 0.003, 0.008, 0.016, 0.04, 0.08, 0.2, 0.4, or 2 mg/kg was orally administered to rats (male, n = 46/vehicle group; n = 4-20/maralixibat group) once daily for 4 days, and fecal bile acid (fBA) amounts on Days 3 to 4 were determined. Table 5 shows the fBA amounts at each dose of maralixibat. The fBA amounts in the maralixibat groups compared with that in the vehicle group showed a dose-dependent increase with the estimated effective dose for 50% of the animals (ED_{50}) of approximately 0.027 mg/kg/day. No remarkable changes in fecal weight were observed in any group.

3) Prepared by genetically modifying BHK/VP16 cell line to express recombinant human IBAT constitutively IBAT on H-14 cell line acted in a sodium-dependent and substrate-specific manner, which agreed with the expected activity manner for human IBAT naturally present on human cells.

4) 0.2% Tween 80 solution

Table 5. Effect of maralixibat on fBA amount in normal rats

Dose of maralixibat (mg/kg/day)	No. of animals (n)	fBA (μmol/day)	Dose of maralixibat (mg/kg/day)	No. of animals (n)	fBA (μmol/day)
0	46	19.5	0.04	4	44.0
0.0006	4	34.0	0.08	20	55.6
0.002	4	26.6	0.2	4	62.7
0.003	8	31.3	0.4	20	62.3
0.008	4	25.8	2	16	71.6
0.016	20	41.6			

Mean

3.1.2.2 Effect of maralixibat in a rat model of cholestatic disease (CTD reference data 4.2.1.1-6)

Maralixibat at 0 (vehicle[5]), 0.3, or 10 mg/kg was orally administered to rats partial bile duct ligation (pBDL) model of cholestatic disease[6] (n = 3-8 males/group), once daily for 14 days, and fBA amounts on Day 10 as well as sBA concentrations and hepatic disorder marker concentrations (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], gamma-glutamyl transpeptidase [GGT], and total bilirubin) on Days 3, 7, and 14 were determined. Table 6 shows the fBA amounts on Day 10 as well as sBA concentrations and hepatic disorder marker concentrations on Day 14 in each group. The data in either maralixibat group compared with those in the vehicle group showed the increased fBA amount, decreased sBA concentration, and decreased hepatic disorder marker concentrations.

Table 6. Effects of maralixibat on fBA, sBA, and hepatic disorder markers in rat model of cholestatic disease

Group	fBA (μmol/day)	sBA (μmol/L)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	GGT (IU/L)	Total bilirubin (mg/dL)
Naive	41.1 ± 7.6	26.0 ± 7.0	63.4 ± 4.7	57.4 ± 2.9	10.6 ± 0.6	1.0 ± 0.0	0.1 ± 0.0
Vehicle	11.8 ± 1.7	384.3 ± 97.8	251.5±51.5	82.8 ± 6.9	51.3 ± 20.8	12.3 ± 3.6	6.3 ± 2.1
Maralixibat 0.3 mg/kg/day	72.4 ± 4.7	114.4 ± 91.9	163.7±97.2	68.7 ± 10.7	16.0 ± 6.0	4.7 ± 3.7	0.3 ± 0.2
Maralixibat 10 mg/kg/day	72.8 ± 8.6	12.5 ± 3.7	76.7 ± 3.7	59.0 ± 3.8	10.0 ± 0.0	1.0 ± 0.0	0.1 ± 0.0

Mean ± standard error (SE)

3.1.2.3 Effect of maralixibat in dogs (CTD reference data 4.2.1.1-10)

Capsules filled with a solution of maralixibat in 0.2% Tween 80 (maralixibat liquid formulation) or with a dry powder of maralixibat (maralixibat solid formulation) at 1 or 4 mg/kg were administered to dogs (n = 4-5 males/group) by gavage before morning feeding once daily for 14 days, and fBA amounts at baseline, on Days 6 to 7, and on Days 13 to 14 as well as serum total cholesterol and HDL cholesterol concentrations at baseline, on Day 7, and on Day 14 were determined. Table 7 shows the fBA amounts, serum total cholesterol, and HDL cholesterol concentrations in each group. Compared with the baseline values, the fBA amounts increased and the serum total cholesterol and HDL cholesterol concentrations decreased on Day 14 in all the groups. Both formulations exerted similar effects.

[5] Sterile water
[6] The model was established by partially ligating the common bile duct to block the bile flow mechanically.

Table 7. Effects of maralixibat on fBA, total cholesterol, and HDL cholesterol in dogs

Formulation	Dose of maralixibat	No. of animals	fBA (μmol/day)[a)]			Total cholesterol (mg/dL)			HDL cholesterol (mg/dL)		
			Baseline	Days 6-7	Days 13-14	Baseline	Day 7	Day 14	Baseline	Day 7	Day 14
Solid	1 mg/kg/day	4	22 ± 2	114 ± 17 (+418%)	114 ± 29 (+418%)	149 ± 7	130 ± 8 (-13%)	123 ± 7 (-17%)	129 ± 5	115 ± 8 (-11%)	109 ± 5 (-15%)
Liquid		5	41 ± 10	127 ± 9 (+210%)	153 ± 26 (+273%)	149 ± 7	127 ± 5 (-15%)	125 ± 3 (-16%)	129 ± 7	116 ± 5 (-10%)	111 ± 4 (-14%)
Solid	4 mg/kg/day	4	32 ± 5	142 ± 36 (+344%)	228 ± 13 (+612%)	147 ± 19	111 ± 12 (-24%)	109 ± 14 (-26%)	127 ± 11	102 ± 8 (-20%)	102 ± 11 (-20%)
Liquid		5	33 ± 3	166 ± 14 (+403%)	209 ± 24 (+533%)	146 ± 17	124 ± 13 (-15%)	121 ± 13 (-17%)	125 ± 11	111 ± 11 (-11%)	113 ± 10 (-10%)

Top, Mean ± SE; Bottom, Percent change from baseline (%)
a) fBA amount per kg of body weight

3.1.2.4 Effect of maralixibat in monkeys (CTD reference data 4.2.1.1-16)

Maralixibat at 1.0, 2.5, 5.0, or 20.0 mg/kg was intragastrically administered to monkeys (n = 3-5/sex/group) by gavage once daily for 7 days, and fBA amounts at baseline, during the treatment with maralixibat, and after the end of the treatment were determined. Table 8 shows the fBA amounts at baseline, during the treatment with maralixibat, and after the end of the treatment. Compared with the baseline values, the fBA amounts increased during the treatment with maralixibat in a dose-dependent manner, and after the end of the treatment, the fBA concentrations were returned to the baseline values in the maralixibat 5.0 mg and 20.0 mg groups.

Table 8. Effect of maralixibat on fBA amount in monkeys

Dose of maralixibat (mg/kg/day)	fBA (μmol/day)[a)]		
	Baseline	During the treatment	After the treatment
1.0	9 ± 0.8	10 ± 1.2	7 ± 1.0
2.5	8 ± 1.0	9 ± 2.5	8 ± 1.4
5.0	7 ± 0.7	17 ± 2.0	8 ± 1.8
20.0	7 ± 1.4	38 ± 3.9	8 ± 2.9

Mean ± SE
a) fBA amount per kg of body weight

3.2 Secondary pharmacodynamics

3.2.1 Off-target effect of maralixibat (CTD reference data 4.2.1.2-1 to 4.2.1.2-3)

Effects of maralixibat on ligand binding to 87 types of non-target receptors, transporters, and ion channels were investigated.

Maralixibat did not interact with any of the target molecules investigated. The highest maralixibat concentration (100 nmol/L) investigated was approximately 415 times higher than the plasma unbound maralixibat concentration (0.162 ng/mL[7)]) at a clinical dose and approximately 5 times higher than the total maralixibat concentration (0.02 μmol/L) in the small intestinal epithelial cells estimated by an analysis using a physiologically-based pharmacokinetic model.

3.2.2 Binding of maralixibat to cholestyramine (CTD reference data 4.2.1.2-4)

Binding of maralixibat to cholestyramine, anion exchange resin used to enhance biliary excretion in patients with cholestatic disease, was investigated. The binding rates of maralixibat at 0.3 to 30 mmol/L

7) Calculated from the C_{max} (1,658 ng/mL) and unbound fraction (0.098) after administration of maralixibat 45 mg in Study MRX-102

to cholestyramine were 0.2% to 10.3% and did not match a linear model, suggesting that the binding of maralixibat to cholestyramine might be non-specific and have low affinity.

3.3 Safety pharmacology

Table 9 shows the summary of safety pharmacology study results.

Table 9. Summary of safety pharmacology study results

Item	Test system	Evaluation items and methods	Test drug, dose, and regimen	Findings	Attached document CTD
Cardiovascular system	HEK293 cells (3 preparations/ group)	hERG current	Maralixibat 0.3, 1 μmol/L	IC_{50} >1 μmol/L	4.2.1.3-1
	Dog (4 males/group)	Blood pressure, heart rate, electrocardiogram	Maralixibat 0,[a)] 2, 6, 20 mg/kg Single oral administration	No findings	4.2.1.3-2 (non-GLP)
	Dog (4 males/group)	Blood pressure, heart rate, electrocardiogram	Maralixibat group: Maralixibat 0.28 mg/kg, intravenous bolus under anesthesia + Maralixibat 0.50 mg/kg/45 minutes, continuous intravenous infusion Control group: Maralixibat 0[b)] mg/kg, intravenous bolus under anesthesia + Maralixibat 0[b)] mg/kg/45 minutes, continuous intravenous infusion	No findings	4.2.1.3-3 (non-GLP)
Central nervous system	Rat (6/sex/group)	Period I: FOB Period II: FOB and locomotor activity	Period I: Maralixibat 0,[c)] 150 mg/kg Oral administration once daily for 4 days Period II: Maralixibat 0,[b)] 0.15, 0.30 mg/kg Intravenous bolus once daily for 4 days	150 mg/kg: Salivation No findings related to maralixibat in FOB and locomotor activity	4.2.1.3-4 (non-GLP)
Respiratory system	Guinea pig (5 males/group)	Plethysmography	Maralixibat group: Maralixibat 0.39 mg/kg, intravenous bolus under anesthesia + Maralixibat 1.9 mg/kg/45 minutes, continuous intravenous infusion Control group: Maralixibat 0[b)] mg/kg, intravenous bolus under anesthesia + Maralixibat 0[b)] mg/kg/45 minutes, continuous intravenous infusion	No findings	4.2.1.3-5 (non-GLP)

a) Empty gelatine capsules; b) 50 mg/mL mannitol + 0.82 mg/mL sodium acetate solution (pH 4.75); c) Distilled water

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effect of maralixibat

The applicant's explanation about pharmacological effects of maralixibat:

ALGS and PFIC are both cholestatic diseases caused by excessive systemic and intrahepatic retention of bile acids at toxic levels and are accompanied by hepatocellular and cholangiocellular damage due to

increased sBA concentrations, hepatic impairment associated with induced necrosis, intractable pruritus, fatigue, jaundice, and hypoplasia (*J. New Rem. & Clin.* 2018;67:1572-6, *Japanese Journal of Pediatrics.* 2020;73:772-6).

IBAT is localized on the luminal surface of intestinal epithelial cells at the ileal terminal, and plays an important role in enterohepatic circulation of bile acids by mediating uptake of bile acid conjugates. Maralixibat is an IBAT-selective inhibitor. By inhibiting IBAT, it reduces reabsorption of bile acids and thereby lowers sBA concentrations. This mechanism of action is considered to be beneficial for the treatment of ALGS and PFIC.

In the primary pharmacodynamic studies, maralixibat inhibited IBAT-mediated uptake of bile acids, increased fBA excretion in rats, dogs, and monkeys, and lowered sBA concentrations in rats. Maralixibat is thus expected to exert effects in the treatment of ALGS and PFIC.

Based on the submitted primary pharmacodynamic study results and the applicant's explanation, PMDA concludes that maralixibat is expected to alleviate cholestasis-related symptoms in patients with ALGS or PFIC.

3.R.2 Safety pharmacology

The applicant's explanation about findings in the safety pharmacology studies:
In the safety pharmacology studies, no problematic findings were noted in the cardiovascular or respiratory system. As a finding in the central nervous system, salivation was observed in rats in the oral maralixibat 150 mg/kg/day group. However, in a repeated-dose toxicity study in rats [see Section 5.2] in which maralixibat 2,000 mg/day was orally administered with feed, no salivation occurred. In view of this result, the concerned finding is related to local irritation associated with the gavage procedure, and thus clinical use of maralixibat is considered unlikely to raise safety problems.

Based on the submitted safety pharmacology study results and the applicant's explanation, PMDA concludes that clinical use of maralixibat is unlikely to have safety-relevant pharmacological effects on the cardiovascular, central nervous, or respiratory system.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Maralixibat or ^{3}H- or ^{14}C-maralixibat was administered to mice, rats, and dogs to investigate the pharmacokinetics. Plasma maralixibat concentrations were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) with the lower limit of quantification of 0.25, 1, and 4.75 ng/mL, respectively. Radioactivity of ^{3}H- or ^{14}C-maralixibat was determined using a liquid scintillation counter. The doses and concentrations of maralixibat are expressed as free base.

4.1 Absorption

4.1.1 Single-dose studies

4.1.1.1 Single-dose study of maralixibat in dogs (CTD 4.2.3.1-4)

A single dose of maralixibat was orally administered to male and female dogs to investigate the toxicokinetics. Table 10 shows plasma pharmacokinetic parameters of maralixibat. C_{max} and $AUC_{0\text{-}24h}$ of

maralixibat increased with the dose of maralixibat in a range from 50 to 600 mg/kg but did not increase with the dose of maralixibat in a range from 600 to 1,000 mg/kg.

Table 10. Plasma pharmacokinetic parameters of maralixibat in dogs after single oral administration of maralixibat[a)]

Dose of maralixibat	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng•h/mL)	Bioavailability[b)] (%)
50 mg/kg	56.8	2.0	132	0.0833
200 mg/kg	130	2.0	244	0.0385
400 mg/kg	170	2.8	690	0.0544
600 mg/kg	237	2.3	908	0.0477
800 mg/kg	206	2.3	735	0.0290
1,000 mg/kg	205	1.5	637	0.0201

Calculated from the mean at each measurement point (n = 4/timepoint)

a) Calculated from the pooled results in males and females because no difference was observed in exposure between males and females

b) ($AUC_{0\text{-}24h}$ of maralixibat after a single oral administration of maralixibat/the oral dose)/($AUC_{0\text{-}24h}$ of maralixibat after a single intravenous administration of maralixibat 3 mg/kg [9,510 ng•hr/mL]/the intravenous dose [3 mg/kg]) × 100

4.1.2 Repeated-dose studies

4.1.2.1 Repeated-dose study of maralixibat in rats (CTD reference data 4.2.3.2-12)

Maralixibat was orally administered to male and female rats once daily for 2 weeks to investigate the toxicokinetics. Table 11 shows plasma pharmacokinetic parameters of maralixibat. Data on C_{max} and $AUC_{0\text{-}24h}$ of maralixibat did not indicate either clear accumulation attributable to the repeated doses or clear differences between males and females.

Table 11. Plasma pharmacokinetic parameters of maralixibat in rats after repeated oral administration of maralixibat[a)]

Dose of maralixibat	Sex	No. of animals	Measurement day	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng•h/mL)
1 mg/kg	Female	9	Day 1	0	0	0
		9	Day 14	1.47	24.0	11.8
	Male	9	Day 1	0	0	0
		9	Day 14	0.793	0	0.397
5 mg/kg	Female	9	Day 1	1.68	2.0	3.37
		9	Day 14	0.817	24.0	6.53
	Male	9	Day 1	0	0	0
		9	Day 14	1.50	3.0	2.25
30 mg/kg	Female	9	Day 1	7.50	2.0	47.1
		9	Day 14	6.82	2.0	21.0
	Male	9	Day 1	15.8	1.0	31.6
		9	Day 14	3.38	3.0	7.64
150 mg/kg	Female	9	Day 1	4.08	2.0	52.3
		9	Day 14	23.7	3.0	193
	Male	9	Day 1	20.3	2.0	133
		9	Day 14	25.9	1.0	62.3

Calculated from the mean at each measurement point

a) The C_{max}, t_{max}, and $AUC_{0\text{-}24h}$ in rats in which measured plasma maralixibat concentrations were below the lower limit of quantification were determined to be 0 ng/mL, 0 h, and 0 ng•h/mL, respectively.

4.1.2.2 Repeated-dose study of maralixibat in dogs (CTD 4.2.3.2-23)

Maralixibat was orally administered to male and female dogs once daily for 4 weeks to investigate the toxicokinetics. Table 12 shows plasma pharmacokinetic parameters of maralixibat. Data on C_{max} and $AUC_{0\text{-}24h}$ of maralixibat did not indicate either clear accumulation attributable to the repeated doses or clear differences between males and females. In the maralixibat 5 and 15 mg/kg groups, measured plasma maralixibat concentrations in many samples were below the lower limit of quantification.

Table 12. Plasma pharmacokinetic parameters of maralixibat in dogs after repeated oral administration of maralixibat[a)]

Dose of maralixibat	Sex	No. of animals	Measurement day	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng•h/mL)
5 mg/kg	Female	4	Day 1	1.60	0.50	3.14
		4	Day 22	1.20	0.25	1.20
	Male	4	Day 1	2.99	1.25	3.78
		4	Day 22	0	0	0
15 mg/kg	Female	4	Day 1	7.43	3.0	14.4
		4	Day 22	16.6	1.25	67.3
	Male	4	Day 1	4.03	0.50	19.0
		4	Day 22	5.35	1.25	16.5
50 mg/kg	Female	8	Day 1	51.1	1.63	145
		8	Day 22	62.3	2.38	256
	Male	8	Day 1	22.5	1.0	55.3
		8	Day 22	62.6	2.63	274

Calculated from the mean at each measurement point

a) The C_{max}, t_{max}, and $AUC_{0\text{-}24h}$ in dogs in which measured plasma maralixibat concentrations were below the lower limit of quantification were determined to be 0 ng/mL, 0 h, and 0 ng•h/mL, respectively.

4.2 Distribution

4.2.1 Tissue distribution in rats (CTD 4.2.2.2-7 and 4.2.2.2-8)

A single dose of ^{3}H-maralixibat 5 mg/kg was orally administered to albino male and female rats, and radioactivity concentrations in the gastrointestinal tract tissues (stomach, duodenum, jejunum, ileum, and colon) at 168 hours post-dose were determined. The highest radioactivity concentration was found in the ileum in both males and females, but the radioactivity amount in this tissue accounted for ≤0.01% of the radioactivity administered.

A single dose of ^{14}C-maralixibat 5 mg/kg was orally administered to pigmented male rats, and radioactivity concentrations in each tissue[8)] at 0.5, 1, 4, 8, 12, 24, 48, 72, 96, and 168 hours post-dose were determined. The radioactivity concentrations in all tissues peaked within 8 hours post-dose and then decreased with time. Tissues with radioactivity concentrations higher than the plasma radioactivity concentration at 4 hours post-dose were small intestine, stomach, cecum, colon, liver, mesenteric lymph node, lung, kidney, thyroid, bone (femur), and pancreas, and in these tissues, radioactivity concentrations were 6,160, 1,510, 715, 102, 11.2, 7.48, 7.13, 5.79, 3.05, 1.91, and 1.50 times, respectively, higher than the plasma radioactivity concentration. At 168 hours post-dose, the radioactivity concentrations in all tissues, except for the bladder, bone marrow (femur), eye (lens), kidney, liver, mesenteric lymph node, muscle (thigh), spleen, and gastrointestinal tract tissues, were below the lower limit of quantification (0.369-9.84 ng Eq./g).

The applicant's explanation about the detection of radioactivity in tissues other than the gastrointestinal tract at 168 hours post-dose:

- In the bone marrow (femur), eye (lens), muscle (thigh), and spleen, the radioactivity was detected in trace amounts in 1 of 3 animals at 168 hours post-dose, but no radioactivity was detected in any animal at 72 and 96 hours post-dose. The radioactivity detected at 168 hours post-dose might have been attributable to samples contaminated with the radioactivity or detection of noise.

8) Adrenal gland, bladder, blood, bone (femur), bone marrow (femur), brain, cecum, cell fractions, colon, eye (lens), eye (other than the lens), fat (brown and gonadal), Harderian gland, heart, kidney, liver, lung, mesenteric lymph node, muscle (thigh), pancreas, pituitary gland, plasma, prostate gland, salivary gland, skin (non-pigmented), skin (pigmented), small intestine, spinal cord, spleen, stomach, testis, thymus, and thyroid

- The mesenteric lymph node is a tissue in the vicinity of the gastrointestinal tract, and thus a part of the radioactivity distributed in the gastrointestinal tract might have been migrated into the mesenteric lymph node through the lymph fluid absorption pathway. However, because the radioactivity amounts in the mesenteric lymph node at 0.5 to 168 hours post-dose accounted for <0.005% of the radioactivity administered; and no adverse events involving the mesenteric lymph node[9] have been reported in the clinical studies, which are included in the main evaluation data, or in post-marketing experience outside Japan, fractional distribution of maralixibat in the mesenteric lymph node in humans is considered very unlikely to affect the clinical safety of maralixibat.

4.2.2 Protein binding (CTD reference data 4.2.2.3-1)

Protein binding of ^{14}C-maralixibat (0.25-25 μg/mL) was investigated using plasma from mice, rats, guinea pigs, rabbits, dogs, and monkeys. Over the concentration range investigated, the protein binding rate was not concentration-dependent and 95.9% to 97.3%, 86.8% to 90.4%, 88.7% to 91.6%, 84.2% to 91.6%, 91.3% to 92.4%, and 90.3% to 92.5%, respectively.

4.2.3 Distribution in blood cells (CTD 4.2.2.3-2)

Distribution of ^{14}C-maralixibat (0.025-25 μg/mL) in blood cells was investigated using rat and dog blood. The mean distribution rate of maralixibat in blood cells was 19.6% to 42.6% and 22.4% to 37.9%, respectively. However, the rate decreased with the increasing concentration ≥2.5 μg/mL in rats and at the concentration of 25 μg/mL in dogs, suggesting that distribution of maralixibat in blood cells might be saturated at these concentrations.

4.2.4 Placental and fetal transfer

Non-clinical pharmacokinetic studies for placental and fetal transfer of maralixibat have not been conducted because (1) the bioavailability of oral maralixibat is extremely low [see Section 4.1.1.1]; and (2) most of maralixibat is excreted into feces as unchanged maralixibat without being metabolized [see Sections 4.3.2 and 6.2.4].

4.3 Metabolism

4.3.1 *In vitro* investigation of metabolites (CTD reference data 4.2.2.4-1)

Metabolism of ^{14}C-maralixibat (10 μg/mL) was investigated using liver microsomes from rats, dogs, and monkeys. The major metabolites were M1 (*N*-demethylated form) and M3 (hydroxylated form) for rats, and M1, M2 (*N*-demethylated form), M3, M4 (*N*-demethylated and hydroxylated form), M5 (*N*-demethylated and hydroxylated form), and M6 (hydroxylated form) for dogs and monkeys, suggesting that maralixibat would mainly undergo *N*-demethylation or hydroxylation as metabolism pathways in all the animal species.

4.3.2 Proportions of unchanged maralixibat and its metabolites in plasma, urine, and feces (CTD reference data 4.2.2.3-3, 4.2.2.4-2, and 4.2.2.4-3)

A single dose of ^{14}C-maralixibat 5 mg/kg was orally administered to male and female mice, and proportions of unchanged maralixibat and its metabolites in plasma, urine, and feces were investigated. Proportions of unchanged maralixibat to the total radioactivity concentration in plasma at 1 and 5 hours

[9] Events coded into MedDRA preferred terms (MedDRA PTs) containing “mesenteric” or “lymph”

post-dose were 100% and 99.7%, respectively, and no metabolites were detected in plasma. The radioactivity in urine collected until 168 hours post-dose accounted for 1.45% of the total radioactivity administered. The radioactivity in feces collected until 168 hours post-dose accounted for 101% of the total radioactivity administered, and unchanged maralixibat and M1 were detected (accounting for 97.9% and 1.98% of the total radioactivity concentration in the feces, respectively).

A single dose of ^{3}H-maralixibat 5 mg/kg was orally administered to male and female rats, and proportions of unchanged maralixibat and its metabolites in urine and feces were investigated. In all samples, only unchanged maralixibat was detected, and no metabolites were detected.

A single dose of ^{3}H-maralixibat 7.5 mg/kg was orally administered to female dogs, and proportions of unchanged maralixibat and its metabolites in urine and feces were investigated. In the feces, only unchanged maralixibat was detected, and no metabolites were detected. The total radioactivity concentration in urine was too low to investigate unchanged maralixibat and its metabolites in the urine.

4.4 Excretion

4.4.1 Urinary and fecal excretion in rats (CTD 4.2.2.2-7, reference data 4.2.2.2-8 to 4.2.2.2-10)

A single dose of ^{14}C- or ^{3}H-maralixibat (5-2,000 mg/kg) was orally administered to male and female rats. The radioactivity excreted into urine and feces within 168 hours post-dose accounted for 0.11% to 9.55% and 65.7% to 95.1% of the dose, respectively, in males and 0.11% to 11.3% and 63.2% to 96.4%, respectively, in females.

4.4.2 Urinary and fecal excretion in dogs (CTD 4.2.2.2-16, reference data 4.2.2.2-17)

A single dose of ^{3}H-maralixibat (7.5 mg/kg) was orally administered to female dogs, and the radioactivity excreted into urine and feces within 168 hours post-dose accounted for 0.10% and 94.3% of the dose, respectively.

A single dose of ^{14}C-maralixibat (50 mg/kg) was orally administered to male and female dogs, and the radioactivity excreted into urine and feces within 168 hours post-dose accounted for 0.93% and 51.5% of the dose, respectively, in males and 0.40% and 22.2%, respectively, in females.

4.4.3 Excretion in milk

Non-clinical pharmacokinetic studies for excretion of maralixibat in milk have not been conducted because (1) the oral bioavailability of maralixibat is extremely low [see Section 4.1.1.1]; and (2) most of maralixibat is excreted into feces as unchanged maralixibat without being metabolized [see Sections 4.3.2 and 6.2.4].

4.R Outline of the review conducted by PMDA

Based on the submitted non-clinical pharmacokinetic study results and the applicant's explanation, PMDA concluded that the non-clinical pharmacokinetics of maralixibat was appropriately evaluated, and no particular concerns for clinical use of maralixibat are presented from a viewpoint of non-clinical pharmacokinetics.

5. Toxicology and Outline of the Review Conducted by PMDA

Toxicity studies of maralixibat conducted were single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, juvenile animal toxicity, and local tolerance studies. The major study results are described below. The doses and concentrations of maralixibat are expressed as free base.

5.1 Single-dose toxicity

Acute toxicity was evaluated in single-dose toxicity studies in rats and dogs. Table 13 shows approximate lethal doses of maralixibat.

Table 13. Summary of single-dose toxicity study results

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female rats (SD)	Oral	0,[a] 1,000, 2,000	≥1,000: Soiled entire body, abnormal feces, salivation, reduced body weight gain 2000: Decreased body weight	>2,000	4.2.3.1-1
	Intravenous	0,[b] 0.06, 0.6, 6	Death: 6 (1 of 6 males) 6: Tremor, decreased activity, mydriasis	6	4.2.3.1-2
Male and female dogs (beagle)	Oral	0,[c] 50, 200, 400, 600, 800, 1,000	≥50: Vomiting ≥200: Abnormal feces	>1,000	4.2.3.1-4
	Intravenous	0,[b] 1, 2.5, 5	5: Tremor, increased activity, lethargy, muscle stiffness	>5	4.2.3.1-5

a) Distilled water
b) Water for injection containing 50 mg/mL mannitol and 0.82 mg/mL sodium acetate trihydrate
c) Empty gelatin capsules

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies in mice (up to 13 weeks), rats (up to 26 weeks), and dogs (up to 52 weeks) were conducted (Table 14). Major toxicity findings were haemorrhagic lesions in rats and vomiting in dogs.

Maralixibat was administered to mice for 13 weeks, rats for 26 weeks, and dogs for 52 weeks, and the no-observed-adverse-effect level (NOAEL) was determined to be 150 mg/kg/day in mice, 150 mg/kg/day (males) and 500 mg/kg/day (females) in rats, and 20 mg/kg/day in dogs. The $AUC_{0\text{-}24h}$ of maralixibat at these NOAELs were 44, 9, 20, and 5 times, respectively, the estimated AUC_{inf}[10] at the maximum human dose.

[10] The estimated AUC_{inf} in humans at the maximum human dose was calculated by doubling the AUC_{inf} (5.73 ng•h/mL) after a single oral administration of maralixibat 45 mg to healthy adults in a foreign phase I study (Study MRX-102).

Table 14. Summary of repeat-dose toxicity study results

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)		Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female mice (CD-1)	Oral	13 weeks (once daily)	0,[a] 50, 150, 500, 1,000		Death or moribundity[b]: 500 (3 of 15 males, 5 of 15 females), 1000 (5 of 15 males, 8 of 15 females) ≥50: Increased fecal bile acid excretion ≥500: Decreased food consumption and body weight 1,000: Decreased bile acid (male)	150	4.2.3.2-4
Male and female rats (SD)	Oral	13 weeks (once daily)	M	0,[a] 5, 30, 75, 150	No toxic changes	150	4.2.3.2-17
			F	0,[a] 5, 30, 150, 500	No toxic changes	500	
Male and female rats (SD)	Oral	13 weeks (once daily) + 4 weeks for recovery	0,[c] 10, 300, 1,000		No toxic changes	1,000	4.2.3.2-18
Male and female rats (SD)	Oral (with feed)	13 weeks (once daily) + 4 weeks for recovery	0, 150, 750, 1,500[d]		Death: 750 (1 of 25 males), 1,500 (18 of 25 males) ≥750: Reduced body weight gain, prolongation of PT and APTT (male), general bleeding (male) Reversible	150 (male) 1,500 (female)	4.2.3.2-20
Male and female rats (SD)	Oral (with feed)	26 weeks (once daily) + 4 weeks for recovery	M	0, 30, 150, 750/300[e]	Death or moribundity: 750/300 (17 of 37 males) ≥30: Reduced body weight gain, prolongation of PT and APTT 750/300: Pale skin and mucous membranes; presence of dark bloody substances in the body cavity and hollow organs[f]; dark and pale tissues; intestinal dilatation; hemosiderosis; lymphocyte necrosis in tissues[g]; erosion, ulcer, and necrosis of the gastric mucosa[h] Reversible	150	4.2.3.2-21
			F	0, 30, 500, 2,000/1,500[i]	Moribundity: 2,000 (7 of 37 females) ≥500: Reduced body weight gain 2,000/1,500: Loss of hair on limbs; prolongation of PT and APTT; dark bloody substances in the body cavity and hollow organs[f]; dark and pale tissues; intestinal dilatation; hemosiderosis; lymphocyte necrosis in tissues[g]; erosion, ulcer, and necrosis of the gastric mucosa[h] Reversible	500	
Male and female dogs (beagle)	Oral	4 weeks (once daily) + 4 weeks for recovery	0,[j] 5, 15, 50		≥5: Increased fecal bile acid excretion	50	4.2.3.2-23
Male and female dogs (beagle)	Oral	4 weeks (once daily)	0,[j] 100, 300, 600[k]		≥100: Vomiting, reduced body weight gain	<100	4.2.3.2-24
Male and female dogs (beagle)	Oral	13 weeks (once daily)	0,[j] 5, 20, 100		100: Vomiting, Increased fecal bile acid excretion	20	4.2.3.2-25
Male and female dogs (beagle)	Oral	26 weeks (once daily) + 4 weeks for recovery or 52 weeks (once daily) + 8 weeks for recovery	0,[j] 1, 5, 20, 100		100: Vomiting Reversible	20	4.2.3.2-26

a) Distilled water
b) Death with findings suggestive of gas distension of the gastrointestinal tract and aspiration of the dosing solution during administration was found in many animals, and the death was considered attributable to respiratory distress.
c) Deionized water
d) Because many rats had died, all surviving males in the 1,500 mg/kg/day group were euthanized on Day 78.

e) Of 37 males, 15 had died or were euthanized in moribund condition by Day 87, and the target dose was reduced to 300 mg/kg/day on Day 88 and thereafter.
f) Bloody substances were observed in the thoracic cavity, peritoneal cavity, cranial cavity, pericardial cavity, bladder, and thymus.
g) Lymphocyte necrosis was observed in the spleen, lymph node, thymus, cecum, and ileum and was considered attributable to stress.
h) The findings of the gastric mucosa were considered attributable to stress.
i) Of 37 females, 7 had died or were euthanized in moribund condition by Day 95, and the target dose was reduced to 1,500 mg/kg/day on Day 102 and thereafter.
j) Empty gelatin capsules
k) Because vomiting was highly frequently observed in the 600 mg/kg/day group, administration of the test article and data collection were discontinued on Day 11 and thereafter, and no necropsy was performed after euthanasia.

5.3 Genotoxicity

A bacterial reverse mutation assay, a chromosomal aberration assay in mammalian cells, and a micronucleus assay in rats were performed (Table 15). All the studies presented negative results, and the applicant explained that maralixibat is unlikely to pose genotoxicity.

Table 15. Summary of genotoxicity study results

Type of study		Test system	S9 (treatment)	Concentration or dose	Study result	Attached document CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA97a, TA98, TA100, TA102, and TA1535	-/+	0,[a] 10, 50, 100, 500, 1000, 5000 µg/plate	Negative	4.2.3.3.1-2
In vitro	Chromosomal aberration assay in mammalian cells	CHO-derived cells	- (17.9 hours)	0,[a] 30, 35, 40, 45 µg/mL	Negative	4.2.3.3.1-4
			- (3 hours)	0,[a] 50, 60, 65, 70 µg/mL		
			+ (3 hours)	0,[a] 80, 90, 100, 110 µg/mL		
In vivo	Micronucleus assay	Male and female rats (SD) bone marrow		0,[b] 500, 1000, 2000 mg/kg (single oral dose)	Negative	4.2.3.3.2-1

a) Dimethyl sulfoxide (DMSO)
b) Distilled water

5.4 Carcinogenicity

Carcinogenicity studies in rats and Tg-ras H2 mice were conducted (Table 16). No carcinogenicity was observed in any study, and the applicant explained that maralixibat is unlikely to pose carcinogenicity.

Table 16. Summary of carcinogenicity study results

<table>
<tr><th>Test system</th><th>Route of administration</th><th>Treatment duration</th><th colspan="6">Results</th><th>Non-carcinogenic dose (mg/kg/day)</th><th>Attached document CTD</th></tr>
<tr><td rowspan="5">Male and female rats (SD)</td><td rowspan="5">Oral</td><td rowspan="5">104 weeks[a] (once daily)</td><td rowspan="3">Major findings</td><td rowspan="3">n</td><td colspan="4">Dose (mg/kg/day)</td><td rowspan="5">100</td><td rowspan="5">4.2.3.4.1-2</td></tr>
<tr><td>0[b]</td><td>10</td><td>30</td><td>100</td></tr>
<tr><td>70 males
70 females</td><td>70 males
70 females</td><td>70 males
70 females</td><td>70 males
70 females</td></tr>
<tr><td>Neoplastic lesions</td><td colspan="6">No remarkable findings</td></tr>
<tr><td>Non-neoplastic lesions</td><td colspan="6">≥10: Basophilic change hepatocyte foci
≥30: Increased alveolar macrophages</td></tr>
<tr><td></td><td>Other findings</td><td colspan="6">≥10: Respiratory sound, loss of hair, crust formation on the head</td></tr>
<tr><td rowspan="6">Male and female mice (Tg-rasH2)</td><td rowspan="6">Oral</td><td rowspan="6">26 weeks (once daily)</td><td rowspan="3">Major findings</td><td rowspan="3">n</td><td colspan="4">Dose (mg/kg/day)</td><td rowspan="6">Male 25
Female 75</td><td rowspan="6">4.2.3.4.2-1</td></tr>
<tr><td>0[b]</td><td>M: 2.5
F: 7.5</td><td>M: 7.5
F: 25</td><td>M: 25
F: 75</td></tr>
<tr><td>25 males
25 females</td><td>25 males
25 females</td><td>25 males
25 females</td><td>25 males
25 females</td></tr>
<tr><td>Neoplastic lesions</td><td colspan="6">No remarkable findings</td></tr>
<tr><td>Non-neoplastic lesions</td><td colspan="6">No remarkable findings</td></tr>
<tr><td></td><td>Other findings</td><td colspan="6">≥2.5 (male)/≥7.5 (female): Piloerection, emaciation, decreased locomotor activity, hunched position, abnormal respiration
≥7.5 (male)/≥25 (female): Decreased body weight and reduced body weight gain
25 (male): Increased early mortality</td></tr>
</table>

a) Because the survival decreased in all groups including the control group, the study was terminated on Day 688 in males and on Day 629 in females
b) Deionized water

5.5 Reproductive and developmental toxicity

Studies for fertility and early embryonic development to implantation in rats, for embryo-fetal development in rats and rabbits as well as for pre- and postnatal development, including maternal function in rats were conducted (Table 17).

The study for fertility and early embryonic development to implantation in female rats showed decreases in food consumption, body weight gain, ovary weight, number of corpora lutea, mean number of implantation, and number of live fetuses (≥500 mg/kg/day).

In the study for fertility and early embryonic development to implantation in rats, the NOAEL for reproductive functions and early embryonic development in female rats was determined to be 30 mg/kg/day, and the $AUC_{0\text{-}24h}$ of maralixibat at the concerned NOAEL was 2 times the estimated AUC_{inf}[10] at the maximum human dose.

Table 17. Summary of reproductive and developmental toxicity study results

Type of study	Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Fertility and early embryonic development to implantation	Male and female rats (SD)	Oral (with feed)	Male: From 28 days before mating to the day before necropsy	0, 30, 150, 750	Death: 750 (1 of 25 rats) ≥30: Decreased food consumption and reduced body weight gain 750: Prolongation of PT and APTT, decreased hematocrit	General toxicity: 150 Reproductive functions: 750 Early embryonic development: 750	4.2.3.5.1-1
			Female: From 14 days before mating to Gestation Day 7	0, 30, 500, 2,000	Death: 2,000 (1 of 25 rats) ≥500: Decreased food consumption and reduced body weight gain; decreased ovary weight; decreased number of corpora lutea, mean number of implantation, and number of live fetuses	General toxicity: 500 Reproductive functions: 30 Early embryonic development: 30	
Embryo-fetal development	Female rat (SD)	Oral (with feed)	Gestation Day 6 to Gestation Day 17	0, 50, 250, 1,000	No toxic changes	Maternal general toxicity: 1000 Embryo-fetal development: 1,000	4.2.3.5.2-2
	Female rabbit (NZW)	Oral	Gestation Day 7 to Gestation Day 18 (once daily)	0,[a] 25, 100, 250	Maternal animal: 100: Reduced body weight gain 250: Decreased food consumption and body weight, abortion Fetus: No toxic changes	Maternal general toxicity: 25 Embryo-fetal development: 250	4.2.3.5.2-4
Effects on pre- and postnatal development, including maternal function	Female rat (SD)	Oral (with feed)	Gestation Day 6 to Lactation Day 21	0, 50, 250, 750	No toxic changes	Maternal general toxicity: 750 F_1 offspring: 750 F_2 offspring: 750	4.2.3.5.3-2

a) Solution containing 0.5% methylcellulose and 0.1% Tween 80

5.6 Other studies

5.6.1 Juvenile animal toxicity

Repeated-dose toxicity studies in juvenile rats were conducted (Table 18). No toxicological findings were obtained. In juvenile rats which received maralixibat for 43 days, the NOAEL was determined to be 200 mg/kg/day for males and 1000 mg/kg/day for females. The $AUC_{0\text{-}24h}$ of maralixibat at these NOAELs were 11 and 215 times, respectively, the estimated AUC_{inf} at the maximum human dose.

Table 18. Summary of juvenile animal toxicity study results

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)		Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (SD)	Oral	14 days (started at the age of 7 days, once daily) + 28 days for recovery	0,[a] 50, 100, 250		No toxic changes	250	4.2.3.5.4-2
Male and female rats (SD)	Oral	43 days (started at the age of 21 days, once daily) + 35 days for recovery	M	0,[b] 50, 100, 200	No toxic changes	200	4.2.3.5.4-3
			F	0,[b] 250, 500, 1000	No toxic changes	1000	

a) Deionized water
b) Distilled water

5.6.2 Local tolerance

A primary skin irritation study in rabbits and a primary eye irritation study in rabbits were conducted (Table 19). Maralixibat caused very mild irritability in the skin and mild to moderate irritability in the eye when instilled, but the applicant explained that maralixibat is unlikely to cause problematic irritability when orally administered.

Table 19. Summary of local tolerance study results

Test system	Study method	Major findings	Attached document CTD
Male rabbit (NZW)	A mixture of 0.5 g of maralixibat and distilled water was applied to the normal skin, which was then kept in a partially occluded condition for 4 and a half hours. The treated skin was observed for skin reactions at 30 to 60 minutes, 24, 48, and 72 hours after the end of the application.	Very mild skin irritability was observed.	4.2.3.6-2
Female rabbit (NZW)	Maralixibat 19 mg was instilled in the lower eyelid of the right eye. In Group 1, no rinsing was performed just after the instillation, and in Group 2, 1-minute rinsing was performed starting approximately 30 seconds after instillation. Draize test was performed 1, 24, 48, 72, and 96 hours, and 7 and 14 days after instillation to assess irritability.	Moderate irritability was observed in Group 1 without rinsing after instillation and mild irritability was observed in Group 2 with rinsing after instillation.	4.2.3.6-3

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the toxicity of maralixibat was appropriately evaluated, and no particular concerns for clinical use of maralixibat are presented from a viewpoint of toxicology.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

In this section, doses of maralixibat are expressed as the amounts of maralixibat chloride, while concentrations of maralixibat are expressed as the amounts of maralixibat free base.

6.1 Biopharmaceutic studies and associated analytical methods

In a foreign phase II study (Study LUM001-304), a foreign phase III study (Study MRX-502), and Japanese phase III studies (Studies TAK-625-3001 and TAK-625-3002), which are included in the main evaluation data for the present application, formulations listed in Table 20 were used.

The applicant's explanation about differences between Formulation B and the proposed formulation: Formulation B and the proposed formulation did not largely differ in viscosity, osmolality, pH, or density, and thus this change is unlikely to affect pharmacokinetic properties of the formulation.

Table 20. Formulations used in the phase II and III studies in the main evaluation data

Clinical study	Formulation
Foreign phase II study (Study LUM001-304)	Formulation A: Oral solution containing 0.14-50 mg/mL maralixibat chloride
Foreign phase III study (Study MRX-502)	Formulation B: Oral solution containing 5, 10, 15, or 20 mg/mL maralixibat chloride
Japanese phase III study (Study TAK-625-3001)	Formulation C: Oral solution containing 10 mg/mL maralixibat chloride (proposed formulation)
Japanese phase III study (Study TAK-625-3002)	Formulation C: Oral solution containing 10 mg/mL maralixibat chloride (proposed formulation) Oral solution containing 5, 15, or 20 mg/mL maralixibat chloride

Plasma maralixibat concentrations were determined by LC-MS/MS with the lower limit of quantification of 0.25 ng/mL. Radioactivity concentrations in plasma, whole blood, urine, and feces were determined using a liquid scintillation counter with the lower limit of quantification of 0.001 μg Eq./mL or 0.001 μg Eq./g. Bile acid concentrations in serum and feces were determined by liquid chromatography-mass spectrometry (LC-MS) and an enzymatic cycling method, respectively.

6.1.1 Studies using human biological samples

6.1.1.1 *In vitro* membrane permeability (CTD 4.2.2.2-1)

Membrane permeability of maralixibat (5, 15, 50, and 150 μmol/L) was investigated using human colon cancer cells (Caco-2 cells). Table 21 shows apparent permeability coefficients (P_{app}) from the apical surface (A) to the basolateral surface (B) (P_{app} A→B) for each compound. The P_{app} A→B of maralixibat is lower than that of atenolol, which was selected as the low permeability compound, and the applicant explained that the membrane permeability of maralixibat is low.

Table 21. Membrane permeability through Caco-2 cell monolayer

Test article	Concentration	P_{app} A→B ($\times 10^{-6}$ cm/s)
Maralixibat	5 μmol/L	0.01
	15 μmol/L	0.02
	50 μmol/L	1.07
	150 μmol/L	2.33
Propranolol[a)]	100 μmol/L	22.4
Atenolol[b)]	100 μmol/L	2.51

a) Selected as a high permeability compound
b) Selected as a low permeability compound

6.1.1.2 Protein binding (CTD reference data 4.2.2.3-1)

Protein binding of ^{14}C-maralixibat (0.25-25 μg/mL) was investigated using human plasma, human serum albumin solution, and α_1-acid glycoprotein solution. The protein binding rate was 90.2% to 91.2%, 97.8% to 98.5%, and 96.2% to 99.3%, respectively, and not concentration-dependent over the concentration range investigated.

6.1.1.3 Distribution in blood cells (CTD reference data 4.2.2.3-2)

Distribution of ^{14}C-maralixibat (0.025-25 μg/mL) in blood cells was investigated using human blood. The mean distribution rate of maralixibat in blood cells was 33.2% to 44.5% and the rate decreased at 25 μg/mL, suggesting that distribution of maralixibat in blood cells might be saturated at this concentration.

6.1.1.4 *In vitro* investigation of metabolites (CTD reference data 4.2.2.4-1)

Metabolism of ^{14}C-maralixibat (10 μg/mL) was investigated using human liver microsomes. The major metabolites detected were M3 (hydroxylated form), M1 (*N*-demethylated form), M2 (*N*-demethylated form), M4 (*N*-demethylated and hydroxylated form), M5 (*N*-demethylated and hydroxylated form), and M6 (hydroxylated form). No human-specific metabolites were detected [see Section 4.3.1].

6.1.1.5 Induction of human hepatic drug-metabolizing enzymes by maralixibat (CTD reference data 4.2.2.6-1)

The inductive effect of maralixibat (0.01-10 μmol/L) on cytochrome P450 (CYP)1A2, CYP2B6, and CYP3A4 was investigated using human hepatocytes. Over the concentration range investigated, maralixibat did not increase mRNA expression or induce enzyme activity of any CYP isoform.

6.1.1.6 Inhibition of human hepatic drug-metabolizing enzymes by maralixibat (CTD reference data 4.2.2.6-2)

The inhibitory effect of maralixibat (0.0022-20 μmol/L) on CYP isoforms[11)] (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was investigated. Maralixibat inhibited CYP3A4 with the IC_{50} of 3.00 to 7.43 μmol/L (midazolam) and 3.19 to 10.9 μmol/L (testosterone), CYP2C9 with the IC_{50} of 3.46 to 4.76 μmol/L, and CYP2C19 with the IC_{50} of 6.95 to 9.16 μmol/L. The other CYP isoforms were not inhibited by maralixibat over the concentration range investigated. The IC_{50} against CYP3A4 changed by a factor of 1.60 to 2.47 (midazolam) and 2.61 to 3.41 (testosterone) depending on the presence or absence of pre-incubation or nicotinamide adenine dinucleotide phosphate (NADPH), indicating that maralixibat inhibits CYP3A4 in a time-dependent manner.

6.1.1.7 Investigation of transporter-mediated transport (CTD 4.2.2.6-4)

Transport of maralixibat (0.1-150 μmol/L) mediated by P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) was investigated using vesicles prepared from human embryonic kidney cell line 293 (HEK293 cells) expressing P-gp or BCRP. Maralixibat was not found to be a substrate of P-gp or BCRP.

Transport of maralixibat (0.1-10 μmol/L) mediated by organic anion transporting polypeptide (OATP)1B1, OATP1B3, and OATP2B1 was investigated using HEK293 cells expressing OATP1B1, OATP1B3, or OATP2B1. Maralixibat was not found to be a substrate of OATP1B1, OATP1B3, or OATP2B1.

11) The following were used as the substrates: Phenacetin for CYP1A2, bupropion for CYP2B6, amodiaquine for CYP2C8, diclofenac for CYP2C9, mephenytoin for CYP2C19, dextromethorphan for CYP2D6, midazolam and testosterone for CYP3A4

6.1.1.8 Investigation of transporter inhibition (CTD 4.2.2.6-4, reference data 4.2.2.6-5)

Using cells expressing P-gp (Mardin-Darby canine kidney cells [MDCK cells]), BCRP (Caco-2 cells), organic cation transporter (OCT)3, OATP1B1, organic cation/carnitine transporter (OCTN)1, OCTN2, and peptide transporter 1 (PEPT1) (MDCKII cells), or OATP2B1 (Chinese hamster ovary [CHO] cells) or vesicles prepared from cells expressing multidrug resistance protein 2 (MRP2) (Sf9 insect cells), effects of maralixibat (10 μmol/L) on transport of the standard substances[12)] corresponding to these transporters were investigated. Maralixibat inhibited transport of the standard substances corresponding to BCRP, OCT3, OATP1B1, OCTN1, OCTN2, OATP2B1, and MRP2[12)] by 13.1%, 16.3%, 96.6%, 27.3%, 50.2%, 95.3%, and 65.8%, respectively. Maralixibat did not inhibit P-gp or PEPT1 clearly.

Using MDCKII cell monolayer expressing multidrug and toxin extrusion (MATE)1 or MATE2-K or HEK293 cells expressing organic anion transporter (OAT)1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2, effects of maralixibat (0.014-10 μmol/L) on transport of the standard substances[13)] corresponding to these transporters were investigated. Maralixibat (10 μmol/L) inhibited transport of the standard substances[13)] corresponding to MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2 by 95% to 96%, 60%, 25%, 22%, 94%, 74%, 94% to 97%, and 75%, respectively. The IC_{50} values of maralixibat against MATE1, OATP1B1, OATP1B3, OATP2B1, and OCT1 were 0.01, 0.02, 0.14, 1.02, and 0.06 μmol/L, respectively. Drug-interaction mediated by OATP2B1 that is one of the transporters potently inhibited by maralixibat and known to be expressed on the gastrointestinal tract is reviewed in Section 6.R.3.

6.2 Clinical pharmacology

6.2.1 Phase I single-dose study (CTD reference data 5.3.3.1-1, Study No. NB4-02-06-002, [redacted] 19[redacted] to [redacted] 20[redacted])

A placebo-controlled randomized double-blind study was conducted at 1 study center outside Japan to evaluate the pharmacokinetics, pharmacodynamics, and safety of maralixibat orally administered as a single dose to healthy non-Japanese adults (target sample size, 82 subjects; 22 in the placebo group and 60 in the maralixibat group).

A single dose of placebo or maralixibat 1, 2.5, 5, 10, 20, 50, 100, 300, or 500 mg was orally administered just before breakfast, or a single dose of placebo or maralixibat 10 mg was orally administered in the fasted state.[14)]

All of 82 subjects who received the study drug were included in the safety analysis set, and 60 subjects who received maralixibat were included in the pharmacokinetic analysis population.

Table 22 shows pharmacokinetic parameters of maralixibat in plasma after a single oral administration of maralixibat. Over the dose range tested, the C_{max} and $AUC_{0\text{-}24h}$ of maralixibat were below the lower

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12) The following were used as the substrates: ^{3}H-digoxin for P-glycoprotein (P-gp), ^{3}H-genistein for BCRP, ^{3}H-1-methyl-4-phenylpyridinium for OCT3, ^{3}H-estradiol-17β-D-glucuronide for OATP1B1, ^{3}H-ergothioneine for OCTN1, ^{3}H-L-carnitine for OCTN2; ^{3}H-glycylsarcosine for PEPT1, ^{3}H-estrone-3-sulfate for OATP2B1, ^{3}H-estradiol-17β-D-glucuronide for MRP2

13) The following were used as the substrates: ^{14}C-metformin hydrochloride for MATE1 and MATE2-K, ^{3}H-tenofovir for OAT1, ^{3}H-estrone-3-sulfate for OAT3, ^{3}H-estradiol-17β-D-glucuronide for OATP1B1, ^{3}H-propionylated cholecystokinin octapeptide for OATP1B3, ^{14}C-metformin hydrochloride for OCT1 and OCT2

14) Subjects received maralixibat after having fasted overnight (≥12 hours) and then further continued fasting for 5 hours post-dose.

limit of quantification in all subjects in the 1 mg to 10 mg (just before breakfast) groups, while the C_{max} and $AUC_{0\text{-}24h}$ increased generally dose-proportionally in the 20 mg to 500 mg groups.

Table 22. Pharmacokinetic parameters of maralixibat in plasma in healthy non-Japanese adults after single oral administration of maralixibat

Maralixibat	State at administration	No. of subjects	C_{max} (ng/mL)	t_{max}[a)] (h)	$AUC_{0\text{-}24\ h}$ (ng•h/mL)	$t_{1/2}$ (h)
1 mg	Just before breakfast	6	NC	NC	NC	NC
2.5 mg	Just before breakfast	6	NC	NC	NC	NC
5 mg	Just before breakfast	6	NC	NC	NC	NC
10 mg	Just before breakfast	6	NC	NC	NC	NC
	Fasted	6	0.454 ± 0.159	2.0 (1.5, 4.0)	0.946 ± 0.431	NC
20 mg	Just before breakfast	6	0.081 ± 0.197	6.0[b)]	0.161 ± 0.394	NC
50 mg	Just before breakfast	6	0.310 ± 0.413	2.0 (1.5, 4.0)[c)]	0.600 ± 0.852	NC
100 mg	Just before breakfast	6	0.727 ± 0.385	2.5 (1.0, 4.0)	1.67 ± 0.642	NC
300 mg	Just before breakfast	6	2.08 ± 0.330	3.0 (1.5, 3.0)	7.51 ± 1.98	1.69, 2.36[d)]
500 mg	Just before breakfast	6	2.40 ± 0.344	2.5 (2.0, 4.0)	14.2 ± 7.60	3.79 ± 3.37[e)]

Mean ± standard deviation (SD); NC, Not calculated (below the lower limit of quantitation in all subjects in the 1-10 mg groups)
a) Median (minimum, maximum); b) Individual value in 1 subject; c) Individual values in 3 subjects; d) Individual values in 2 subjects; e) n = 5

For pharmacodynamics, Table 23 shows data on fBA excretion after a single oral administration of placebo or maralixibat. On Day 1, maralixibat increased fBA excretion compared to placebo.

Table 23. fBA excretion (µmol/day)

Study drug		State at administration	Day -1[a)]	Day 1	Day 2
Placebo		Just before breakfast	132 ± 125 (18)	79.1 ± 134 (18)	155 ± 218 (19)
Maralixibat	1 mg	Just before breakfast	172 ± 292 (6)	355 ± 474 (6)	6.70 ± 16.4 (6)
	2.5 mg	Just before breakfast	241 ± 94.9 (6)	620 ± 511 (6)	110 ± 125 (6)
	5 mg	Just before breakfast	454 ± 254 (6)	1,704 ± 1,118 (6)	34.3 ± 53.1 (6)
	10 mg	Just before breakfast	208 ± 381 (6)	1,177 ± 1,500 (6)	51.4 ± 97.8 (6)
		Fasted	110 ± 143 (6)	363 ± 373 (6)	40.2 ± 69.3 (6)
	20 mg	Just before breakfast	198 ± 193 (6)	2,440 ± 1,179 (6)	37.1 ± 91.0 (6)
	50 mg	Just before breakfast	114 ± 64.3 (5)	1,482 ± 588 (6)	38.1 ± 55.3 (6)
	100 mg	Just before breakfast	118 ± 154 (6)	1,469 ± 1,140 (6)	402 ± 395 (6)
	300 mg	Just before breakfast	168 ± 148 (6)	1,830 ± 1,101 (6)	564 ± 632 (6)
	500 mg	Just before breakfast	420 ± 407 (5)	1,808 ± 1,192 (6)	249 ± 305 (6)

Mean ± SD (number of subjects)
a) Before administration of the study drug

For safety, adverse events occurred in 13.6% (3 of 22) of subjects in the placebo group, 16.7% (1 of 6) of subjects in the maralixibat 1 mg group, 16.7% (1 of 6) of subjects in the 2.5 mg group, 33.3% (2 of 6) of subjects in the 10 mg (just before breakfast) group, 33.3% (2 of 6) of subjects in the 20 mg group, 33.3% (2 of 6) of subjects in the 50 mg group, 50.0% (3 of 6) of subjects in the 100 mg group, 16.7% (1 of 6) of subjects in the 300 mg group, and 33.3% (2 of 6) of subjects in the 500 mg group. Except for 1 event each in the placebo group and the maralixibat 50 mg group, all the events were classified as the adverse drug reactions. No deaths, serious adverse events, or adverse events leading to treatment discontinuation occurred.

6.2.2 Phase I multiple-dose study (CTD 5.3.3.1-3, Study No. NB4-02-06-003, [redacted] 19[redacted] to [redacted] 20[redacted])

A placebo-controlled randomized double-blind study was conducted at 1 study center outside Japan to evaluate the pharmacokinetics, pharmacodynamics, and safety of maralixibat orally administered as

multiple doses in healthy non-Japanese adults (target sample size, 167 subjects; 20 in the placebo group and 147 in the maralixibat group).

Placebo or maralixibat 0.5, 1, 2.5, 5, or 0.5 to 5 mg (ascending doses)[15] was orally administered just before breakfast once daily for 28 days; maralixibat 10, 20, 60, or 100 mg was orally administered just before breakfast once daily for 28 days; or maralixibat 5 mg was orally administered evening once daily for 28 days.[16]

All of 167 subjects who received the study drug were included in the safety analysis set, and 80 subjects[17] who received maralixibat were included in the pharmacokinetic analysis population.

Table 24 shows pharmacokinetic parameters of maralixibat in plasma after multiple oral administration of maralixibat. Over the dose range tested, the C_{max} and $AUC_{0\text{-}24h}$ of maralixibat were below the lower limit of quantification in many subjects in the 0.5 mg to 20 mg groups, and the C_{max} and $AUC_{0\text{-}24h}$ of maralixibat did not increase with the increasing number of doses.

Table 24. Pharmacokinetic parameters of maralixibat in plasma in healthy non-Japanese adults after multiple oral administration of maralixibat

Maralixibat	Measurement point	No. of subjects	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0\text{-}24h}$ (ng•h/mL)	$t_{1/2}$ (h)
0.5 mg	Day 1	16	0.036 ± 0.10	7.5 (3.0, 12.0)[b]	0.042 ± 0.13[c]	NC
	Day 14	16	NC	NC	NC	NC
1 mg	Day 1	8	NC	NC	NC [c]	NC
	Day 14	8	NC	NC	NC	NC
2.5 mg	Day 1	8	NC	NC	NC [c]	NC
	Day 14	8	NC	NC	NC	NC
5 mg	Day 1	8	NC	NC	NC [c]	NC
	Day 14	8	0.032 ± 0.091	3.0[d]	0.032 ± 0.091	NC
10 mg	Day 1	8	0.147 ± 0.158	3.5 (2.0, 6.0)[e]	0.118 ± 0.167[c]	NC
	Day 14	8	0.129 ± 0.185	2.0 (1.0, 4.0)[b]	0.248 ± 0.417	NC
20 mg [a]	Day 1	8	0.437 ± 0.167	4.0 (0.5, 12.0)	1.08 ± 0.884[c]	1.10[d]
	Day 14	8	0.376 ± 0.190	3.0 (0.5, 4.0)[f]	1.15 ± 0.779	1.28[d]
20 mg [b]	Day 1	8	0.180 ± 0.194	1.0 (0.5, 4.0)[e]	0.262 ± 0.349[c]	NC
	Day 14	8	0.310 ± 0.342	1.0 (0.5, 3.0)[g]	0.424 ± 0.408	NC
60 mg	Day 1	8	0.641 ± 0.219	3.0 (1.0, 4.0)	2.92 ± 1.87[c]	4.36, 9.50[i]
	Day 14	8	0.781 ± 0.256	3.0 (0.5, 23.5)	5.00 ± 2.20	4.17, 4.57[h]
100 mg	Day 1	8	0.805 ± 0.325	2.5 (1.0, 6.0)	3.23 ± 2.16[c]	4.98, 5.63[h]
	Day 14	8	1.15 ± 0.327	2.5 (0.5, 4.0)	4.61 ± 1.80	3.49, 5.07[h]

Mean ± SD; NC, Not calculated (below the lower limit of quantitation in many subjects in the 0.5-20 mg groups)
a) Median (minimum, maximum); b) n = 3; c) Calculated as $AUC_{0\text{-}last}$
d) Individual value in 1 subject; e) n = 4; f) n = 7; g) n = 5; h) Individual values in 2 subjects

For pharmacodynamics, Table 25 shows data on fBA excretion after multiple oral administration of placebo or maralixibat. Maralixibat increased fBA excretion compared to placebo.

[15] Maralixibat was administered just before breakfast at 0.5 mg on Days 1 to 7, 1 mg on Days 8 to 14, 2.5 mg on Days 15 to 21, and 5 mg on Days 22 to 28.
[16] The maralixibat 2.5, 5, and 20 mg groups were each consisted of 2 duplicate groups using the same dosage regimen (groups [a] and [b]).
[17] In the maralixibat 2.5 mg group [b], maralixibat 5 mg group [b], maralixibat 0.5 to 5 mg (ascending doses) group, and maralixibat 5 mg (evening) group, plasma maralixibat concentrations were not determined.

Table 25. fBA excretion (μmol)

Study drug		State at administration	No. of subjects	Day 9-14	Day 23-28
Placebo		Just before breakfast	16	155 ± 162	163 ± 182
Maralixibat	0.5 mg	Just before breakfast	16	267 ± 210	295 ± 173
	1 mg	Just before breakfast	8	643 ± 439	780 ± 671
	2.5 mg	Just before breakfast	8	478 ± 403	591 ± 281
	5 mg	Just before breakfast	8	1,105 ± 863	848 ± 684
		Evening	16	514 ± 340	593 ± 438 a)
	10 mg	Just before breakfast	8	1,237 ± 685	1,126 ± 434
	20 mg [a]	Just before breakfast	8	1,140 ± 541	1,031 ± 371
	20 mg [b]	Just before breakfast	8	666 ± 468	700 ± 511
	60 mg	Just before breakfast	8	973 ± 759	965 ± 684
	100 mg	Just before breakfast	8	2,406 ± 843	1,718 ± 889

Mean ± SD
a) n = 15

For safety, adverse events occurred in 50.0% (10 of 20) of subjects in the placebo group, 50.0% (8 of 16) of subjects in the maralixibat 0.5 mg group, 100% (8 of 8) of subjects in the 1 mg group, 22.2% (2 of 9) of subjects in the 2.5 mg group [a], 81.3% (13 of 16) of subjects in the 2.5 mg group [b], 50.0% (4 of 8) of subjects in the 5 mg group [a], 88.9% (16 of 18) of subjects in the 5 mg group [b], 62.5% (10 of 16) of subjects in the 5 mg (evening) group, 18.8% (3 of 16) of subjects in the 0.5 to 5 mg (ascending doses) group, 62.5% (5 of 8) of subjects in the 10 mg group, 75.0% (6 of 8) of subjects in the 20 mg group [a], 75.0% (6 of 8) of subjects in the 20 mg group [b], 75.0% (6 of 8) of subjects in the 60 mg group, and 75.0% (6 of 8) of subjects in the 100 mg group. Adverse drug reactions occurred in 10.0% (2 of 20) of subjects in the placebo group, 18.8% (3 of 16) of subjects in the maralixibat 0.5 mg group, 37.5% (3 of 8) of subjects in the 1 mg group, 11.1% (1 of 9) of subjects in the 2.5 mg group [a], 43.8% (7 of 16) of subjects in the 2.5 mg group [b], 33.3% (6 of 18) of subjects in the 5 mg group [b], 12.5% (2 of 16) of subjects in the 5 mg (evening) group, and 62.5% (5 of 8) of subjects in the 100 mg group. No deaths, serious adverse events, or adverse events leading to treatment discontinuation occurred.

6.2.3 Phase I study (food effect and effect on QT/QTc) (CTD 5.3.3.1-4, Study No. MRX-102 [redacted] 20[redacted] to [redacted])

A randomized single-blind study was conducted at 1 study center outside Japan to investigate the food effect on pharmacokinetics of maralixibat and its effects on QT interval (QT)/corrected QT interval (QTc) in healthy non-Japanese adults (target sample size 36 subjects, 12 each in 3 cohorts) after a single oral administration of maralixibat.

This study consisted of 3 cohorts. Both Cohort 1 and Cohort 2 had 2 periods, the fasted- and fed-state administration periods, which were separated by a ≥3-day drug-free period; and Cohort 3 had only 1 period, the fasted-state administration period.

In each period of Cohort 1, a single dose of placebo was orally administered in the fasted state before administration of maralixibat (Day −1), and then a single dose of maralixibat 30 mg was orally administered in the fasted or fed state (Day 1). In each period of Cohort 2, a single dose of placebo was orally administered in the fasted state before administration of maralixibat (Day −1), and then a single dose of maralixibat 45 mg was orally administered in the fasted or fed state (Day 1). In Cohort 3, a single dose of placebo was orally administered in the fasted state before administration of maralixibat

(Day −1), and then a single dose of maralixibat 100 mg was orally administered in the fasted state (Day 1).

All of 36 subjects who received maralixibat[18)] were included in the safety and pharmacokinetic analysis populations.

Table 26 shows pharmacokinetic parameters of maralixibat in plasma after a single oral administration of maralixibat in the fasted or fed state. The geometric mean ratios [90% confidence interval (CI)] of C_{max} and $AUC_{0\text{-last}}$ after administration in the fasted state to those after administration in the fed state were 26.8 [20.2, 35.6] and 14.2 [5.80, 34.7] in the maralixibat 30 mg group and 35.2 [27.8, 44.6] and 30.7 [18.2, 51.9] in the 45 mg group, demonstrating the food effect on pharmacokinetics of maralixibat.

Table 26. Pharmacokinetic parameters of maralixibat in plasma in healthy non-Japanese adults after single oral administration of maralixibat in the fasted or fed state

Maralixibat	State at administration	No. of subjects	C_{max} (ng/mL)	t_{max}[a)] (h)	$AUC_{0\text{-last}}$ (ng•h/mL)
30 mg	Fasted	12	1.65 ± 1.10	0.75 (0.50, 2.0)	3.43 ± 2.13
	Fed	8	0.477 ± 0.241	2.5 (0.50, 6.0)	0.788 ± 0.613
45 mg	Fasted	12	1.66 ± 0.630	0.50 (0.50, 2.6)	4.12 ± 2.07
	Fed	9	0.616 ± 0.286	3.0 (0.50, 4.0)	1.92 ± 1.81
100 mg	Fasted	12	3.39 ± 1.60	0.75 (0.50, 3.0)	12.5 ± 7.54

Mean ± SD
a) Median (minimum, maximum)

For QT/QTc, the maximum upper limit of one-sided 95% CI of a difference in change in QTcF from baseline after administration in the fasted state between maralixibat and placebo (Day −1) (ΔΔFridericia-corrected QT interval [QTcF]) was 5.63 ms at 30 mg, 10.7 ms at 45 mg, and 12.71 ms at 100 mg. Although the maximum upper limits of 95% CI in the maralixibat 45 and 100 mg groups exceeded 10 ms, the applicant explained that maralixibat is unlikely to pose a risk of prolongation of QT/QTc because clinical study results in patients with ALGS and those with PFIC did not suggest a risk of prolongation of QT/QTc or related safety risk.

For safety, adverse events occurred in 58.3% (7 of 12) of subjects during administration in the fasted state and 100% (12 of 12) of subjects during administration in the fed state in the maralixibat 30 mg group, 91.7% (11 of 12) of subjects and 100% (12 of 12) of subjects in the 45 mg group, and 83.3% (10 of 12) of subjects during administration in the fasted state in the 100 mg group. Except for 1 event during administration in the fasted state in the maralixibat 30 mg group, all the events were classified as adverse drug reactions. No deaths, serious adverse events, or adverse events leading to treatment discontinuation occurred.

6.2.4 Phase I study (mass balance study) (CTD 5.3.3.1-2, Study No. NB4-02-06-004, [redacted] 20[redacted])

An open-label study was conducted at 1 study center outside Japan to investigate the mass balance of ^{14}C-maralixibat orally administered as a single dose to healthy non-Japanese adults (target sample size, 8 subjects).

18) In a total of 7 subjects who received maralixibat in the fed state (4 in the maralixibat 30 mg group, 3 in the maralixibat 45 mg group), calculation of pharmacokinetic parameters of maralixibat in plasma was not possible.

A single dose of ^{14}C-maralixibat 5 mg was orally administered.

All of 8 subjects who received the study drug were included in the pharmacokinetic analysis population.

Until 72 hours after administration of ^{14}C-maralixibat, the radioactivity detected in plasma and whole blood was below the lower limit of quantification.

Of the radioactivity administered, 72.5% was excreted into feces by 216 hours post-dose, and 0.066% was excreted into urine by 168 hours post-dose. In the feces up to 216 hours post-dose, unchanged maralixibat was mainly detected (accounting for 94.4% of the total radioactivity in the feces).

6.2.5 Foreign phase II study (CTD 5.3.5.1-1, Study No. LUM001-304, October 2014 to May 2020)

Multiple doses of maralixibat were orally administered to non-Japanese patients with ALGS aged 1 to 18 years to investigate the pharmacokinetics [for outline of the study and results on the efficacy and safety, see Section 7.1.1].

During an open-label run-in period of 18 weeks, maralixibat was orally administered once daily at doses increased up to 400 μg/kg/day or 20 mg/day over a period of 6 weeks and then continued for 12 weeks.

A pharmacokinetic analysis was not feasible because of low plasma maralixibat concentrations after multiple doses of maralixibat. The maximum plasma maralixibat concentration was 5.93 ng/mL after administration at 400 μg/kg/day at Week 12.

6.2.6 Japanese phase III study (CTD 5.3.5.2-5, Study No. TAK-625-3001, ongoing since January 2023, data cut-off on [redacted] 20[redacted])

Multiple doses of maralixibat were orally administered to Japanese patients with ALGS aged ≥1 month to investigate the pharmacokinetics [for outline of the study and results on the efficacy and safety, see Section 7.2.1].

During an dose-escalation period of 2 weeks, maralixibat was orally administered at 200 μg/kg/day once daily for the first week and then at doses ascending to 400 μg/kg/day for the second week.[19)] During a stable-dosing period of 46 weeks, maralixibat was continued at the same dose as that at the end of the dose-escalation period, and during a long-term follow-up period, maralixibat was continued at the same dose as that at the end of the stable-dosing period.

After multiple oral administration of maralixibat, measured plasma maralixibat concentrations before administration at Week 12 were below the lower limit of quantification in all subjects (n = 6), and those at 4 hours post-dose at Week 12 were below the lower limit of quantification in 2 of 7 subjects. The maximum plasma maralixibat concentration 4 hours post-dose at Week 12 was 3.630 ng/mL in the overall population and 1.140 ng/mL in the ≥1-year old population. The mean plasma maralixibat

[19)] In a subject who experienced moderate or severe treatment-emergent maralixibat-related gastrointestinal tract toxicity at 400 μg/kg/day, the dose reduction to 200 μg/kg/day was allowed.

concentration[20)] 4 hours post-dose at Week 12 was 0.961 ng/mL in the overall population and 0.516 ng/mL in the ≥1-year old population. The plasma maralixibat concentrations in Japanese patients with ALGS did not clearly differ from those in non-Japanese patients with ALGS [see Section 6.2.5].

6.2.7 Foreign phase III study (CTD 5.3.5.1-4, Study No. MRX-502 July 2019 to September 2022)

Multiple doses of maralixibat were orally administered to non-Japanese patients with PFIC aged ≥1 year to investigate the pharmacokinetics [for outline of the study and results on the efficacy and safety, see Section 7.2.2].

Maralixibat was started at 150 μg/kg on a twice-daily regimen, increased up to 600 μg/kg on the same regimen over 4 to 6 weeks, and continued for the subsequent 20 to 22 weeks or longer.

Pharmacokinetic analysis showed that after multiple oral administration of maralixibat, plasma maralixibat concentrations were 0 to 6.130 ng/mL. The mean plasma maralixibat concentration 2.5 hours post-dose at Week 26 was 0.520 ng/mL, and measured plasma maralixibat concentrations were below the lower limit of quantification in 15 of 35 patients.

6.2.8 Japanese phase III study (CTD 5.3.5.2-9, Study No. TAK-625-3002, ongoing since January 2023, data cut-off in [redacted])

Multiple doses of maralixibat were orally administered to Japanese patients with PFIC aged ≥1 month to investigate the pharmacokinetics [for outline of the study and results on the efficacy and safety, see Section 7.2.3].

Maralixibat was started at 150 μg/kg on a twice-daily regimen, increased up to 600 μg/kg on the same regimen over 4 to 6 weeks, and continued for the subsequent 42 to 44 weeks or longer.

Pharmacokinetic analysis showed that after multiple oral administration of maralixibat, measured plasma maralixibat concentrations before administration at Week 10 were below the lower limit of quantification in 4 of 5 patients, and those 2.5 hours post-dose at Week 10 were below the lower limit of quantification in 2 of 5 patients. The maximum plasma maralixibat concentration 2.5 hours post-dose at Week 10 of maralixibat treatment was 1.10 ng/mL, and the mean plasma maralixibat concentration[20)] 2.5 hours post-dose at Week 12 was 0.386 ng/mL. Plasma maralixibat concentrations in Japanese patients with PFIC did not clearly differ from those in non-Japanese patients with PFIC [see Section 6.2.7].

6.2.9 Phase I study (study for drug-interaction with simvastatin and lovastatin) (CTD 5.3.3.4-1, Study No. NB4-01-06-019, [redacted])

An open-label, randomized, 2-treatment, 4-period crossover study was conducted at 1 study center outside Japan to investigate effects of maralixibat on pharmacokinetics of simvastatin and lovastatin (substrate of CYP3A) in healthy non-Japanese adults (target sample size, 24 subjects).

[20)] Measured plasma maralixibat concentrations below the lower limit of quantification were handled as 0 ng/mL in the calculation.

In this study, the following 4 dosage regimens were planned, and subjects received treatment in the order of ABCD or CDAB. The second and third treatment periods were separated by a 7-day washout period.

- A: Simvastatin 20 mg is orally administered once daily at evening meal time for 5 days.
- B: Maralixibat 5 mg is orally administered before breakfast and simvastatin 20 mg at evening meal time, once daily for 5 days.
- C: Lovastatin 20 mg is orally administered once daily at evening meal time for 5 days.
- D: Maralixibat 5 mg is orally administered before breakfast and lovastatin 20 mg at evening meal time, once daily for 5 days.

Table 27 shows the geometric mean ratios of C_{max} and $AUC_{0\text{-}24h}$ of simvastatin and its active metabolite, β-hydroxysimvastatin, as well as lovastatin and its active metabolite, β-hydroxylovastatin, after administration of either of the drugs in combination with maralixibat to those after administration of either of the drugs alone. Pharmacokinetic parameters of simvastatin and lovastatin as well as their active metabolites in plasma after administration of either of the drugs in combination with maralixibat were not clearly different from those after administration of either of the drugs alone.

Table 27. Geometric mean ratio of pharmacokinetic parameters of simvastatin, β-hydroxysimvastatin, lovastatin, and β-hydroxylovastatin in plasma after administration of either of the drugs in combination with maralixibat to those after administration of either of the drugs alone

Maralixibat	Concomitant drug (oral)	Analyte	No. of subjects	C_{max}	$AUC_{0\text{-}24h}$
5 mg	Simvastatin	Simvastatin	24	0.90 [0.77, 1.05]	0.83 [0.75, 0.91]
		β-hydroxysimvastatin	24	0.95 [0.85, 1.07]	0.96 [0.83, 1.11][a)]
	Lovastatin	Lovastatin	24	0.93 [0.78, 1.10]	0.97 [0.88, 1.08]
		β-hydroxylovastatin	24	0.99 [0.86, 1.15]	1.11 [0.97, 1.26]

Geometric mean ratio [90% CI]
a) n = 19

6.2.10 Phase I study (study for drug-interaction with atorvastatin) (CTD 5.3.3.4-2, Study No. NB4-02-06-020, [redacted] to [redacted] 20[redacted])

An open-label, randomized, 2-treatment, 4-period crossover study was conducted at 1 study center outside Japan to investigate effects of maralixibat on pharmacokinetics of atorvastatin (substrate of CYP3A) in healthy non-Japanese adults (target sample size, 24 subjects).

In this study, the following 4 dosage regimens were planned, and subjects received treatment in the order of ABCD or CDAB. The second and third treatment periods were separated by a 7-day washout period.

- A: Atorvastatin 20 mg is orally administered once daily before breakfast for 5 days.
- B: Maralixibat 5 mg and atorvastatin 20 mg are orally administered once daily before breakfast for 5 days.
- C: Atorvastatin 20 mg is orally administered once daily before an evening meal for 5 days.
- D: Maralixibat 5 mg is orally administered before breakfast and atorvastatin 20 mg before an evening meal, once daily for 5 days.

Table 28 shows the geometric mean ratios of C_{max} and $AUC_{0\text{-}24h}$ of atorvastatin as well as its active metabolites, *o*-hydroxyatorvastatin and *p*-hydroxyatorvastatin, after administration of atorvastatin in combination with maralixibat to those after administration of atorvastatin alone. CYP3A4-mediated drug-interactions are reviewed in Section 6.R.2.

Table 28. Geometric mean ratios of pharmacokinetic parameters of atorvastatin, *o*-hydroxyatorvastatin, and *p*-hydroxyatorvastatin in plasma after administration of atorvastatin in combination with maralixibat to those after administration of atorvastatin alone

Maralixibat	Concomitant drug (oral)	Analyte	No. of subjects	C_{max}	$AUC_{0\text{-}24h}$
5 mg	Atorvastatin (administered before breakfast)	Atorvastatin	19	0.95 [0.81, 1.12]	0.83 [0.77, 0.89]
		o-hydroxyatorvastatin	19	0.88 [0.73, 1.07]	0.90 [0.81, 0.99]
		p-hydroxyatorvastatin	13	0.88 [0.76, 1.02]	0.89 [0.69, 1.16]
	Atorvastatin (administered before an evening meal)	Atorvastatin	20	0.86 [0.61, 1.23]	0.86 [0.66, 1.13]
		o-hydroxyatorvastatin	20	1.02 [0.82, 1.27]	1.08 [0.98, 1.19]
		p-hydroxyatorvastatin	16	1.13 [0.90, 1.42]	1.77 [1.22, 2.57]

Geometric mean ratio [90% CI]

6.R Outline of the review conducted by PMDA

PMDA's view:

The submitted data show that the pharmacokinetics of maralixibat has been appropriately evaluated in general. Based on results from the review in Sections 6.R.1 to 6.R.3, maralixibat should be administered before a meal, and information on its use in combination with drugs acting as a substrate of OATP2B1 should be included in the package insert.

6.R.1 Timing of administration

The applicant's explanation about timing of administration of maralixibat:

The C_{max} and $AUC_{0\text{-}last}$ of maralixibat after a single oral administration of maralixibat 30 or 45 mg in the fed state decreased by 64.8% to 73.2% and 69.3% to 85.8%, respectively, compared to those in the fasted state, indicating that food intake affects the pharmacokinetics of maralixibat [see Section 6.2.3]. In Studies LUM001-304, TAK-625-3001, MRX-502, and TAK-625-3002 defined as pivotal studies, maralixibat was administered at least or approximately 30 minutes before a meal with expectation that maralixibat, an inhibitor against IBAT, present in the gastrointestinal tract before release of bile induced by food would exert a more definitive pharmacological effect.

On the other hand, in Study NB4-02-06-002, a single dose of maralixibat was orally administered in the fasted state or just before a meal in healthy non-Japanese adults, and increased fBA excretion was also observed even with administration just before a meal [see Section 6.2.1], indicating that administration of maralixibat with food would not lead to the decreased efficacy. In addition, pathological conditions of ALGS and PFIC are not dependent on the age, and inhibitory action of maralixibat against IBAT is unlikely to differ between healthy adults and patients with ALGS or PFIC. For the above and other reasons, maralixibat administered to pediatric and adult patients with ALGS or PFIC even within 30 minutes before a meal or with food was expected to be effective in decreasing sBA concentrations and relieving pruritus.

Then, the safety data were analyzed by timing of maralixibat administration. The incidence of gastrointestinal adverse events[21)] was 33.3% (2 of 6 subjects) in the maralixibat 10 mg (just before breakfast) group and 0.0% in the maralixibat 10 mg (in the fasted state) group in Study NB4-02-06-002, and 50.0% (6 of 12 subjects) during administration in the fasted-state and 100% (12 of 12 subjects)

21) Adverse events coded to MedDRA SOC "Gastrointestinal disorders"

during administration in the fed-state in the maralixibat 30 mg group, and 91.7% (11 of 12 subjects) during administration in the fasted-state and 100% (12 of 12 subjects) during administration in the fed-state in the maralixibat 45 mg group in Study MRX-102. The incidence of gastrointestinal adverse events tended to be slightly higher with administration of maralixibat just before or after a meal than with the administration in the fasted state, but no serious adverse events. The safety and tolerability of maralixibat administered either just before or after a meal were favorable. Maralixibat administered either within 30 minutes before a meal or with food is unlikely to raise considerable problems with the safety of maralixibat, compared to maralixibat administered approximately 30 minutes before a meal.

Based on the above, maralixibat administered within 30 minutes before a meal or with food can be expected to have the efficacy as with maralixibat administered at least or approximately 30 minutes before a meal and is unlikely to raise problems with the safety. Therefore, maralixibat should be administered within 30 minutes before a meal or with food in pediatric and adult patients with ALGS or PFIC.

PMDA's view:
The protocols of the main clinical studies in patients with ALGS or PFIC specified that maralixibat was to be administered at least or approximately 30 minutes before a meal, with expectation that maralixibat present in the gastrointestinal tract before release of bile induced by food would exert a more definitive pharmacological effect. Consequently, the studies demonstrated the efficacy and safety of maralixibat [see Sections 7.R.1 and 7.R.2]. Since the biokinetics of bile acids differ between patients with cholestasis and healthy adults, the efficacy and safety of maralixibat in patients with ALGS or PFIC should not be extrapolated from data on fBA excretion in healthy adults who received maralixibat. In conclusion, maralixibat should be administered to patients with ALGS or PFIC before a meal as specified in the protocols of the clinical studies as pivotal studies.

6.R.2 CYP3A4-mediated drug-interactions

The applicant's explanation about interactions of maralixibat with drugs acting as a substrate of CYP3A:
In an *in vitro* study, maralixibat inhibited CYP3A4 [see Section 6.1.1.6]. In response to this finding, effects of concomitant maralixibat 5 mg on the pharmacokinetics of simvastatin, lovastatin, and atorvastatin (all acting as a substrate of CYP3A) were investigated in healthy non-Japanese adults, and concomitant maralixibat did not increase the exposure to these drugs [see Sections 6.2.9 and 6.2.10]. However, the applicant considered that the concerned finding obtained in a study where the dose of maralixibat was 5 mg was not enough to explain the effect of maralixibat at the maximum human dose (the estimated maximum human dosages of maralixibat in patients with ALGS and those with PFIC were 28 mg and 42 mg, respectively) on profiles of the substrates of CYP3A. Then, an effect of maralixibat orally administered at the maximum human dose in combination with midazolam on the pharmacokinetics of midazolam (substrate of CYP3A) was analyzed using a physiologically based pharmacokinetic (PBPK) model.[22)] Using the fraction unbound in gut ($f_{u,gut}$) of 0.096[23)] for maralixibat, which was predicted based on physical properties and tissue parameters of maralixibat, the AUC_{inf} and

[22)] Simcyp version 19 was used in the analysis using the PBPK model. For the distribution model and absorption model of maralixibat, the Minimal PBPK model and the Advanced dissolution, absorption and metabolism (ADAM) model were selected, respectively.
[23)] Predicted based on the report by Rodgers, et.al. (*J Pharm Sci.* 2006;95:1238-57).

C_{max} of midazolam orally administered at 5 mg in combination with maralixibat 600 μg/kg twice daily were inferred to be 1.101 and 1.098 times, respectively, those of midazolam alone. Using the $f_{u,gut}$ of 1.0 for maralixibat, the AUC_{inf} and C_{max} of midazolam orally administered at 5 mg in combination with maralixibat 600 μg/kg twice daily were inferred to be 1.262 and 1.266 times, respectively, those of midazolam alone. Although a method to determine $f_{u,gut}$ is not established, the $f_{u,gut}$ of 1.0 is unlikely in clinical settings in view of the unbound fractions of maralixibat in plasma ($f_{u,plasma}$ = 0.093) and in a microsome reaction mixture ($f_{u,mic}$ for inhibition constant [K_i] = 0.022 and $f_{u,mic}$ for inhibitor concentration at 50% of maximum inhibition rate [K_I] = 0.005).

In Studies LUM001-304 and TAK-625-3001 as pivotal studies, some enrolled patients received maralixibat concomitantly with drugs acting as a substrate of CYP3A but they did not tend to pose safety problems compared to those who received maralixibat without such concomitant drugs.

Based on the above, maralixibat when administered at a clinical dose is unlikely to cause clinically relevant CYP3A-mediated drug-interactions, and thus advising caution about coadministration of maralixibat with drugs acting as a substrate of CYP3A is not necessary.

Results of the PBPK model analysis and the applicant's explanation do not indicate that coadministration of maralixibat at the maximum human dose with drugs acting as a substrate of CYP3A could increase concentrations of the drugs acting as a substrate of CYP3A, causing clinical problems. At present, PMDA considers it unnecessary to advise caution about coadministration of maralixibat with drugs acting as a substrate of CYP3A.

6.R.3 OATP2B1-mediated drug-interactions

The applicant's explanation about coadministration of maralixibat with drugs acting as a substrate of OATP2B1:

Of transporters potently inhibited by maralixibat in an *in vitro* study, only OATP2B1 is known to be expressed on the gastrointestinal tract (*Biochem Pharmacol.* 2021;188:114534). The inhibition against OATP2B1 in the gastrointestinal tract was investigated as done for P-gp and BCRP expressed on the gastrointestinal tract with reference to the "Guideline on Drug Interaction for Drug Development and Appropriate Provision of Information" (PSEHB/PED Notification No. 0723-4 dated July 23, 2018). The predicted maximum concentration of maralixibat in the gastrointestinal tract at the recommended clinical dose (236 μmol/L) exceeded 10 times the IC_{50} (1.02 μmol/L) of maralixibat against OATP2B1, suggesting that maralixibat might affect the absorption of drugs acting as a substrate of OATP2B1. However, there are no drugs known to act as a selective substrate of OATP2B1 at present and administration of maralixibat 5 mg did not clearly increase the exposure to atorvastatin (substrate of OATP2B1) in healthy non-Japanese adults [see Section 6.2.10], thus coadministration of maralixibat with drugs acting as a substrate of OATP2B1 is considered unlikely to cause clinically relevant drug-interaction. Furthermore, in Studies LUM001-304, TAK-625-3001, and TAK-625-3002 as pivotal studies, 6 patients received maralixibat concomitantly with drugs[24)] acting as a substrate of OATP2B1, of which doses remained the same without increasing the dose during the treatment period.

[24)] Atenolol, atorvastatin, fexofenadine, montelukast, and pitavastatin were concomitantly used.

Based on the above, maralixibat is unlikely to decrease the exposure to drugs acting as a substrate of OATP2B1, clearly affecting the efficacy, and thus advising caution about coadministration of maralixibat with drugs acting as a substrate of OATP2B1 is not necessary.

PMDA's view:
In Study NB4-02-06-020, the effect of maralixibat on the pharmacokinetics of atorvastatin was investigated, but the dose of maralixibat was 5 mg, which was lower than the recommended clinical dose. Therefore, the concerned study should not be used to evaluate the inhibitory action of maralixibat against OATP2B1. In view of the predicted maximum concentration in the gastrointestinal tract at the recommended clinical dose of maralixibat and the IC_{50} against OATP2B1, the possibility cannot be denied that maralixibat at the recommended clinical dose may decrease exposure to a drug potentially acting as a substrate of OATP2B1 and thereby attenuate the efficacy of the concomitant drug. Nevertheless, drugs shown to be absorbed from the gastrointestinal tract via OATP2B1 as a selective substrate are unclear at present, and the clinical studies as pivotal studies do not show that maralixibat clearly affected the efficacy of drugs acting as a substrate of OATP2B1. Based on the above, advising caution about coadministration of maralixibat with drugs acting as a substrate of OATP2B1 is not necessary but the finding of inhibition of OATP2B1 by maralixibat should be included in the package insert to provide the information.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results from 4 Japanese and foreign clinical studies shown in Table 29.

Table 29. Summary of clinical studies for efficacy and safety

Region	Study	Phase	Patient population	No. of patients	Dosage regimen	Main efficacy endpoints
Foreign	LUM001 -304	II	Patients with ALGS aged ≥12 months and ≤18 years	Placebo: 16 Maralixibat: 13	Run-in period: Maralixibat is orally administered QD at ascending doses from an initial 14 μg/kg up to 400 μg/kg at maximum over a period of 6 weeks and then continued at the same dose as that at Week 6 for 12 weeks. RWD period: Placebo or maralixibat (at the same dose as that at the end of the run-in period) is orally administered QD for 4 weeks. Stable-dosing period: Placebo group in the RWD period: Maralixibat is orally administered QD at ascending doses as done during the run-in period and then at up to 400 μg/kg for 26 weeks. Maralixibat group in the RWD period: Maralixibat is orally administered QD for 26 weeks at the same dose as that at the end of the RWD period. Long-term treatment period (Period 1): Maralixibat is orally administered QD at 400 μg/kg (or lower but maximum tolerated dose). Long-term treatment period (Period 2): Maralixibat is orally administered QD at 400 μg/kg (or lower but maximum tolerated dose) (in case of inadequate response, the dose may be increased up to 400 μg/kg BID).	Change in fasting sBA concentration from Week 18 (baseline in the RWD period) to Week 22
Japan	TAK-625 -3001	III	Patients with ALGS aged ≥1 month and weighing ≥3.0 kg	Maralixibat: 7	Dose-escalation period: Maralixibat is orally administered QD at 200 μg/kg for 1 week and then at 400 μg/kg for 1 week (or 200 μg/kg for 1 week at the discretion of the investigator). Stable-dosing period: Maralixibat is orally administered QD at 200 or 400 μg/kg (at the same dose as that at the end of the dose-escalation period) for 46 weeks. Long-term follow-up period: Maralixibat is orally administered QD at 200 or 400 μg/kg (at the same dose as that at the end of the stable-dosing period).	Change in fasting sBA concentration from Week 18 to Week 22
Foreign	MRX -502	III	Patients with PFIC aged ≥12 months and <18 years	Placebo: 46 Maralixibat: 47	Dose-escalation period: Placebo group: Placebo is orally administered BID for 4-6 weeks. Maralixibat group: Maralixibat is orally administered BID for up to 6 weeks at ascending doses from an initial 150 μg/kg to 600 μg/kg at maximum over a period of 4-6 weeks. Stable-dosing period: Placebo or maralixibat (at the same dose as that at the end of the dose-escalation period) is orally administered BID for 20-22 weeks.	Change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26
Japan	TAK-625 -3002	III	Patients with PFIC aged ≥1 month and weighing ≥3.0 kg	Maralixibat: 5	Dose-escalation period: Maralixibat is orally administered BID for up to 6 weeks at ascending doses from an initial 150 μg/kg to 600 μg/kg at maximum over a period of 4-6 weeks. Stable-dosing period: Maralixibat (at the same dose as that at the end of the dose-escalation period) is orally administered BID for 42-44 weeks. Long-term follow-up period: Maralixibat (at the same dose as that of the stable-dosing period) is orally administered BID.	Change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26

The itch reported outcome (ItchRO) score used as the efficacy endpoint in the clinical studies in the submitted data (*Patient.* 2018;11:69-82, Table 30) is a rating scale developed to assess pruritus in pediatric patients with cholestatic liver disease. Table 31 shows the ItchRO scoring method.

Table 30. ItchRO score (Japanese version)

ItchRO (Obs) questionnaire[a)]		Response and score
Morning	(severity of pruritus) Based on observations or what your child told you about his/her itching, how severe were your child's itch-related symptoms (rubbing, scratching, skin damage, sleep disturbances, or irritability) from when he/she went to bed last night until he/she woke up this morning?	None observed or reported: 0 points Mild: 1 point Moderate: 2 points Severe: 3 points Very severe: 4 points I don't know[c)]: Handled as missing data
	(frequency of pruritus) While you were observing your child from when he/she went to bed last night until he/she woke up this morning, how much of the time was your child rubbing or scratching?	None: 0 points A little bit of the time: 1 point Some of the time: 2 points Most of the time: 3 points Almost all of the time/constantly: 4 points I don't know[c)]: Handled as missing data
Evening	(severity of pruritus) Based on observations or what your child told you about his/her itching, how severe were your child's itch-related symptoms (rubbing, scratching, skin damage, sleep disturbances, or irritability) from the time he/she woke up this morning until he/she went to bed?	None observed or reported: 0 points Mild: 1 point Moderate: 2 points Severe: 3 points Very severe: 4 points I don't know[c)]: Handled as missing data
	(frequency of pruritus) While you were observing your child from the time he/she woke up this morning until he/she went to bed, how much of the time was your child rubbing or scratching?	None: 0 points A little bit of the time: 1 point Some of the time: 2 points Most of the time: 3 points Almost all of the time/constantly: 4 points I don't know[c)]: Handled as missing data
ItchRO (Pt) questionnaire[b)]		Response and score
Morning	(severity of pruritus) How itchy did you feel last night after you went to bed until you woke up this morning?	I didn't feel itchy: 0 points I felt a little bit itchy: 1 point I felt pretty itchy: 2 points I felt very itchy: 3 points I felt very, very itchy: 4 points
	(frequency of pruritus) *Performed only for patients with PFIC How much of the night did feeling itchy make you rub or scratch?	None at all: 0 points Sometimes during nighttime: 1 point Approximately half of nighttime: 2 points Almost always during nighttime: 3 points Always throughout nighttime: 4 points
Evening	(severity of pruritus) How itchy were you all day today from the time when you woke up until now?	I didn't feel itchy: 0 points I felt a little bit itchy: 1 point I felt pretty itchy: 2 points I felt very itchy: 3 points I felt very, very itchy: 4 points
	(frequency of pruritus) *Performed only for patients with PFIC How much of today did feeling itchy make you rub or scratch?	None at all: 0 points Sometimes during daytime: 1 point Approximately half of daytime: 2 points Almost always during daytime: 3 points Always throughout daytime: 4 points

a) Questionnaire entered by the parent or caregiver
b) Questionnaire entered by the patient him/herself
c) In Study LUM001-304, the old version before addition of this response option was used, and in Study TAK-625-3001, the same old version was used for comparison with Study LUM001-304.

Table 31. Assessment items using ItchRO score

Weekly average morning severity score	Average of morning severity scores of pruritus on 7 days of the 1 week before visit
Weekly average evening severity score	Average of evening severity scores of pruritus on 7 days of the 1 week before visit
Weekly average severity (daily maximum) score	Average of the daily maximum scores (the largest of the morning and evening scores each day) on 7 days of the 1 week before visit
4-week average severity score	Average of severity scores of pruritus on 28 days before visit (as defined above)

The average was calculated by dividing the sum of daily scores (on 7 days or 28 days) by the number of days with ItchRO-based itchy rating completed.

7.1 Phase II study

7.1.1 Foreign phase II study in patients with ALGS (CTD 5.3.5.1-1, Study No. LUM001-304, October 2014 to May 2020)

A multi-center, placebo-controlled, randomized withdrawal (RWD) study was conducted at 9 study centers in 6 foreign countries to investigate the efficacy and safety of maralixibat in patients with ALGS (Table 32) (target sample size, 30 subjects[25)]).

Table 32. Main inclusion criteria and exclusion criteria

Main inclusion criteria
- Aged ≥12 months and ≤18 years
- Diagnosis of ALGS based on any of Diagnostic criteria 1 to 7 below

	Family history of ALGS[1)]	Interlobular bile duct paucity as a pathological finding in the liver	*JAGGED1* or *NOTCH2* gene mutation	Major clinical criteria or features[2)]
1	Present or absent	Present	Identified[3)]	Any or no features
2	None (proband)	Absent or unknown	Identified	1 or more features
3	None (proband)	Present	Not identified	3 or more features
4	None (proband)	Absent or unknown	Not identified	4 or more features
5	Present	Absent or unknown	Identified	Any or no features
6	Present	Present	Not identified	1 or more features
7	Present	Absent or unknown	Not identified	2 or more features

1) Presence of a first-degree relative with ALGS was deemed as "Present for family history."
2) Cholestasis; ALGS-consistent cardiac, renal, vascular, ocular, or skeletal involvement; or characteristic Alagille facies.
3) *JAGGED1* or *NOTCH2* mutation identified by gene test

- One or more of the following findings indicative of cholestasis:
  a) Total sBA concentration >3 × the upper limit of normal (ULN) for age
  b) Direct bilirubin >1 mg/dL
  c) Fat-soluble vitamin deficiency otherwise unexplainable
  d) GGT >3 × ULN for age
  e) Intractable pruritus explainable only by liver disease
- Average ItchRO daily score[a)] for 2 weeks before enrollment >2

Main exclusion criteria
- Chronic diarrhea requiring ongoing intravenous fluid or nutritional intervention
- Prior surgical interruption of the enterohepatic circulation
- Prior liver transplant
- Decompensated hepatic cirrhosis (ALT >15 × ULN, prothrombin-time international normalized ratio [PT-INR] >1.5 [unresponsive to vitamin K supplementation], albumin <3.0 g/dL, clinically significant ascites, variceal haemorrhage, or history or presence of hepatic encephalopathy)
- History or presence of other liver diseases
- History or presence of the other diseases or pathological conditions that are known to inhibit absorption, distribution, metabolism, or excretion of drugs in the intestinal tract, including metabolism of bile salt (e.g., inflammatory bowel disease)
- History or presence of gallstones or kidney stones

a) A daily score is the higher of the scores for the morning and evening ItchRO. The average daily score is the sum of all daily scores divided by the number of days the ItchRO was completed.

This study consisted of the run-in period (18 weeks), RWD period (4 weeks), and stable-dosing period (26 weeks), and after completion of the stable-dosing period, subjects were allowed to enter the long-term treatment period (Period 1, 52 weeks; Period 2, until enrollment of the subject in another study of maralixibat, launch of maralixibat, or termination of development of maralixibat).

During the run-in period, maralixibat was orally administered QD at ascending doses from an initial 14 μg/kg to, as long as tolerated, 35, 70, 140, 280, and 400 μg/kg in this order for 1 week for each dose in an open-label manner and then, at Week 7 and afterward, at the same dose as that at Week 6 (400 μg/kg

25) The target sample size was determined based on the feasibility but not test of hypothesis.

or lower but maximum tolerated dose) for 12 weeks. During the RWD period, subjects were randomized in a 1:1 ratio to orally receive placebo or maralixibat at the same dose as that at the end of the run-in period QD for 4 weeks in a double-blind manner. During the stable-dosing period of 26 weeks, subjects who had received placebo during the RWD period received maralixibat at ascending doses as done during the run-in period in an open-label manner, and subjects who had received maralixibat during the RWD period continued maralixibat at the same dose as that at the end of the RWD period in an open-label manner. During Period 1 of the long-term treatment period, maralixibat was continued at 400 μg/kg or lower but maximum tolerated dose[26)] in an open-label manner, and during Period 2, the increased dose of maralixibat up to 800 μg/kg/day (400 μg/kg BID)[27)] was allowed in case of inadequate response and acceptable safety.

All of 31 subjects enrolled received the study drug and were included in the intent-to-treat (ITT) population and the safety analysis set. Of 29 subjects who had completed the run-in period and had been randomized (16 in the placebo group, 13 in the maralixibat group), 15 subjects (10 in the placebo group, 5 in the maralixibat group) showed a ≥50% decrease in sBA concentration from baseline in the run-in period to Week 12 or Week 18 and were included in the modified intent-to-treat (MITT) population and the primary efficacy analysis population. All of 29 subjects who had entered the RWD period entered the stable-dosing period, and then 23 subjects entered the long-term treatment period. Discontinuation (number of subjects by reason for discontinuation) occurred in 2 subjects during the run-in period (adverse events in 2 subjects), 6 subjects during the stable-dosing period (consent withdrawal in 5 subjects and adverse events in 1 subject), and 9 subjects during the long-term treatment period (consent withdrawal in 4 subjects, adverse events in 3 subjects, investigator's decision in 1 subject, and request from the parent in 1 subject), and none of the subjects discontinued during the RWD period.

The primary efficacy endpoint was a change in fasting sBA concentration from Week 18 (baseline in the RWD period) to Week 22, and results on this endpoint are shown in Table 33.

Table 33. Change in fasting sBA concentration (μmol/L) from Week 18 to Week 22 (MITT population, Observed cases [OC])

	Placebo (n = 10)	Maralixibat (n = 5)	Difference between groups (maralixibat - placebo)
Week 18 (baseline in the RWD period)	123.68 ± 89.54 (10)	117.12 ± 102.97 (5)	
Week 22	219.97 ± 180.82 (10)	93.90 ± 76.51 (5)	
Change from Week 18 to Week 22[a)]	95.55 [29.12, 161.97]	-21.73 [-115.69, 72.23]	-117.28 [-232.38, -2.18]

Mean ± SD (number of subjects); Change is expressed as least squares mean [95% CI].
a) Analysis of covariance using the dose group and fasting sBA concentration at Week 18 as explanation variables

Table 34 shows the summary of incidences of adverse events. No death occurred during any period.

[26)] In cases where maralixibat was not interrupted or interrupted for <7 days during a period from the end of the stable-dosing period to the entry of the long-term treatment period, the same dose as that at the end of the stable-dosing period was continued; or in cases where maralixibat was interrupted for ≥7 days, the dose was increased from an initial 35 μg/kg QD up to 400 μg/kg QD to continue the maximum tolerated dose.

[27)] The pre-increase dose (400 μg/kg or lower but maximum tolerated dose) was given as a morning dose, and then an afternoon dose was added to increase the dose. The afternoon dose was continued for 4 weeks, starting at 140 μg/kg, and then, if tolerated, increased to 400 μg/kg (800 μg/kg/day at maximum).

Adverse drug reactions reported by ≥2 subjects during the run-in period were abdominal pain (9 subjects), diarrhoea (6 subjects), and vomiting (3 subjects). Serious adverse events occurred in 4 subjects (abdominal pain, rotavirus infection, viral pharyngitis, extradural haematoma, subdural haematoma, and seizure in 1 subject each [some subjects had multiple events], but no serious adverse drug reactions occurred. Adverse events leading to treatment discontinuation occurred in 2 subjects (extradural haematoma, subdural haematoma, and Staphylococcal infection in 1 subject each [some subjects had multiple events]), but no adverse drug reactions leading to treatment discontinuation occurred.

An adverse drug reaction reported by ≥2 subjects during the RWD period was pruritus (3 subjects in the placebo group, 1 in the maralixibat group). Serious adverse events occurred in 1 subject in the placebo group (chest pain, pyrexia, multiple injuries, splenic rupture, and shock haemorrhagic) and in 1 subject in the maralixibat group (viral infection), but no serious adverse drug reactions occurred. No adverse events leading to treatment discontinuation occurred.

There were no adverse drug reactions reported by ≥2 subjects during the stable-dosing period. Serious adverse events occurred in 5 subjects (diarrhoea, vomiting, Epstein-Barr virus infection, gastroenteritis, toxicity to various agents, blood bilirubin increased, acute kidney injury, and hypertension in 1 subject each [some subjects had multiple events]), but no serious adverse drug reactions occurred. Adverse events leading to treatment discontinuation occurred in 2 subjects (acute kidney injury and blood bilirubin increased in 1 subject each) but no adverse drug reactions leading to treatment discontinuation occurred.

Adverse drug reactions reported by ≥2 subjects during the long-term treatment period (Period 1) were abdominal pain (4 subjects), ALT increased (4 subjects), and AST increased (2 subjects). Serious adverse events occurred in 6 subjects (aplasia pure red cell, cardiac dysfunction, influenza like illness, pyrexia, Campylobacter gastroenteritis, tonsillitis, forearm fracture, toxicity to various agents, and marrow hyperplasia in 1 subject each [some subjects had multiple events]), but no serious adverse drug reactions occurred. Adverse events leading to treatment discontinuation occurred in 2 subjects (ALT increased in 2 subjects) and were both assessed as adverse drug reactions but non-serious.

Table 34. Incidences of adverse events (safety analysis set)

	Run-in period 18 weeks (n = 31)	RWD period 4 weeks		Stable-dosing period 26 weeks (n = 29)	Long-term treatment period Period 1: 52 weeks (n = 23)	Entire period (n = 31)
		Placebo (n = 16)	Maralixibat (n = 13)			
All adverse events	96.8 (30)	75.0 (12)	53.8 (7)	86.2 (25)	100.0 (23)	100 (31)
All adverse drug reactions	38.7 (12)	18.8 (3)	7.7 (1)	3.4 (1)	34.8 (8)	51.6 (16)
Death	0	0	0	0	0	0
Serious adverse events	12.9 (4)	6.3 (1)	7.7 (1)	17.2 (5)	26.1 (6)	41.9 (13)
Serious adverse drug reactions	0	0	0	0	0	0
Adverse events leading to treatment discontinuation	6.5 (2)	0	0	6.9 (2)	8.7 (2)	19.4 (6)
Adverse events reported by ≥3 subjects during any period or in any group						
Abdominal pain	38.7 (12)	6.3 (1)	7.7 (1)	20.7 (6)	52.2 (12)	58.1 (18)
Diarrhoea	41.9 (13)	6.3 (1)	7.7 (1)	17.2 (5)	30.4 (7)	54.8 (17)
Vomiting	35.5 (11)	6.3 (1)	7.7 (1)	10.3 (3)	34.8 (8)	51.6 (16)
Pyrexia	19.4 (6)	12.5 (2)	0	24.1 (7)	43.5 (10)	51.6 (16)
Nasopharyngitis	12.9 (4)	6.3 (1)	7.7 (1)	27.6 (8)	39.1 (9)	41.9 (13)
Cough	9.7 (3)	0	0	10.3 (3)	34.8 (8)	41.9 (13)
Upper respiratory tract infection	19.4 (6)	0	15.4 (2)	10.3 (3)	17.4 (4)	29.0 (9)
Headache	16.1 (5)	0	0	6.9 (2)	17.4 (4)	29.0 (9)
Ear infection	9.7 (3)	0	0	13.8 (4)	21.7 (5)	25.8 (8)
Viral infection	3.2 (1)	0	7.7 (1)	3.4 (1)	17.4 (4)	25.8 (8)
Gastroenteritis	0	6.3 (1)	0	6.9 (2)	21.7 (5)	22.6 (7)
Oropharyngeal pain	3.2 (1)	0	0	10.3 (3)	13.0 (3)	22.6 (7)
Fall	12.9 (4)	0	0	10.3 (3)	0	19.4 (6)
Pruritus	9.7 (3)	31.3 (5)	7.7 (1)	6.9 (2)	0	16.1 (5)
ALT increased	0	0	0	0	17.4 (4)	12.9 (4)
Pain in extremity	0	0	0	0	17.4 (4)	12.9 (4)
Contusion	3.2 (1)	0	0	0	13.0 (3)	12.9 (4)
Pharyngitis	0	6.3 (1)	0	0	13.0 (3)	9.7 (3)
Ear pain	3.2 (1)	0	0	10.3 (3)	4.3 (1)	9.7 (3)

Incidence (%) (number of subjects with events), Medical dictionary for regulatory activities (MedDRA) ver. 22.1

7.2 Phase III studies

7.2.1 Japanese phase III study in patients with ALGS (CTD 5.3.5.2-5, Study No. TAK-625-3001, ongoing since January 2023, data cut-off in [redacted] 20[redacted])

A multi-center, open-label, uncontrolled study was conducted at 4 study centers in Japan to investigate the efficacy and safety of maralixibat in patients with ALGS (Table 35) (target sample size, 5 subjects[28)]).

[28)] The target sample size was determined based on the feasibility but not test of hypothesis.

Table 35. Main inclusion criteria and exclusion criteria

Main inclusion criteria
- Patients weighing ≥3.0 kg and aged ≥1 month
- Diagnosis of ALGS based on any of the following diagnostic criteria

Family history of ALGS[1)]	Interlobular bile duct paucity as a pathological finding in the liver	*JAGGED1* or *NOTCH2* gene mutation	Major clinical criteria or features[2)]
Present or absent	Present	Identified[3)]	Any or no features
None (proband)	Absent or unknown	Identified	1 or more features
None (proband)	Present	Not identified	3 or more features
None (proband)	Absent or unknown	Not identified	4 or more features
Present	Absent or unknown	Identified	Any or no features
Present	Present	Not identified	1 or more features
Present	Absent or unknown	Not identified	2 or more features

1) Presence of a first-degree relative with ALGS was deemed as "Present for family history."
2) Cholestasis; ALGS-consistent cardiac, renal, vascular, ocular, or skeletal involvement; or characteristic Alagille facies.
3) *JAGGED1* or *NOTCH2* mutation identified by laboratory test

- One or more of the following findings indicative of cholestasis:
  a) Total sBA concentration >3 × the ULN for age
  b) Direct bilirubin >1 mg/dL
  c) Fat-soluble vitamin deficiency otherwise unexplainable
  d) GGT >3 × ULN for age
  e) Intractable pruritus explainable only by liver disease
- Average ItchRO daily score[a)] for 2 weeks before enrollment >2

Main exclusion criteria
- Chronic diarrhea requiring ongoing intravenous fluid or nutritional intervention
- Prior surgical interruption of the enterohepatic circulation
- Prior liver transplant
- Decompensated hepatic cirrhosis (ALT >15 × ULN, PT-INR >1.5 [unresponsive to vitamin K supplementation], albumin <3.0 g/dL, clinically significant ascites, variceal haemorrhage, or history or presence of hepatic encephalopathy)
- History or presence of other liver diseases
- History or presence of the other diseases or pathological conditions that are known to inhibit absorption, distribution, metabolism, or excretion of drugs in the intestinal tract, including metabolism of bile salt (e.g., inflammatory bowel disease)
- History or presence of gallstones or kidney stones

a) A daily score is the higher of the scores for the morning and evening ItchRO. The average daily score is the sum of all daily scores divided by the number of days the ItchRO was completed.

This study consisted of the dose-escalation period (2 weeks), stable-dosing period (46 weeks), and long-term follow-up period.[29)]

During the dose-escalation period, maralixibat was orally administered QD at 200 μg/kg for the first week and then at 400 μg/kg. In subjects who experienced a moderate or severe gastrointestinal adverse drug reaction while receiving maralixibat 400 μg/kg QD, the dose was reduced to 200 μg/kg QD at discretion of the investigator and then allowed to be re-increased to 400 μg/kg QD according to the subject's condition. During the stable-dosing period, maralixibat was orally administered QD at the same dose as that at the end of the dose-escalation period (200 or 400 μg/kg). During the long-term follow-up period, maralixibat was orally administered QD at the same dose as that at the end of the stable-dosing period (200 or 400 μg/kg).

All of 7 subjects enrolled received the study drug and were included in the ITT population as well as the primary efficacy and safety analysis populations. Of them, 3 subjects showed a ≥50% decrease in sBA

29) Maralixibat was to be continued until its launch in Japan, discontinuation of the study based on request from the subject or investigator's decision, or termination of its development.

concentration from baseline to Week 12 or Week 18 and were included in the MITT population. No discontinuation occurred during any period.

The primary efficacy endpoint was a change in fasting sBA concentration from Week 18 to Week 22, and results on this endpoint are shown in Table 36.

Table 36. Change in fasting sBA concentration (μmol/L) from Week 18 to Week 22 (ITT population, OC)

	Maralixibat (n = 7)
Week 18[a)]	96.03 ± 169.75 (7)
Week 22	113.67 ± 221.16 (7)
Change from Week 18 to Week 22[b)]	17.64 [-31.64, 66.92]

Mean ± SD (number of subjects); Change is expressed as mean [95% CI]

a) Missing data at Week 18, if any, were planned to be substituted according to the last observation carried forward (LOCF) method, but no missing data occurred.

b) 95% CI was calculated based on the t-distribution.

Adverse events occurred in 100% (7 of 7) of subjects during the dose-escalation period and stable-dosing period (up to Week 48). The reported adverse events were upper respiratory tract infection in 3 subjects; influenza, upper respiratory tract inflammation, and dermatitis diaper in 2 subjects each; anaemia, ocular hyperaemia, chapped lips, defaecation urgency, diarrhoea, vomiting, administration site extravasation, COVID-19, nasopharyngitis, otitis media, arthropod bite, eyelid injury, skin abrasion, ALT increased, hypercholesterolaemia, malnutrition, weight gain poor, bronchitis chronic, dermatitis atopic, dry skin, and pruritus in 1 subject each (some subjects had multiple events). Defaecation urgency in 1 subject was assessed as an adverse drug reaction. No death occurred, and serious adverse events occurred in 1 subject (weight gain poor and malnutrition), but no serious adverse drug reactions occurred. No adverse events leading to treatment discontinuation occurred.

7.2.2 Foreign phase III study in patients with PFIC (CTD 5.3.5.1-4, Study No. MRX-502, July 2019 to September 2022)

A multi-center, placebo-controlled, randomized, double-blind, parallel-group study was conducted at 29 study centers in 16 foreign countries to investigate the efficacy and safety of maralixibat in patients with PFIC (Table 37) (target sample size, 90 subjects[30)31)]).

[30)] Consisted of 30 subjects in the primary cohort (patients with PFIC2) and 60 subjects in the supplemental cohort (patients with non-PFIC2 subtype)

[31)] Based on results from a foreign phase II study in patients with PFIC (Study LUM001-501) and foreign phase II studies in patients with ALGS (Studies LUM001-301 and LUM001-302), a difference between groups and its SD for the primary endpoint were assumed to be 0.663 and 0.563, respectively. On the above assumption, the number of patients needed to ensure a power of 80% in a two-sample t-test at a two-sided significance level of 5% was calculated to be 26 (13 per group). In view of a drop-out rate of approximately 10% in previous clinical studies in patients with PFIC, the target sample size in the primary cohort was specified as 30 (15 per group).

Table 37. Main inclusion criteria and exclusion criteria

Main inclusion criteria
• Patients weighing ≥5.0 kg and aged ≥12 months and <18 years
• Cholestasis (total sBA concentration ≥3 × ULN)
• Average morning ItchRO (Obs) score for 4 weeks before enrollment ≥1.5
• Diagnosis of PFIC based on the criteria below
  • Chronic cholestasis finding (>6-month pruritus, and abnormal finding in biochemistry test, or pathological finding indicative of progressive liver disease)
  Primary cohort only
  • Biallelic mutations in *ABCB11* identified by gene test (PFIC2) and remaining BSEP function predicted (nt-PFIC2)[a)]
  Supplemental cohort only
  • Biallelic mutations in *ATP8B1* (PFIC1), *ABCB4* (PFIC3), or *TJP2* (PFIC4) identified by gene test
  • PFIC phenotype without a known mutation or with another known mutation not described above or with intermittent cholestasis as manifested by fluctuating sBA concentrations
  • After internal or external biliary diversion surgery or after its restoration surgery
 	
Main exclusion criteria
• Recurrent intrahepatic cholestasis, indicated by sBA concentration <3 × ULN or intermittent pruritus (applies to primary cohort only)
• Current or recent history (<1 year) of other non-cholestatic diseases accompanied by pruritus.
• History of surgical disruption of the enterohepatic circulation (applies to primary cohort only)
• Chronic diarrhea requiring intravenous fluid or nutritional intervention or its sequelae during a period of 6 months before screening
• Previous or need for imminent liver transplant
• Decompensated hepatic cirrhosis (PT-INR >1.5, albumin <3.0 g/L, history or presence of clinically significant ascites, variceal haemorrhage, or encephalopathy)
• ALT or total serum bilirubin (TSB) >15 × ULN
• Presence of other liver diseases

a) Patients with PFIC2 (t-PFIC2) due to *ABCB11* mutation, as determined by genotyping, which is predicted to be accompanied by complete absence of BSEP function may be enrolled in the supplemental cohort.

This study consisted of the dose-escalation period (4-6 weeks) and stable-dosing period (20-22 weeks).

During the dose-escalation period, in the placebo group, placebo was orally administered BID, and in the maralixibat group, maralixibat was orally administered BID at ascending doses from an initial 150 μg/kg to, as long as tolerated, 300, 450, and 600 μg/kg in this order for 1 week for each dose, and the dose reduction[32)] was also allowed in cases where any tolerability concern was raised so that the maximum tolerated dose was determined over a period of 4 to 6 weeks.[33)] During the stable-dosing period, placebo or maralixibat at the maximum tolerated dose determined during the dose-escalation period was administered for 20 to 22 weeks (26 weeks in total, including the dose-escalation period).

All of 93 subjects randomized (46 in the placebo group, 47 in the maralixibat group) were included in the ITT population, and all also received the study drug and thus were included in the safety analysis set. In the ITT population, 31 subjects enrolled in the primary cohort (Table 37) (14 in the placebo group, 17 in the maralixibat group) were included in the primary efficacy analysis population (primary cohort ITT population). Discontinuation occurred in 7 subjects (4 in the placebo group, 3 in the maralixibat group) because of consent withdrawal in 4 subjects (3 in the placebo group, 1 in the maralixibat group), adverse events and liver transplant in 1 subject each (maralixibat group), and disease progression in 1 subject (placebo group).

32) The dose was reduced to a previously tolerated dose, and any subject who did not tolerate the lowest dose (maralixibat 150 μg/kg BID) was withdrawn from the study.

33) Subjects who had successfully increased the dose of maralixibat up to 600 μg/kg BID entered the stable-dosing period with the maximum tolerated dose of 600 μg/kg BID, while subjects who had failed to increase the dose of maralixibat up to 600 μg/kg BID entered the stable-dosing period with the maximum tolerated dose being the dose at Week 6.

The primary efficacy endpoint was a change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26, and results on this endpoint are shown in Table 38. The difference between the maralixibat group and placebo group was statistically significant.

Table 38. Change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26 (primary cohort ITT population, OC)

	Placebo (n = 17)	Maralixibat (n = 14)	Difference between groups (maralixibat - placebo)
Baseline[a)]	2.611 ± 0.893 (17)	2.876 ± 0.912 (14)	
Average at Weeks 15-18	2.092 ± 1.192 (15)	1.032 ± 0.933 (14)	
Average at Weeks 19-22	2.078 ± 1.186 (15)	1.036 ± 0.889 (13)	
Average at Weeks 23-26	2.082 ± 1.229 (15)	1.141 ± 1.106 (13)	
Change from baseline to Weeks 15-26[b)]	-0.628 [-1.136, -0.121]	-1.718 [-2.272, -1.163]	-1.089 [-1.845, -0.334]
P value[b)c)]			0.0063

Mean ± SD (number of subjects); Change is expressed as least squares mean [95% CI].

a) Average during a period of 4 weeks before baseline visit

b) Average of estimated values for each of 3 periods (Weeks 15-18, Weeks 19-22, Weeks 23-26), which were obtained in a mixed-effects model for repeated measures (MMRM) on the hypothesis of an unstructured variance-covariance matrix on intra-subject error using the dose group, period, interaction between the dose group and period, baseline value, and interaction between the baseline value and period as explanation variables

c) Two-sided significance level of 5%

Table 39 shows the summary of incidences of adverse events. Adverse drug reactions reported by ≥2 subjects in either group were diarrhoea (1 subject in the placebo group, 13 subjects in the maralixibat group), abdominal pain, and blood bilirubin increased (3 subjects in the maralixibat group each). No death occurred. Serious adverse events occurred in 3 subjects in the placebo group (coagulopathy, gastroenteritis viral, accidental exposure to product, vitamin K deficiency, and seizure in 1 subject each [some subjects had multiple events]) and 5 subjects in the maralixibat group (urinary tract infection in 2 subjects, constipation, cholestasis, blood bilirubin increased and idiopathic pneumonia syndrome in 1 subject each [some subjects had multiple events]). A serious adverse drug reaction occurred in 1 subject in the maralixibat group (blood bilirubin increased) with an outcome of “resolved.” An adverse event leading to treatment discontinuation occurred in 1 subject in the maralixibat group (diarrhoea) and was assessed as an adverse drug reaction but the outcome was reported as “resolved.”

Table 39. Incidences of adverse events (safety analysis set)

	Placebo (n = 46)	Maralixibat (n = 47)
All adverse events	93.5 (43)	100 (47)
All adverse drug reactions	4.3 (2)	38.3 (18)
Death	0	0
Serious adverse events	6.5 (3)	10.6 (5)
Serious adverse drug reactions	0	2.1 (1)
Adverse events leading to treatment discontinuation	0	2.1 (1)
Adverse events reported by ≥5% of subjects in either group		
Diarrhoea	19.6 (9)	57.4 (27)
Pyrexia	28.3 (13)	36.2 (17)
Abdominal pain	6.5 (3)	21.3 (10)
Rhinorrhoea	10.9 (5)	17.0 (8)
Cough	10.9 (5)	14.9 (7)
Blood bilirubin increased	8.7 (4)	14.9 (7)
ALT increased	6.5 (3)	12.8 (6)
Influenza	4.3 (2)	12.8 (6)
Pruritus	17.4 (8)	10.6 (5)
Nasopharyngitis	4.3 (2)	10.6 (5)
Vitamin D deficiency	8.7 (4)	8.5 (4)
Vitamin E decreased	6.5 (3)	8.5 (4)
Constipation	4.3 (2)	8.5 (4)
Vitamin D decreased	4.3 (2)	8.5 (4)
Vitamin E deficiency	8.7 (4)	6.4 (3)
Vomiting	10.9 (5)	6.4 (3)
Corona virus infection	8.7 (4)	6.4 (3)
Upper respiratory tract infection	13.0 (6)	6.4 (3)
Gastroenteritis	4.3 (2)	6.4 (3)
Urinary tract infection	2.2 (1)	6.4 (3)
Viral upper respiratory tract infection	2.2 (1)	6.4 (3)
Haematochezia	2.2 (1)	6.4 (3)
Headache	0	6.4 (3)

Incidence (%) (number of subjects), MedDRA ver. 22.1

7.2.3 Japanese phase III study in patients with PFIC (CTD 5.3.5.2-9, Study No. TAK-625-3002, ongoing since January 2023, data cut-off in [redacted] 20[redacted])

A multi-center, open-label, uncontrolled study was conducted at 4 study centers in Japan to investigate the efficacy and safety of maralixibat in patients with PFIC (Table 40) (target sample size, 9 subjects[34)35)]).

[34)] Consisted of 3 subjects in the primary cohort (patients with PFIC2) and 6 subjects in the supplemental cohort (patients with non-PFIC2 subtype)

[35)] The target sample size was determined based on the feasibility but not test of hypothesis.

Table 40. Main inclusion criteria and exclusion criteria

Main inclusion criteria Common to both primary cohort and supplemental cohort • Patients weighing ≥3.0 kg and aged ≥1 month • Average morning ItchRO (Obs) score for 4 weeks before enrollment ≥1.5 • Chronic cholestasis (>6-month pruritus, and abnormal finding in biochemistry test, or pathological finding indicative of progressive liver disease) Primary cohort only • Cholestasis (total sBA concentration ≥3 × ULN) • Biallelic mutations in *ABCB11* identified by gene test (PFIC2) and remaining BSEP function predicted (nt-PFIC2)[a)] Supplemental cohort only • Biallelic mutations in *ATP8B1* (PFIC1), *ABCB4* (PFIC3), or *TJP2* (PFIC4) identified by gene test • PFIC phenotype without a known mutation or with another known mutation not described above • After internal or external biliary diversion surgery or after its restoration surgery Main exclusion criteria • Diagnosis of benign recurrent intrahepatic cholestasis based on a history of intermittent cholestasis without progressive disease • Current or recent history (<1 year) of other non-cholestatic diseases accompanied by pruritus. • History of surgical disruption of the enterohepatic circulation (applies to primary cohort only) • Chronic diarrhea requiring intravenous fluid or nutritional intervention or its sequelae during a period of 6 months before screening • Previous or need for imminent liver transplant • Decompensated hepatic cirrhosis (PT-INR >1.5, albumin <3.0 g/L, history or presence of clinically significant ascites, variceal haemorrhage, or encephalopathy) • ALT or TSB >15 × ULN • Presence of other liver diseases

a) Patients with PFIC2 (t-PFIC2) due to *ABCB11* mutation, as determined by genotyping, which is predicted to be accompanied by complete absence of BSEP function may be enrolled in the supplemental cohort.

This study consisted of the dose-escalation period (4-6 weeks), stable-dosing period (42-44 weeks), and long-term follow-up period.[29)]

During the dose-escalation period, maralixibat was orally administered BID at ascending doses from an initial 150 μg/kg to, as long as tolerated, 300, 450, and 600 μg/kg in this order for 1 week for each dose, and the dose reduction[36)] was also allowed in cases where any tolerability concern was raised so that the maximum tolerated dose was determined over a period of 4 to 6 weeks. During the stable-dosing period, maralixibat at the maximum tolerated dose determined during the dose-escalation period was administered for 42 to 44 weeks (48 weeks in total, including the dose-escalation period), and during the long-term follow-up period, maralixibat was continued at the same dose.

A total of 5 subjects received the study drug and were included in the ITT population and the safety analysis set. In the ITT population, 3 subjects enrolled in the primary cohort (Table 36) were included in the primary efficacy analysis population (primary cohort ITT population). No discontinuation occurred during any period.

The primary efficacy endpoint was a change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26, and results on this endpoint are shown in Table 41.

36) The dose was allowed to be reduced to a previously tolerated dose. The lowest dose of maralixibat required to continue the study was 150 μg/kg BID, and any subject who did not tolerate this dose was withdrawn from the study.

Table 41. Change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26 (primary cohort ITT population, OC)

	Maralixibat (n = 3)
Baseline[a)]	2.618 ± 0.216 (3)
Average at Weeks 15-18	1.615 ± 0.544 (2)
Average at Weeks 19-22	1.088 ± 1.052 (3)
Average at Weeks 23-26	1.133 ± 1.206 (3)
Change in average from baseline to Weeks 15 to 26[b)]	-1.514 [-3.654, 0.626]

Mean ± SD (number of subjects); Change is expressed as mean [95% CI]
a) Average during a period of 4 weeks before baseline visit
b) 95% CI was calculated based on the t-distribution.

For safety, adverse events occurred in 100% (5 of 5) of subjects up to Week 48 (dose-escalation period and stable-dosing period). The reported adverse events were upper respiratory tract infection in 4 subjects; COVID-19 in 3 subjects; dermatitis in 2 subjects; diarrhoea, gastroenteritis, influenza, nasopharyngitis, auricular haematoma, fall, skin abrasion, sunburn, ALT increased, AST increased, blood bilirubin increased, tendonitis, asthma, and epistaxis in 1 subject each (some subjects had multiple events). Diarrhoea and dermatitis in 1 subject (the subject had more than 1 event) were assessed as adverse drug reactions. No deaths, serious adverse events, or adverse events leading to treatment discontinuation occurred.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the submitted data and the review in Sections 7.R.1.1 and 7.R.1.2, PMDA considers that maralixibat can be expected to have clinically meaningful efficacy in patients with ALGS or PFIC.

7.R.1.1 Efficacy of maralixibat in patients with ALGS

7.R.1.1.1 Development program of maralixibat

The applicant's explanation about the development program of maralixibat in patients with ALGS:

The diagnostic criteria for ALGS in Japan are applied as follows: A diagnosis of typical ALGS is given to individuals who have a pathological finding of intrahepatic bile duct paucity and at least 3 of 5 major symptoms and features (cholestasis, cardiovascular malformation, vertebral abnormality, ocular abnormality, and characteristic facies), and those who do not meet the major symptoms and features are diagnosed as atypical ALGS if they have the other applicable symptoms (characteristic abnormalities such as renal, vascular, and pancreatic dysfunctions), consistent family history, and positive gene test results (*JAGGED1* or *NOTCH2* mutation). The diagnostic criteria in Japan are not largely different from those outside Japan. Drugs used for treatment of ALGS include oral ursodeoxycholic acid, oral bile acid adsorbent, and supplementation with fat-soluble vitamins and essential fatty acids for cholestasis as well as oral antihistamines and oral phenobarbital for pruritus. The treatment algorithm for ALGS in Japan is also not largely different from that outside Japan. Maralixibat is hardly absorbed or metabolized in the gastrointestinal tract and acts on IBAT present in the gastrointestinal tract lumen, thus intrinsic ethnic factors are unlikely to affect the efficacy of maralixibat. When the development was initiated in Japan, the foreign phase II study (Study LUM001-304 [Study 304]) was completed, and maralixibat was approved for the indication of ALGS in Europe and the US. However, because of the very limited number of patients with ALGS in Japan, a placebo-controlled study with the sample size enough to evaluate the efficacy and safety of maralixibat cannot be conducted only in Japan. Based on the above, the Japanese phase III study was designed to obtain data that would be eligible for comparison with

results from Study 304 and conducted as an open-label uncontrolled study. The clinical data package was compiled additionally including results from foreign studies in non-Japanese patients with ALGS and used to evaluate the efficacy and safety of maralixibat in Japanese patients with ALGS.

Study 304 was designed as a placebo-controlled RWD study because (i) the study design would enable evaluation of the durability of the therapeutic effect in patients with ALGS suffering from severe pruritus, avoiding long-term placebo treatment and (ii) it was expected to detect the therapeutic effect more efficiently by lowering the placebo effect. Patients who received a diagnosis of ALGS, were aged ≥12 months and <18 years, had findings indicative of cholestasis, and presented with certain symptoms of pruritus were deemed as eligible (Table 32). The primary efficacy endpoint was fasting sBA concentration, because (1) elevated sBA concentrations in a cholestatic disease cause pruritus and affect progression of hepatic cirrhosis (*Arch Intern Med.* 1972;130:632-7, *World J Gastroenterol.* 2009;15:804-16); (2) the sBA concentration reflects a pharmacodynamic potential of maralixibat, an inhibitor against IBAT; and (3) Study 304 was positioned as a phase II study. In addition, since pruritus during nighttime would lead to sleep disorders and subsequently growth disorder (*J Pediatr Gastroenterol Nutr.* 2018;67:148-56, *Japanese Journal of Pediatric Medicine.* 2011;43:1073-6), the weekly average morning ItchRO (Obs) severity score was specified as the secondary endpoint to assess pruritus during nighttime (Tables 30 and 31). For timing of efficacy evaluation, with reference to study designs of the foreign phase II studies (Studies LUM001-301 and LUM001-302), which were conducted before Study 304, Week 18 when subjects received maralixibat at a dose individually determined up to Week 6 (400 μg/kg or lower but maximum tolerated dose) for at least 12 weeks was specified as the baseline in the RWD period. Flare of pruritus was predicted during the RWD period in the placebo group, and thus the RWD period of 4 weeks was specified for the efficacy evaluation to avoid the protracted RWD period. Based on the above, a change in fasting sBA concentration from Week 18 to Week 22 was specified as the primary endpoint. In a group of subjects who had responded to maralixibat during the run-in period, the efficacy was predicted to be maintained with continued administration of maralixibat, while the bile acid concentrations were predicted to increase after a switchover to placebo. In view of such predictions, subjects who showed a ≥50% decrease in sBA concentration from baseline to Week 12 or Week 18 were included in the primary efficacy analysis population (MITT population).

The Japanese phase III study in patients with ALGS (Study TAK-625-3001 [Study 3001]) was designed as an open-label uncontrolled study with the patient population (Table 35)[37)] and efficacy endpoints similar to those in Study 304. Results on the primary endpoint of Study 3001 were analyzed for similarity to those of Study 304 from the following 2 viewpoints:

- A point estimate of a "change in fasting sBA concentration from Week 18 to Week 22" in the maralixibat group does not largely differ between these studies, and 95% CIs in these studies mostly overlap.

[37)] In Study 304, patients aged ≥1 year and ≤18 years were included, but the range of age eligible for Study 3001 was expanded to the lower limit of 1 month without the upper limit, taking into account that (1) unmet medical needs in patients aged <1 year and >18 years were deemed to be high in Japan; (2) a foreign open-label uncontrolled study (Study MRX-801) was being conducted in patients with ALGS and those with PFIC aged <1 year; and (3) the safety information in patients aged <1 year in the concerned study supported conduct of Study 3001. The lower limit of eligible body weight was not specified in Study 304, but in Study 3001, the lower limit of eligible body weight was initially specified as 5.0 kg based on the settings in Study 502, which included patients with PFIC weighing ≥5.0 kg [see Section 7.R.1.2.1], and then expanded to 3.0 kg, in view of the presumed body weight of patients with ALGS aged 1 month and the settings in Study MRX-801, which was ongoing at that time and included patients weighing ≥2.5 kg.

- The point estimate of a “change in fasting sBA concentration from Week 18 to Week 22” in Study 3001 is smaller than the point estimate in the placebo group in Study 304.

Considering that analysis results in all patients treated with maralixibat were more important than those only in patients who responded to maralixibat, the applicant specified the ITT population as the primary analysis set and also performed a supplemental analysis in the MITT population. Data on the key secondary endpoint of pruritus were analyzed as with data on the primary endpoint. Furthermore, because the number of patients included in Study 3001 was very limited, data on individual subjects were investigated in detail, and thereby the efficacy of maralixibat was evaluated comprehensively.

PMDA’s view:
Conducting Study 3001 as an open-label uncontrolled study is unavoidable, taking into account that (1) Study 304 was completed when the development was initiated in Japan; and (2) the number of patients with ALGS in Japan is very limited. On that premise, in view of the diagnostic criteria and treatment methods for ALGS in Japan, which are not largely different from those outside Japan, and the pharmacological effect of maralixibat, the efficacy and safety of maralixibat in Japanese patients with ALGS can be evaluated using data from Study 304 as much as possible, with consideration for impacts of ethnic factors, after analyzing results from Study 3001 for similarity to those from Study 304.

The primary endpoint in Study 3001, which is based on fasting sBA concentrations as done for the primary endpoint in Study 304, is appropriate from a viewpoint of ensuring comparability with results from Study 304. However, the fasting sBA concentration is a factor that may be related to pruritus and liver prognosis in patients with ALGS but is not established as a measure reflecting these conditions. The efficacy of maralixibat should be comprehensively evaluated using not only data on fasting sBA concentration but also data on effects on clinical symptoms, such as ItchRO (Obs) score for pruritus assessment.

7.R.1.1.2 Results from Studies 304 and 3001

The applicant’s explanation about efficacy results from Studies 304 and 3001 is presented in the subsections below.

(i) Results from Study 304

Table 42 shows results on the primary endpoint in Study 304. In the MITT population used as the primary efficacy analysis set (a population of subjects who showed a ≥50% decrease in sBA concentration from baseline to Week 12 or Week 18), the fasting sBA concentration increased during the RWD period in the placebo group, while the fasting sBA concentration did not increase in the maralixibat group. Results in the ITT population were similar to the above (Table 42).

Table 42. Change in fasting sBA concentration (μmol/L) during the RWD period (Study 304, OC)

	MITT population		ITT population	
	Placebo (n = 10)	Maralixibat (n = 5)	Placebo (n = 16)	Maralixibat (n = 13)
Week 18 (baseline in the RWD period)	123.68 ± 89.54 (10)	117.12 ± 102.97 (5)	159.62 ± 129.69 (16)	232.96 ± 190.92 (13)
Week 22	219.97 ± 180.82 (10)	93.90 ± 76.51 (5)	253.19 ± 208.38 (16)	216.23 ± 207.33 (13)
Change from Week 18 to Week 22[a)]	95.55 [29.12, 161.97]	-21.73 [-115.69, 72.23]	95.21 [30.08, 160.34]	-18.74 [-91.20, 53.72]
Difference between groups (maralixibat - placebo)[a)]	-117.28 [-232.38, -2.18]		-113.95 [-212.68, -15.21]	

Mean ± SD (number of subjects); Change is expressed as least squares mean [95% CI].
a) Analysis of covariance using the dose group and fasting sBA concentration at Week 18 as explanation variables

Table 43 shows results on the key secondary endpoints during the run-in period (open-label). Results on the fasting sBA concentration showed a decreasing trend from baseline to Week 18. Results on each ItchRO (Obs)-based severity score of pruritus also showed a decrease of >1 point[38)] from baseline to Week 18, which is a clinically meaningful change.

Table 43. Results on key secondary endpoints in the run-in period (Study 304, ITT population, OC)

	Baseline (n = 31)	Week 18 (n = 29)	Change from baseline to Week 18
Fasting sBA (μmol/L)	283.43 ± 210.57 (31)	192.50 ± 161.28 (29)	-87.73 [-133.37, -42.09]
Weekly average morning ItchRO (Obs) severity score	2.909 ± 0.548 (31)	1.203 ± 0.845 (29)	-1.704 [-2.051, -1.357]
Weekly average ItchRO (Obs) severity (daily maximum) score	3.129 ± 0.466 (31)	1.382 ± 0.894 (29)	-1.736 [-2.100, -1.373]

Mean ± SD (number of subjects); Change is expressed as mean [95% CI]

Table 44 shows results on key secondary endpoints in the RWD period. As with results on the primary endpoint (Table 42), ItchRO (Obs)-based assessment results on symptoms of pruritus showed that the symptoms worsened in the placebo group during the RWD period, but mostly maintained in the maralixibat group from Week 18 to Week 22.

Table 44. Results on key secondary endpoints in the RWD period (Study 304, ITT population, OC)

		Placebo (n = 16)	Maralixibat (n = 13)	Difference between groups (maralixibat - placebo)
Weekly average morning ItchRO (Obs) severity score	Week 18	1.127 ± 0.849 (16)	1.297 ± 0.864 (13)	
	Week 22	2.839 ± 0.851 (16)	1.380 ± 0.930 (12)	
	Change from Week 18 to Week 22	1.700 [1.282, 2.119]	0.217 [-0.266, 0.700]	-1.483 [-2.122, -0.844]
Weekly average ItchRO (Obs) severity (daily maximum) score	Week 18	1.281 ± 0.925 (16)	1.505 ± 0.874 (13)	
	Week 22	3.063 ± 0.810 (16)	1.659 ± 1.067 (13)	
	Change from Week 18 to Week 22	1.732 [1.305, 2.159]	0.215 [-0.259, 0.688]	-1.517 [-2.157, -0.877]

Mean ± SD (number of subjects); Change is expressed as least squares mean [95% CI].

In Study 304, the sBA concentrations in patients with ALGS receiving maralixibat decreased and the result in the MITT population, the primary analysis set, was similar to that in the ITT population. Symptoms of pruritus were also improved. The above results are considered to have demonstrated the efficacy of maralixibat in the treatment of cholestasis and pruritus in non-Japanese patients with ALGS.

38) Quantitative research to characterize the average morning ItchRO (Obs) severity score as a scale indicated that a change in ItchRO (Obs) score ≥1.0 was clinically meaningful in view of variability of the score.

(ii) Results from Study 3001

Study 3001, unlike Study 304, enrolled patients with ALGS aged <1 year, and thus the protocol prespecified that a supplemental analysis would be performed in the population of patients aged ≥1 year for comparison with results from Study 304 in addition to the analysis in the overall population. Table 45, Table 46, and Table 47 show results on the primary endpoint and key secondary endpoints in each population.

Results on a "change in fasting sBA concentration from Week 18 to Week 22," the primary endpoint in Study 3001, did not show substantial variations in either the ITT population (the primary analysis set) or the MITT population, to which a similar population was used as the primary analysis set in Study 304. ItchRO (Obs)-based assessment results on symptoms of pruritus showed improvement from baseline to Week 18 and then maintained improvement from Week 18 to Week 22.

Table 45. Change in fasting sBA concentration (μmol/L) from Week 18 to Week 22 (Study 3001, OC)

	MITT population		ITT population	
	Overall population (n = 3)	Population aged ≥1 year (n = 3)	Overall population (n = 7)	Population aged ≥1 year [redacted]
Week 18	29.93 ± 20.48	29.93 ± 20.48	96.03 ± 169.75	32.22 ± 19.34
Week 22	19.23 ± 8.54	19.23 ± 8.54	113.67 ± 221.16	30.33 ± 18.85
Change from Week 18 to Week 22	-10.70 [-41.02, 19.62]	-10.70 [-41.02, 19.62]	17.64 [-31.64, 66.92]	-1.88 [-16.90, 13.13]

Mean ± SD; Change is expressed as the mean [95% CI]; No missing data occurred at either timepoint.

Table 46. Results on key secondary endpoints at Week 18 (Study 3001, ITT population, OC)

	Overall population (n = 7)			Population aged ≥1 year [redacted]		
	Baseline	Week 18	Change from baseline	Baseline	Week 18	Change from baseline
Fasting sBA (μmol/L)	87.73 ± 124.68	96.03 ± 169.75	8.30 [-37.41, 54.01]	41.17 ± 21.06	32.22 ± 19.34	-8.95 [-30.76, 12.86]
Weekly average morning ItchRO (Obs) severity score	2.580 ± 0.451	1.253 ± 0.470	-1.327 [-2.107, -0.546]	2.676 ± 0.407	1.081 ± 0.128	-1.595 [-2.118, -1.072]
Weekly average ItchRO (Obs) severity (daily maximum) score	2.857 ± 0.429	1.327 ± 0.493	-1.531 [-2.340, -0.721]	3.000 ± 0.221	1.167 ± 0.277	-1.833 [-2.240, -1.426]

Mean ± SD; Change is expressed as the mean [95% CI]; No missing data occurred at either timepoint.

Table 47. Results on key secondary endpoints at Week 22 (Study 3001, ITT population, OC)

	Overall population (n = 7)			Population aged ≥1 year [redacted]		
	Week 18	Week 22	Change from Week 18	Week 18	Week 22	Change from Week 18
Weekly average morning ItchRO (Obs) severity score	1.253 ± 0.470	0.973 ± 0.634	-0.280 [-0.677, 0.116]	1.081 ± 0.128	0.778 ± 0.404	-0.303 [-0.791, 0.185]
Weekly average ItchRO (Obs) severity (daily maximum) score	1.327 ± 0.493	1.041 ± 0.582	-0.286 [-0.659, 0.088]	1.167 ± 0.277	0.857 ± 0.350	-0.310 [-0.768, 0.149]

Mean ± SD; Change is expressed as the mean [95% CI]; No missing data occurred at either timepoint.

In comparison of results in the ITT population between Study 304 and Study 3001, the point estimate (17.64 μmol/L) of the "change in fasting sBA concentration from Week 18 to Week 22" in Study 3001

(overall population) was smaller than that (95.21 μmol/L) in the placebo group in Study 304. Comparison of results on the "change in fasting sBA concentration from Week 18 to Week 22" between the maralixibat group in Study 304 and Study 3001 (overall population) showed that the 95% CIs in these studies mostly overlap each other ([−91.20, 53.72] μmol/L in Study 304, [−31.64, 66.92] μmol/L in Study 3001), and the point estimate (17.64 μmol/L) in Study 3001 is closer to that (−18.74 μmol/L) in the maralixibat group in Study 304 than to that (95.21 μmol/L) in the placebo group, indicating that the point estimate does not largely differ between these studies. Based on the above, the pre-determined criteria for similarity of Study 3001 to Study 304 [see Section 7.R.1.1.1] were met. However, the point estimate of the "change in fasting sBA concentration from Week 18 to Week 22" in Study 3001 (overall population) was opposite to that in the maralixibat group in Study 304 in terms of positive and negative numbers (−18.74 μmol/L in Study 304 and 17.64 μmol/L in Study 3001). This discrepancy is considered largely attributable to 1 subject in Study 3001 (Table 48, Subject 5) who showed a clear increase in fasting sBA concentration from Week 18 to Week 22 (134.8 μmol/L). Although 1 subject in the maralixibat group in Study 304 also showed a clear increase (288.4 μmol/L), the increase in 1 subject in Study 3001 may have had a greater impact than that in Study 304 because of the very limited sample size in Study 3001. Actually, when the concerned 1 subject ([redacted]) was excluded from the overall population in Study 3001, results in the resultant population [redacted] were not largely different from the results in the maralixibat group in Study 304 in terms of point estimates of the change, and the 95% CIs in these studies mostly overlapped each other (−18.74 [−91.20, 53.72] μmol/L in Study 304 and −1.88 [−16.90, 13.13] μmol/L in Study 3001).

For a "change in fasting sBA concentration from baseline to Week 18" (ITT population), a secondary endpoint in Study 3001, the point estimate in the maralixibat group in Study 3001 (overall population) was opposite to that in the maralixibat group in Study 304 in terms of positive and negative numbers, and the 95% CIs did not overlap (−87.73 [−133.37, −42.09] μmol/L in Study 304 and 8.30 [−37.41, 54.01] μmol/L in Study 3001). This discrepancy is considered potentially attributable to 1 subject (Table 48, Subject 5), who showed a clear increase in fasting sBA concentration from baseline to Week 18 (111.8 μmol/L), and the lower baseline fasting sBA concentration (87.73 μmol/L) in Study 3001 than that (283.43 μmol/L) in Study 304. Actually, in a population of 9 subjects with the low baseline fasting sBA concentration (<102 μmol/L)[39] in Study 304, the point estimate [95% CI] of the "change in fasting sBA concentration from baseline to Week 18" was −13.30 [−28.46, 1.86] μmol/L, which was not largely different from the point estimate (−8.95 [−30.76, 12.86] μmol/L) of the change in a population of subjects aged ≥1 year (the baseline fasting sBA concentration was <102 μmol/L in all subjects) in Study 3001, and the 95% CIs overlapped as well. In a population of subjects with the low baseline fasting sBA concentration (population of subjects aged ≥1 year) in Study 3001, the result on the "change in fasting sBA concentration from baseline to Week 18" was smaller than that in the overall population in Study 304 (−8.95 μmol/L in Study 3001 and −87.73 μmol/L in Study 304), but the point estimate [95% CI] of the "change in weekly average morning ItchRO (Obs) severity score from baseline to Week 18" was −1.874 [−2.769, −0.978] in the concerned population in Study 304 and −1.595 [−2.118, −1.072] in the

[39] The fasting serum bile acid concentrations <102 μmol/L were deemed to be low based on a report (*J Hepatol*. 2020;73:84-93) that showed that patients with PFIC who had fasting serum bile acid concentrations <102 μmol/L after biliary drainage such as partial bile duct fistulization survived long without undergoing liver transplant.

population of subjects aged ≥1 year in Study 3001. Symptoms of pruritus tended to improve in both studies without any large difference in terms of the extent of improvement.

Furthermore, given the very limited sample size, the efficacy of maralixibat was investigated for each of the subjects in Study 3001. Table 48 shows changes of sBA concentrations and weekly average morning ItchRO (Obs) severity scores over time in individual subjects in Study 3001. In Subjects 4, 6, and 7, fasting sBA concentrations decreased from baseline to Week 18, and weekly average morning ItchRO (Obs) severity scores also improved by ≥1 point. In Subjects 1, 2, and 3, fasting sBA concentrations tended to increase from baseline to Week 18, but in view of a variable nature of the fasting sBA concentration, the concerned changes were within a range of variations. In addition, weekly average morning ItchRO (Obs) severity scores improved ≥1 point, and 7alpha-hydroxy-4-cholesten-3-one (7αC4) concentrations in blood,[40] which indirectly reflect the total amount of bile acids in the body, tended to increase generally after administration of maralixibat. In Subject 5, the fasting sBA concentration increased from baseline after administration of maralixibat, and the weekly average morning ItchRO (Obs) severity score did not worsen from baseline ≥1 point or improve either. Subject 5 had remarkably high baseline total bilirubin of 10.50 mg/dL and thus was deemed to have severe ALGS accompanied by advanced hepatic symptoms, which was potentially refractory to maralixibat, based on a report that patients aged 6 to 12 months with total bilirubin ≥10.0 mg/mL have a higher risk of liver transplant with a hazard ratio of 15.6 relative to those with total bilirubin <5.0 mg/mL (*Hepatology.* 2023;77:512-29).

Table 48. Changes of sBA concentration and weekly average morning ItchRO (Obs) severity score over time in each subject (Study 3001, ITT population)

	Age	sBA concentration (μmol/L)			Weekly average morning ItchRO (Obs) severity score		
		Baseline	Week 18	Week 22	Baseline	Week 18	Week 22
Subject 1	[redacted]	32.7	43.2	37.0	3.00	1.00	0.67
Subject 2		48.0	51.2	64.4	2.43	1.00	1.00
Subject 3		43.6	48.2	25.5	2.20	1.20	0.00
Subject 4		76.0	33.8	22.7	3.29	1.00	1.00
Subject 5		367.1	478.9	613.7	2.00	2.29	2.14
Subject 6		34.4	7.8	9.5	2.71	1.00	1.00
Subject 7		12.3	9.1	22.9	2.43	1.29	1.00

The above comprehensive evaluation of the efficacy of maralixibat indicates that results from Study 3001 support the efficacy similar to that observed in Study 304, as suggested by results in individual subjects except Subject 5, and thus the efficacy of maralixibat can be expected in Japanese patients with ALGS, although baseline fasting sBA concentration differed between Study 3001 and Study 304, and results in the patient with advanced hepatic symptoms accompanying ALGS (Subject 5) affected the overall results because of the limited sample size in Study 3001.

(iii) Efficacy by patient characteristic

Table 49 and Table 50 show results on "change in fasting sBA concentration from Week 18 to Week 22" and "change in weekly average morning ItchRO (Obs) severity score from Week 18 to Week 22," respectively, in Study 304 by patient characteristic. Although the number of subjects in each subgroup

[40] 7αC4 is an intermediate in the synthesis of bile acids from cholesterol. It is considered that a decrease in total amount of bile acids in the body enhances the synthesis of bile acids in a compensatory manner, leading to elevated 7αC4 concentrations in blood.

is very limited, the changes tended to be smaller in the maralixibat group than in the placebo group in any subgroup, suggesting the efficacy of maralixibat. For efficacy in subgroups by gene mutation, patients with ALGS harboring *NOTCH2* mutation were not enrolled in Study 304, but the efficacy of maralixibat can be expected irrespective of the gene mutation type, taking into account that the patients with ALGS harboring *NOTCH2* mutation share the pathogenesis of cholestasis, which is resulted from interlobular bile duct paucity, with those harboring *JAGGED1* mutation; and in a subject harboring *NOTCH2* mutation (Table 48, Subject 1) in Study 3001, symptoms of pruritus improved after administration of maralixibat.

Table 49. Change in fasting sBA concentration (μmol/L) from Week 18 to Week 22 by patient characteristic (Study 304, ITT population, OC)

Patient characteristic		Placebo (n = 16)	Maralixibat (n = 13)
Age	<7 years	89.10 ± 108.21 (11)	-5.01 ± 130.66 (9)
	≥7 years	103.43 ± 191.74 (5)	-43.11 ± 35.05 (4)
Sex	Male	106.85 ± 114.33 (10)	-41.06 ± 47.99 (9)
	Female	71.46 ± 168.83 (6)	38.01 ± 190.22 (4)
Duration of disease	<60 months	83.11 ± 72.34 (6)	6.74 ± 134.51 (8)
	≥60 months	99.86 ± 162.49 (10)	-54.29 ± 39.32 (5)
Interlobular bile duct paucity	No	36.92 (1)	-33.64 ± 73.73 (3)
	Yes	116.58 ± 147.20 (12)	18.65 ± 199.07 (4)
Baseline ALT	<171 U/L	75.18 ± 113.09 (10)	-20.37 ± 51.13 (5)
	≥171 U/L	124.25 ± 167.76 (6)	-14.46 ± 138.21 (8)
Baseline total bilirubin	<4.6 mg/dL	34.96 ± 34.60 (9)	-27.39 ± 53.02 (6)
	≥4.6 mg/dL	168.95 ± 175.40 (7)	-7.60 ± 146.61 (7)
Baseline fasting sBA concentration	<275 μmol/L	29.26 ± 26.78 (9)	-46.56 ± 72.23 (5)
	≥275 μmol/L	176.27 ± 170.30 (7)	1.91 ± 128.83 (8)
Baseline weekly average morning ItchRO (Obs) severity score	<3	149.81 ± 161.42 (7)	21.22 ± 129.06 (7)
	≥3	49.84 ± 92.98 (9)	-61.01 ± 67.10 (6)
Gene mutation	*JAGGED1*	93.58 ± 132.88 (16)	-16.73 ± 109.65 (13)
	NOTCH2	- (0)	- (0)

Mean ± SD (number of subjects); Individual values for ≤2 subjects (number of subjects); -, Not applicable

Table 50. Change in weekly average morning ItchRO (Obs) severity score from Week 18 to Week 22 by patient characteristic (Study 304, ITT population, OC)

Patient characteristic		Placebo (n = 16)	Maralixibat (n = 13)
Age	<7 years	1.745 ± 0.833 (11)	0.454 ± 0.401 (8)
	≥7 years	1.638 ± 1.430 (5)	-0.304 ± 1.098 (4)
Sex	Male	1.674 ± 0.842 (10)	0.213 ± 0.878 (9)
	Female	1.775 ± 1.322 (6)	0.167 ± 0.230 (3)
Duration of disease	<60 months	1.529 ± 0.973 (6)	0.519 ± 0.385 (7)
	≥60 months	1.822 ± 1.060 (10)	-0.243 ± 0.960 (5)
Interlobular bile duct paucity	No	1.571 (1)	0.393 ± 0.376 (3)
	Yes	1.568 ± 0.920 (12)	-0.476 ± 1.215 (3)
Baseline ALT	<171 U/L	1.765 ± 1.131 (10)	0.512 ± 0.440 (5)
	≥171 U/L	1.624 ± 0.847 (6)	-0.020 ± 0.882 (7)
Baseline total bilirubin	<4.6 mg/dL	1.929 ± 1.065 (9)	0.355 ± 0.326 (6)
	≥4.6 mg/dL	1.433 ± 0.924 (7)	0.048 ± 1.045 (6)
Baseline fasting sBA concentration	<275 μmol/L	1.901 ± 1.045 (9)	0.211 ± 0.382 (4)
	≥275 μmol/L	1.469 ± 0.975 (7)	0.196 ± 0.913 (8)
Baseline weekly average morning ItchRO (Obs) severity score	<3	1.722 ± 0.858 (7)	0.311 ± 0.361 (7)
	≥3	1.704 ± 1.159 (9)	0.048 ± 1.150 (5)
Gene mutation	*JAGGED1*	1.712 ± 1.005 (16)	0.201 ± 0.755 (12)
	NOTCH2	- (0)	- (0)

Mean ± SD (number of subjects); Individual values for ≤2 subjects (number of subjects); -, Not applicable

(iv) Long-term efficacy

Table 51 shows changes in the sBA concentration and weekly average morning ItchRO (Obs) severity score over the entire period of Study 304. For either endpoint, an improving trend observed in

maralixibat-treated subjects at Week 18, the end of the run-in period, was maintained throughout the treatment period, albeit the limited number of subjects assessed at >1 year.

Table 51. Changes of sBA concentration and weekly average morning ItchRO (Obs) severity score over time (Study 304, ITT population, OC)

Timepoint	Fasting sBA concentration (μmol/L)	Weekly average morning ItchRO (Obs) severity score
Baseline	283.43 ± 210.57 (31)	2.909 ± 0.548 (31)
Week 12	172.32 ± 181.81 (29)	1.352 ± 0.855 (29)
Week 18	192.50 ± 161.28 (29)	1.203 ± 0.845 (29)
Week 22[a)]	216.23 ± 207.34 (13)	1.380 ± 0.930 (12)
Week 48	169.61 ± 210.80 (27)	1.279 ± 1.140 (28)
Week 96[b)]	128.72 ± 140.56 (19)	0.799 ± 0.795 (13)
Week 144	110.64 ± 119.04 (15)	0.500 ± 0.767 (9)
Week 192	112.94 ± 130.71 (15)	0.424 ± 0.683 (12)
Week 240	90.06 ± 89.84 (5)	0.694 ± 0.782 (6)

Mean ± SD (number of subjects)
a) As the period from Week 18 to Week 22 constituted the RWD period, data in the placebo group at Week 22 were excluded.
b) For weekly average morning ItchRO (Obs) severity score, data at Week 98

Table 52 shows changes in the sBA concentration and weekly average morning ItchRO (Obs) severity score in the population of subjects aged ≥1 year over the entire period of Study 3001. For either endpoint, an improving trend observed in maralixibat-treated subjects at Week 18, the end of the dose-escalation period, and at Week 22, the primary timepoint, was generally maintained until Week 48.

Table 52. Changes of fasting sBA concentration and weekly average morning ItchRO (Obs) severity score over time (Study 3001, population of subjects aged ≥1 year, OC)

Timepoint	Fasting sBA concentration (μmol/L)	Weekly average morning ItchRO (Obs) severity score
Baseline	41.17 ± 21.06 [redacted]	2.676 ± 0.407 [redacted]
Week 12	30.18 ± 18.23 [redacted]	1.028 ± 0.600 [redacted]
Week 18	32.22 ± 19.34 [redacted]	1.081 ± 0.128 [redacted]
Week 22	30.33 ± 18.85 [redacted]	0.778 ± 0.404 [redacted]
Week 28	27.05 ± 14.31 [redacted]	0.943 ± 0.128 [redacted]
Week 38	23.32 ± 15.79 [redacted]	0.774 ± 0.560 [redacted]
Week 48	35.93 ± 25.08 [redacted]	0.690 ± 0.482 [redacted]

Mean ± SD (number of subjects)

As shown above, the long-term efficacy of maralixibat can be promising in patients with ALGS including Japanese patients [for the long-term efficacy in patients with ALGS aged <1 year, see (v)].

(v) Efficacy in patients with ALGS aged <1 year

[redacted]. However, in the currently ongoing foreign open-label uncontrolled study to investigate the efficacy and safety of maralixibat in patients with ALGS and those with PFIC aged <1 year (Study MRX-801 [Study 801]), an interim analysis was performed. Table 53

shows changes of the fasting sBA concentration and Clinician Scratch Scale (CSS)[41] score over time in patients with ALGS. Because of the limited number of subjects, variations were observed at some timepoints for both fasting sBA concentration and CSS, but a decreasing trend was observed starting at Week 3 or Week 13, and during the long-term treatment with maralixibat, the decreasing trends for both fasting sBA concentration and CSS were maintained overall.

In view of results on the efficacy in patients with ALGS aged <1 year in Study 801, the efficacy of maralixibat can be expected in patients with ALGS aged <1 year as in those aged ≥1 year, including the long-term efficacy.

Table 53. Changes of fasting sBA concentration and CSS over time (Study 801, patients with ALGS, OC)

Timepoint	Fasting sBA concentration (μmol/L)	CSS
Baseline	292.81 ± 218.76 (17)	2.06 ± 1.07 (17)
Week 3	143.80 ± 136.22 (11)	- (0)
Week 13	167.72 ± 112.45 (14)	1.69 ± 1.20 (16)
Week 29	201.83 ± 144.93 (12)	1.69 ± 1.11 (13)
Week 45	152.79 ± 141.54 (5)	1.60 ± 0,97 (10)
Week 61	251.34 ± 181.40 (5)	1.00 ± 0.94 (10)
Week 77	134.47 ± 161.67 (3)	1.75 ± 1.50 (4)
Week 93	9.95 (1)	1.00, 1.00 (2)

Mean ± SD (number of subjects); Individual values for ≤2 subjects (number of subjects); -, Not applicable

PMDA's view on the efficacy of maralixibat in patients with ALGS based on descriptions in the above Subsections (i) to (v):
Study 304 provided results on the primary endpoint, "change in fasting sBA concentration from Week 18 to Week 22," and all the secondary endpoints including pruritus assessment that suggest the efficacy of maralixibat. Thus, at least in the region where the concerned study was conducted, maralixibat has been shown to be effective in the treatment of cholestasis and pruritus in patients with ALGS.

In comparison between Study 3001 (overall population) and the maralixibat group in Study 304 (ITT population), the point estimates of the "change in fasting sBA concentration from Week 18 to Week 22" were opposite in terms of positive and negative numbers. However, this discrepancy is considered largely attributable to 1 subject (Subject 5) who showed a clear increase in fasting sBA concentration from Week 18 to Week 22. The impact of this outlier in Study 3001 with the very limited sample size was potentially greater than that of 1 outlier in Study 304. In view of the result of the "change in fasting sBA concentration from Week 18 to Week 22" in the population of subjects aged ≥1 year [redacted], which showed the same direction as that in Study 304, maralixibat is inferred to have the efficacy in the treatment of cholestasis in Japanese patients with ALGS as shown in non-Japanese patients with ALGS. Results in the ItchRO-based pruritus assessment in Study 3001 showed changes over time similar to those in Study 304, indicating that maralixibat can be expected to be effective in improving pruritus symptoms in Japanese patients with ALGS as in non-Japanese patients with ALGS. The result on the "change in fasting sBA concentration from baseline to Week 18" was smaller in Study 3001 than in Study 304, but when the comparison was limited to the population with the low fasting sBA concentration (<102 μmol/L), no large difference was noted between Study 304 and

[41] Scale for assessment of pruritus. Physicians rated severity of pruritus based on an extent of scratch scar and skin damage by scratching as follows: None = 0 points; rubbing or slightly scratching when finding no relief = 1 point; actively scratching with no evident excoriation, though = 2 points; evident excoriation = 3 points; and evident skin damage, bleeding, and scar = 4 points.

Study 3001. In addition, results in the ItchRO-based pruritus assessment did not largely differ between Study 304 and Study 3001. In view of the above findings on pruritus, maralixibat can be expected to be effective in improving pruritus symptoms even in a population with low fasting sBA concentrations. Response to maralixibat is thus not considered to differ between Japanese and non-Japanese patients with ALGS. Evaluation on data from individual subjects showed a clinically meaningful improvement ≥1 point in the ItchRO-based pruritus assessment, a decrease in fasting sBA concentration, or an elevation in 7αC4 concentration in blood in all subjects, except for one who had a severe disease (Subject 5), suggesting the efficacy of maralixibat.

For patients with ALGS aged <1 year, [redacted] enrolled in Study 3001 did not show any improving trend of the fasting sBA concentration or symptoms of pruritus after administration of maralixibat, but the concerned subject had a severe disease with advanced hepatic symptoms and thus is deemed to be refractory. Patients with ALGS aged <1 year in Study 801 showed improving trends of both fasting sBA concentration and symptoms of pruritus as with patients in Study 304. In addition, the efficacy in patients with ALGS aged ≥1 year can be expected for both Japanese and non-Japanese. Taking account of the above, the efficacy of maralixibat can be expected in Japanese patients with ALGS aged <1 year, as well.

Given that the response to maralixibat measured as the fasting sBA concentration and weekly average morning ItchRO (Obs) severity score was maintained during the long-term treatment with maralixibat in Studies 304, 3001, and 801, the long-term efficacy of maralixibat can be expected as well.

Based on the above, the results in Study 3001 are considered similar to those in Study 304. As a result of comprehensive evaluation with the findings described below taken into account, maralixibat can be expected to have the efficacy in the treatment of cholestasis and pruritus in Japanese patients with ALGS, including its long-term use and use in patients aged <1 year: (1) The results in Study 801 and results on long-term efficacy in each study were supportive; (2) maralixibat is a drug that is hardly absorbed and acts in the gastrointestinal tract lumen; and (3) the diagnostic criteria and treatment methods for ALGS in Japan are not largely different from those outside Japan [see Section 7.R.1.1.1].

7.R.1.2 Efficacy of maralixibat in patients with PFIC

7.R.1.2.1 Development program of maralixibat

The applicant's explanation about the development program of maralixibat in patients with PFIC:
In Japan, a diagnosis of PFIC is given based on the diagnostic criteria of PFIC consisted of clinical symptoms and findings (e.g., persistent jaundice, white faeces, steatorrhoea, hepatosplenomegaly, marked pruritus), haematological findings (e.g., increased direct bilirubin, total bile acids, AST, and ALT levels), liver biopsy findings, and gene test results (mutations in *ATP8B1* [PFIC1], *ABCB11* [PFIC2], *ABCB4* [PFIC3] genes, etc.). The diagnostic criteria in Japan are not largely different from those outside Japan. Drugs used for treatment of PFIC include ursodeoxycholic acid and bile acid adsorbent, and those for treatment of pruritus include antihistamines and phenobarbital. The treatment algorithm for PFIC in Japan is also not largely different from that outside Japan. Furthermore, maralixibat is hardly absorbed or metabolized in the gastrointestinal tract and acts on IBAT present in the gastrointestinal tract lumen, thus intrinsic ethnic factors are unlikely to affect the efficacy of maralixibat. When the development was initiated in Japan, patient enrollment in the foreign phase III study (Study MRX-502 [Study 502]) was

completed. Because of the very limited number of patients with PFIC in Japan, a placebo-controlled study with the sample size enough to evaluate the efficacy and safety of maralixibat cannot be conducted only in Japan. Therefore, the Japanese phase III study was designed to obtain data that would be eligible for comparison with results from Study 502 and conducted as an open-label uncontrolled study. The clinical data package was compiled additionally including results from foreign studies in non-Japanese patients with PFIC and used to evaluate the efficacy and safety of maralixibat in Japanese patients with PFIC.

The study population of Study 502 was patients with PFIC who were aged ≥12 months and <18 years, had at least a certain level of symptoms of pruritus during nighttime, and weighed ≥5 kg. The minimum body weight was specified based on the accurately deliverable minimum dosing volume with a 0.5 mL-dosing dispenser for oral use, which was the smallest one (Table 37). In patients with PFIC, pruritus causes exhaustion and impaired QOL, and especially, pruritus during nighttime potentially leads to sleep disorders and subsequently growth disorder. For this reason, the average morning ItchRO (Obs) severity score was specified as the primary efficacy measure. Primary efficacy was evaluated between Week 15 and Week 26 to minimize outliers, missing data, and variations due to temperature changes, etc. This time-point was determined based on results from the foreign phase II study (Study LUM001-501 [Study 501]) conducted before Study 502, because Study 501 suggested that the effect of maralixibat would peak at Week 13 or later. In view of these points, the primary endpoint was specified as a "change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26." The secondary endpoint was specified as a change in fasting sBA concentration since (i) elevated sBA concentrations in a cholestatic disease cause pruritus and affect progression of hepatic cirrhosis (*Arch Intern Med.* 1972;130:632-7, *World J Gastroenterol.* 2009;15:804-16), and (ii) the sBA concentration reflects a pharmacodynamic potential of maralixibat, an IBAT inhibitor. In view of the following points (a) to (d), the primary cohort included patients with nt-PFIC2 who were predicted to have remaining BSEP function (except for patients with heterozygous nt-PFIC2, those with low or fluctuating sBA concentrations, and those with a prior surgery for treatment of PFIC), and the cohort was used as the primary efficacy analysis set: (a) In Study 501, responders were all patients with PFIC2; (b) in general, patients with PFIC2 have no extrahepatic symptoms; (c) PFIC2 is the most common subtype outside Japan; and (d) patients with t-PFIC2 caused by *ABCB11* mutation and accompanied by complete absence of BSEP function have almost no enterohepatic circulation of bile acids and thus are unlikely to respond to maralixibat. However, since it has been reported that patients with PFIC1 and those with PFIC3 also responded to drugs in the same class with the same mechanism of action as that of maralixibat (*Clin Res Hepatol Gastroenterol.* 2021;45:101751), the protocol allowed enrollment of any patient with PFIC other than nt-PFIC2 in the supplemental cohort. Then, of all subjects (primary cohort or supplemental cohort), the following subjects were excluded: Subjects with confirmed known genotypes (PFIC1-6 subtypes) who additionally had t-PFIC2, heterozygous mutations, low or fluctuating sBA concentrations, a prior surgery for treatment of PFIC, or no confirmed mutations related to PFIC. The remaining subjects were included in the PFIC cohort, which was used in the efficacy evaluation in addition to the primary cohort.

A Japanese phase III study in patients with PFIC (Study TAK-625-3002 [Study 3002]) was designed as an open-label, uncontrolled study in which the target patients,[42] primary cohort (Table 37), and efficacy endpoints were similar to those in Study 502. Results on the primary endpoint in the primary cohort ITT population in Study 3002 were analyzed for their similarity to those in Study 502 based on the following 2 viewpoints.

- A point estimate of a "change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26" in the maralixibat group does not largely differ between these studies, and 95% CIs in these studies mostly overlap.
- The point estimate of the "change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26" in Study 3002 was smaller than that in the placebo group in Study 502.

Because of the very limited sample size in Study 3002, evaluation was also performed in the PFIC cohort ITT population in Study 502 and overall cohort ITT population in Study 3002 as done above, and data from individual subjects were further investigated in detail. Thereby, the efficacy of maralixibat was comprehensively evaluated.

PMDA's view:
Conducting Study 3002 as an open-label uncontrolled study in a design similar to that in Study 502 is unavoidable, taking into account that (1) Patient enrollment in Study 502 was completed when the development was initiated in Japan; and (2) the number of patients with PFIC in Japan is very limited. On that premise, in view of the diagnostic criteria and treatment methods for PFIC in Japan, which are not largely different from those outside Japan, and the pharmacological effect of maralixibat, the efficacy and safety of maralixibat in Japanese patients with PFIC can be evaluated using data from Study 502 as much as possible, with consideration for impacts of ethnic factors, after analyzing results from Study 3002 for similarity to those from Study 502.

7.R.1.2.2 Results in Studies 502 and 3002

The applicant's explanation about efficacy results from Studies 502 and 3002 is presented in the subsections below.

(i) Results from Study 502

Table 54 shows results on the primary endpoint in Study 502. In the primary cohort ITT population, the primary efficacy analysis set, the results on the "change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26" in the maralixibat group were demonstrated to be statistically superior to those in the placebo group, and a decrease in score from baseline >1 point, which is deemed as a clinically meaningful change, was observed in the maralixibat group. Similar results were obtained in the PFIC cohort (Table 54).

[42] In Study 502, patients weighing ≥5 kg and aged ≥1 year and <18 years were included, but the range of age of subjects eligible for Study 3002 was expanded to the lower limit of 1 month without the upper limit, and the lower limit of body weight of subjects eligible for Study 3002 was further lowered to 3 kg on the condition that the study drug should be diluted for patients weighing <5 kg, because (1) unmet medical needs in patients aged <1 year and patients aged >18 years were deemed to be high in Japan; (2) Study 801 was being conducted in patients with ALGS and those with PFIC aged <1 year; (3) the safety information in patients weighing <5 kg and aged <1 year in the concerned study supported the conduct of Study 3002; and (4) the presumed body weight of patients with PFIC aged 1 month was taken into account.

Table 54. Change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26 (Study 502, ITT population, OC)

	Primary cohort		PFIC cohort	
	Placebo (n = 17)	Maralixibat (n = 14)	Placebo (n = 31)	Maralixibat (n = 33)
Baseline[a)]	2.611 ± 0.893 (17)	2.876 ± 0.912 (14)	2.732 ± 0.881 (31)	2.850 ± 0.876 (33)
Average at Weeks 15-18	2.092 ± 1.192 (15)	1.032 ± 0.933 (14)	2.098 ± 1.220 (28)	1.065 ± 1.094 (33)
Average at Weeks 19-22	2.078 ± 1.186 (15)	1.036 ± 0.889 (13)	2.075 ± 1.175 (28)	1.013 ± 1.049 (32)
Average at Weeks 23-26	2.082 ± 1.229 (15)	1.141 ± 1.106 (13)	2.171 ± 1.235 (28)	1.073 ± 1.164 (32)
Change from baseline to Weeks 15-26[b)]	-0.628 [-1.136, -0.121]	-1.718 [-2.272, -1.163]	-0.610 [-1.000, -0.221]	-1.811 [-2.178, -1.444]
Difference from the result in the placebo *P* value[b)]	-1.089 [-1.845, -0.334] 0.0063[c)]		-1.200 [-1.727, -0.674] -	

Mean ± SD (number of subjects); Change is expressed as least squares mean [95% CI].

a) Average during a period of 4 weeks before baseline visit

b) Average of estimated values for each of 3 periods (Weeks 15-18, Weeks 19-22, Weeks 23-26), which were obtained in an MMRM on the hypothesis of an unstructured variance-covariance matrix on intra-subject error using the dose group, period, interaction between the dose group and period, baseline value, and interaction between the baseline value and period as explanation variables (for the PFIC cohort, PFIC subtype is added as an explanation variable).

c) Two-sided significance level of 5%

Table 55 shows results on fasting sBA concentrations selected as a secondary endpoint in Study 502. The fasting sBA concentrations tended to decrease from baseline to Weeks 18 to 26 in the maralixibat group in both primary cohort and PFIC cohort.

Table 55. Changes of fasting sBA concentration (μmol/L) over time and changes from baseline (Study 502, ITT population, OC)

	Primary cohort		PFIC cohort	
	Placebo (n = 17)	Maralixibat (n = 14)	Placebo (n = 31)	Maralixibat (n = 33)
Baseline	312.28 ± 151.99 (17)	311.88 ± 157.60 (12)	272.30 ± 147.40 (31)	254.33 ± 139.52 (31)
Week 18	318.02 ± 181.89 (13)	161.09 ± 175.28 (12)	275.41 ± 162.32 (25)	116.57 ± 139.68 (29)
Week 22	281.46 ± 171.24 (13)	111.89 ± 138.48 (12)	247.78 ± 150.99 (26)	91.82 ± 109.19 (30)
Week 26	319.84 ± 170.24 (15)	130.79 ± 158.92 (12)	275.85 ± 154.30 (28)	111.94 ± 123.33 (30)
Change from baseline to Week 26	18.55 [-53.22, 90.31]	-164.64 [-248.89, -80.38]	5.80 [-40.71, 52.31]	-149.68 [-193.81, -105.55]
Change from baseline to Weeks 18, 22, and 26[a)]	11.19 [-58.07, 80.45]	-175.54 [-256.72, -94.36]	2.91 [-42.32, 48.15]	-157.49 [-200.28, -114.70]
Difference from the result in the placebo[a)]	-186.72 [-293.45, -79.99]		-160.40 [-220.84, -99.97]	

Mean ± SD (number of subjects); Change is expressed as least squares mean [95% CI].

a) Average of estimated values at each of 3 timepoints (Week 18, Week 22, Week 26), which were obtained in an MMRM on the hypothesis of an unstructured variance-covariance matrix on intra-subject error using the dose group, timepoint, interaction between dose group and timepoint, baseline value, and interaction between the baseline value and timepoint as explanation variables (for the PFIC cohort, PFIC subtype is added as an explanation variable).

Based on the above, in Study 502, maralixibat was shown to improve symptoms of pruritus associated with PFIC, and the results in the primary cohort, the primary analysis set, were similar to those in the PFIC cohort, which also included patients with any of PFIC1 and PFIC3 to PFIC6 subtypes. Maralixibat was also shown to decrease fasting sBA concentrations. These results are considered to demonstrate the efficacy of maralixibat in the treatment of pruritus and cholestasis in non-Japanese patients with PFIC.

(ii) Results from Study 3002

Table 56 and Table 57 show results on the "change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26" and fasting sBA concentrations, the primary and secondary endpoints in Study 3002, respectively.

Table 56. Change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26 (Study 3002, ITT population)

	Primary cohort (n = 3)	Overall cohort (n = 5)
Baseline[a)]	2.618 ± 0.216 (3)	2.557 ± 0.349 (5)
Average at Weeks 15-18	1.615 ± 0.544 (2)	1.891 ± 0.454 (4)
Average at Weeks 19-22	1.088 ± 1.052 (3)	1.476 ± 0.914 (5)
Average at Weeks 23-26	1.133 ± 1.206 (3)	1.706 ± 1.184 (5)
Change in average from baseline to Weeks 15 to 26[b)]	-1.514 [-3.654, 0.626]	-0.989 [-2.184, 0.205]

Mean ± SD (number of subjects); Change is expressed as mean [95% CI].
a) Average during a period of 4 weeks before baseline visit
b) 95% CI was calculated based on the t-distribution.

Table 57. Changes of fasting sBA concentration (μmol/L) over time and changes from baseline (Study 3002, ITT population)

	Primary cohort (n = 3)	Overall cohort (n = 5)
Baseline	296.33 ± 252.01 (3)	289.04 ± 178.76 (5)
Week 18	154.50 ± 131.29 (3)	174.54 ± 97.48 (5)
Week 22	166.90 ± 146.84 (3)	222.76 ± 129.24 (5)
Week 26	146.43 ± 126.03 (3)	191.80 ± 108.64 (5)
Change from baseline to Week 26[a)]	-149.90 [-561.40, 261.60]	-97.24 [-268.37, 73.89]

Mean ± SD (number of subjects); Change is expressed as mean [95% CI].
a) 95% CI was calculated based on the t-distribution.

Comparison of the results in the primary cohort ITT population between Study 502 and Study 3002 showed that the point estimate of "change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26" in the maralixibat group did not largely differ between these studies, and the 95% CIs in these studies mostly overlapped (−1.718 [−2.272, −1.163] in Study 502, −1.514 [−3.654, 0.626] in Study 3002). The point estimate (−1.514) of the concerned change in the maralixibat group in Study 3002 was smaller than that (−0.628) in the placebo group in Study 502. The above results on the primary endpoint met the pre-determined criteria for similarity of Study 3002 to Study 502 [see Section 7.R.1.2.1].

The point estimate of "change in fasting sBA concentration from baseline to Week 26," the secondary endpoint, in the maralixibat group in the primary cohort ITT population did not largely differ between Study 502 and Study 3002 either, and the 95% CIs in these studies mostly overlapped (−164.64 [−248.89, −80.38] μmol/L in Study 502, −149.90 [−561.40, 261.60] μmol/L in Study 3002), and the point estimate (−149.90 μmol/L) in the maralixibat group in Study 3002 was smaller than that (18.55 μmol/L) in the placebo group in Study 502. Comparisons on the same endpoints as the above between the PFIC cohort in Study 502 and overall cohort in Study 3002 showed similar results.

Given the very limited sample size, the efficacy of maralixibat was investigated for individual subjects in Study 3002. Table 58 shows results on the average morning ItchRO (Obs) severity score and sBA concentrations in individual subjects in Study 3002. Fasting sBA concentrations showed a decreasing trend from baseline to Week 26 in all subjects, and average morning ItchRO (Obs) severity scores also

showed an improving trend in almost all subjects. Average morning ItchRO (Obs) severity scores in Subjects 2 and 3 decreased from baseline to Week 28 by >1 point.

Table 58. Changes of sBA concentration and average morning ItchRO (Obs) severity score over time in individual subjects (Study 3002, ITT population)

		Age	Average morning ItchRO (Obs) severity score				sBA concentration (μmol/L)			
			Baseline	Week 18	Week 22	Week 26	Baseline	Week 18	Week 22	Week 26
Primary cohort	Subject 1	[redacted] years	2.85	2.00	2.18	2.40	255.4	229.4	285.6	212.6
	Subject 2	1[redacted] years	2.42	-	0.08	0	67.3	2.9	2.7	1.1
	Subject 3	[redacted] years	2.59	1.23	1.00	1.00	566.3	231.2	212.4	225.6
Supplemental cohort (PFIC1)	Subject 4	1[redacted] years	2.89	2.26	2.08	2.91	292.4	220.7	318.6	261.9
	Subject 5	[redacted] years	2.04	2.07	2.04	2.22	263.8	188.5	294.5	257.8

-, Not applicable

As shown above, results from Study 3002 are similar to those from Study 502, and results in individual subjects in Study 3002 also suggest the efficacy. Therefore, the efficacy of maralixibat can be expected in Japanese patients with PFIC.

(iii) Efficacy by patient characteristic

Table 59 and Table 60 show results on the "change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26" and "change in fasting sBA concentration from baseline to Week 26" by patient characteristic in Study 502, respectively. Although the number of subjects in each subgroup is very limited, the changes tended to be smaller in the maralixibat group than in the placebo group in any subgroup in the primary cohort, and similar trends were observed in the PFIC cohort as well, suggesting the efficacy of maralixibat. For efficacy in subgroups by gene mutation in the PFIC cohort, changes in sBA concentration in patients with PFIC harboring *TJP2* mutation (PFIC4 subtype) did not show any difference between the groups, but in view of the points described below, there are no definitive reasons for attenuated efficacy of maralixibat in patients with PFIC4, and thus the efficacy of maralixibat can be expected irrespective of the gene mutation type: (1) In the concerned subgroup, the placebo group included only 1 subject, and the maralixibat group showed a decrease in sBA concentration as with the maralixibat group in the subgroups of patients with the other PFIC subtypes; (2) in the subgroup of patients with PFIC4, results on the average morning ItchRO (Obs) severity score in the maralixibat group also showed a large improvement compared to the placebo group; (3) PFIC4 is characterized by cholestasis involving hepatocytes as with the other PFIC subtypes; and (4) maralixibat acts by inhibiting IBAT at the ileal terminal.

Table 59. Change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26 by patient characteristic (Study 502, ITT population, OC)

Patient characteristic		Primary cohort		PFIC cohort	
		Placebo (n = 17)	Maralixibat (n = 14)	Placebo (n = 31)	Maralixibat (n = 33)
Age	<7 years	-0.713 ± 0.818 (10)	-1.535 ± 1.033 (9)	-0.751 ± 0.817 (20)	-1.578 ± 1.282 (24)
	≥7 years	-0.370 ± 1.327 (5)	-2.285 ± 1.886 (5)	-0.288 ± 1.020 (8)	-2.382 ± 1.373 (9)
Sex	Male	0.215 ± 0.606 (4)	-1.638 ± 1.455 (7)	-0.410 ± 0.954 (11)	-1.608 ± 1.484 (17)
	Female	-0.895 ± 0.935 (11)	-1.967 ± 1.384 (7)	-0.754 ± 0.840 (17)	-1.997 ± 1.174 (16)
Duration of disease	<22 months	-0.991 ± 0.986 (8)	-1.651 ± 1.661 (4)	-0.959 ± 0.913 (16)	-1.714 ± 1.533 (14)
	≥22 months	-0.150 ± 0.817 (7)	-1.863 ± 1.340 (10)	-0.166 ± 0.630 (12)	-1.858 ± 1.211 (19)
Baseline ALT	<82 U/L	-0.245 ± 0.916 (6)	-1.863 ± 0.911 (7)	-0.494 ± 0.961 (13)	-1.706 ± 1.251 (19)
	≥82 U/L	-0.835 ± 1.000 (9)	-1.742 ± 1.804 (7)	-0.727 ± 0.834 (15)	-1.920 ± 1.482 (14)
Baseline total bilirubin	<2.7 mg/dL	-0.475 ± 0.964 (10)	-1.851 ± 1.256 (9)	-0.485 ± 0.886 (15)	-2.201 ± 1.196 (16)
	≥2.7 mg/dL	-0.845 ± 1.077 (5)	-1.716 ± 1.724 (5)	-0.773 ± 0.895 (13)	-1.417 ± 1.383 (17)
Baseline fasting sBA concentration	<250 µmol/L	-0.359 ± 1.160 (6)	-0.843 ± 0.940 (4)	-0.314 ± 0.876 (14)	-1.590 ± 1.414 (16)
	≥250 µmol/L	-0.759 ± 0.877 (9)	-2.075 ± 1.484 (8)	-0.924 ± 0.813 (14)	-1.906 ± 1.310 (15)
Baseline average morning ItchRO (Obs) severity score	<2.9	-0.229 ± 0.738 (8)	-0.667 ± 0.675 (7)	-0.483 ± 0.786 (15)	-0.982 ± 0.946 (16)
	≥2.9	-1.021 ± 1.103 (7)	-2.938 ± 0.793 (7)	-0.775 ± 0.998 (13)	-2.564 ± 1.200 (17)
Gene mutation	*ATP8B1*	- (0)	- (0)	-0.347 ± 0.714 (6)	-1.324 ± 1.662 (7)
	ABCB11	-0.599 ± 0.980 (15)	-1.803 ± 1.375 (14)	-0.599 ± 0.980 (15)	-1.803 ± 1.375 (14)
	ABCB4	- (0)	- (0)	-1.255 ± 0.693 (5)	-1.712 ± 0.832 (4)
	TJP2	- (0)	- (0)	-0.062 (1)	-1.827 ± 1.098 (6)
	MYO5B	- (0)	- (0)	0.071 (1)	-4.000, -2.986 (2)

Mean ± SD (number of subjects); Individual values for ≤2 subjects (number of subjects); -, Not applicable

Table 60. Change in fasting sBA concentration (µmol/L) from baseline to Week 26 by patient characteristic (Study 502, ITT population, OC)

Patient characteristic		Primary cohort		PFIC cohort	
		Placebo (n = 17)	Maralixibat (n = 14)	Placebo (n = 31)	Maralixibat (n = 33)
Age	<7 years	-1.60 ± 80.14 (10)	-118.54 ± 117.98 (7)	11.59 ± 81.53 (20)	-95.17 ± 115.05 (21)
	≥7 years	63.40 ± 223.96 (5)	-277.10 ± 215.33 (4)	-6.69 ± 203.23 (8)	-274.51 ± 155.49 (8)
Sex	Male	70.30 ± 258.67 (4)	-166.03 ± 171.75 (5)	33.18 ± 172.13 (11)	-144.97 ± 153.75 (15)
	Female	1.80 ± 76.17 (11)	-184.68 ± 183.12 (6)	-10.98 ± 82.16 (17)	-144.30 ± 149.19 (14)
Duration of disease	<22 months	-5.26 ± 49.40 (8)	-217.97 ± 132.44 (4)	2.83 ± 70.38 (16)	-160.33 ± 148.76 (14)
	≥22 months	49.01 ± 201.84 (7)	-152.33 ± 192.80 (7)	11.08 ± 176.47 (12)	-130.01 ± 152.59 (15)
Baseline ALT	<82 U/L	80.62 ± 203.19 (6)	-121.56 ± 140.24 (5)	51.04 ± 148.34 (13)	-124.44 ± 138.37 (16)
	≥82 U/L	-20.30 ± 60.65 (9)	-221.74 ± 190.04 (6)	-32.35 ± 86.54 (15)	-169.51 ± 162.93 (13)
Baseline total bilirubin	<2.7 mg/dL	35.91 ± 164.48 (10)	-119.64 ± 184.74 (6)	13.55 ± 149.99 (15)	-111.76 ± 136.35 (12)
	≥2.7 mg/dL	-11.61 ± 73.32 (5)	-244.06 ± 135.79 (5)	-1.92 ± 91.61 (13)	-167.86 ± 156.86 (17)
Baseline fasting sBA concentration	<250 µmol/L	69.22 ± 187.96 (6)	-10.00 ± 49.51 (3)	38.00 ± 137.86 (14)	-58.08 ± 73.76 (14)
	≥250 µmol/L	-12.70 ± 94.67 (9)	-238.52 ± 154.81 (8)	-25.26 ± 104.60 (14)	-225.44 ± 157.38 (15)
Baseline average morning ItchRO (Obs) severity score	<2.9	43.35 ± 172.84 (8)	-90.49 ± 116.99 (5)	-2.16 ± 151.322 (15)	-101.65 ± 118.56 (14)
	≥2.9	-6.54 ± 94.96 (7)	-247.62 ± 181.40 (6)	16.21 ± 88.69 (13)	-184.77 ± 166.38 (15)
Gene mutation	*ATP8B1*	- (0)	- (0)	53.95±63.51 (6)	-82.02±126.71 (7)
	ABCB11	20.07 ± 139.52 (15)	-176.20 ± 169.30 (11)	20.07 ± 139.52 (15)	-176.20 ± 169.30 (11)
	ABCB4	- (0)	- (0)	-54.33 ± 119.45 (5)	-107.33 ± 114.72 (4)
	TJP2	- (0)	- (0)	-174.47 (1)	-150.42 ± 138.30 (5)
	MYO5B	- (0)	- (0)	-0.29 (1)	-416.03, -84.91 (2)

Mean ± SD (number of subjects); Individual values for ≤2 subjects (number of subjects); -, Not applicable

(iv) Long-term efficacy

Table 61 and Table 62 show changes of the average morning ItchRO (Obs) severity score and fasting sBA concentration over time in Study MRX-503 (Study 503), an extension study in patients who had completed Study 502.[43] For either endpoint, an improvement was observed after administration of maralixibat, and the improving trend was mostly maintained throughout the treatment period, although the number of subjects at timepoints of >1 year is limited.

Table 61. Changes of average morning ItchRO (Obs) severity score over time (Study 503, ITT population, OC)

Timepoint	Primary cohort		PFIC cohort	
	Placebo - maralixibat[a)]	Maralixibat - maralixibat[b)]	Placebo - maralixibat[a)]	Maralixibat - maralixibat[b)]
Baseline	2.083 ± 1.289 (13)	2.876 ± 0.912 (14)	2.204 ± 1.321 (24)	2.850 ± 0.876 (33)
Weeks 15-18	0.820 ± 1.290 (10)	1.032 ± 0.933 (14)	1.219 ± 1.438 (19)	1.065 ± 1.094 (33)
Weeks 19-22	0.281 ± 0.502 (8)	1.036 ± 0.889 (13)	1.107 ± 1.289 (15)	1.013 ± 1.049 (32)
Weeks 23-26	0.949 ± 1.362 (8)	1.141 ± 1.106 (13)	1.508 ± 1.480 (15)	1.073 ± 1.164 (32)
Weeks 51-54	1.104 ± 1.350 (4)	0.532 ± 0.650 (8)	1.276 ± 1.487 (6)	0.723 ± 0.918 (19)
Weeks 75-78	1.29 (1)	0.277 ± 0.463 (4)	1.286 (1)	0.900 ± 1.096 (8)
Weeks 87-90	- (0)	0.00, 1.08 (2)	- (0)	0.573 ± 0.664 (4)

Mean ± SD (number of subjects); Individual values for ≤2 subjects (number of subjects); -, Not applicable
a) Group of subjects who received placebo in Study 502 and then started maralixibat in Study 503
b) Group of subjects who received maralixibat in Study 502 and then continued maralixibat in Study 503.

Table 62. Changes of fasting sBA concentration (µmol/L) over time (Study 503, ITT population, OC)

Timepoint	Primary cohort		PFIC cohort	
	Placebo - maralixibat[a)]	Maralixibat - maralixibat[b)]	Placebo - maralixibat[a)]	Maralixibat - maralixibat[b)]
Baseline	303.01 ± 177.22 (13)	311.88 ± 157.60 (12)	285.10 ± 140.27 (24)	254.33 ± 139.52 (31)
Week 18	156.37 ± 177.02 (10)	161.09 ± 175.28 (12)	173.93 ± 150.66 (17)	116.57 ± 139.68 (29)
Week 22	163.98 ± 159.80 (8)	111.89 ± 138.48 (12)	183.26 ± 127.85 (15)	91.82 ± 109.19 (30)
Week 26	113.66 ± 105.18 (8)	121.60 ± 155.71 (13)	129.83 ± 92.52 (14)	108.70 ± 122.59 (31)
Week 58	147.91 ± 101.10 (5)	32.53 ± 69.96 (8)	142.09 ± 81.04 (8)	51.51 ± 75.00 (17)
Week 82	- (0)	3.77 ± 1.33 (4)	- (0)	34.57 ± 53.56 (7)
Week 94	- (0)	5.03, 5.76 (2)	- (0)	32.69 ± 56.01 (4)

Mean ± SD (number of subjects); Individual values for ≤2 subjects (number of subjects); -, Not applicable
a) Group of subjects who received placebo in Study 502 and then started maralixibat in Study 503
b) Group of subjects who received maralixibat in Study 502 and then continued maralixibat in Study 503.

Table 63 and Table 64 show changes of the average morning ItchRO (Obs) severity score and fasting sBA concentration over an entire period of Study 3002. For either endpoint, an improving trend observed in maralixibat-treated subjects at up to Week 26, the primary timepoint for efficacy evaluation, was maintained until Week 48.

[43] To keep Study 502 blinded, all subjects received maralixibat irrespective of the dose group in Study 502 at acceding doses over a period of 4 to 6 weeks as done in Study 502 and then continued maralixibat at the maximum tolerated dose determined for each subject (range, 150-600 µg/kg BID).

Table 63. Changes of average morning ItchRO (Obs) severity score over time (Study 3002, ITT population, OC)

Timepoint	Primary cohort	Overall cohort
Baseline	2.618 ± 0.216 (3)	2.557 ± 0.349 (5)
Week 14	1.363 ± 0.663 (3)	1.704 ± 0.680 (5)
Week 18	1.615 ± 0.544 (2)	1.891 ± 0.454 (4)
Week 22	1.088 ± 1.052 (3)	1.476 ± 0.914 (5)
Week 26	1.133 ± 1.206 (3)	1.706 ± 1.184 (5)
Week 36	1.091 ± 1.139 (3)	1.543 ± 1.025 (5)
Week 48	0.742 ± 1.286 (3)	1.276 ± 1.167 (5)

Mean ± SD (number of subjects)

Table 64. Changes of fasting sBA concentration (μmol/L) over time (Study 3002, ITT population, OC)

Timepoint	Primary cohort	Overall cohort
Baseline	296.33 ± 252.01 (3)	289.04 ± 178.76 (5)
Week 14	153.90 ± 138.13 (3)	171.42 ± 100.58 (5)
Week 18	154.50 ± 131.29 (3)	174.54 ± 97.48 (5)
Week 22	166.90 ± 146.84 (3)	222.76 ± 129.24 (5)
Week 26	146.43 ± 126.03 (3)	191.80 ± 108.64 (5)
Week 36	60.10 ± 99.95 (3)	145.00 ± 136.53 (5)
Week 48	42.30 ± 64.12 (3)	95.38 ± 87.11 (5)

Mean ± SD (number of subjects)

Based on the above, the long-term efficacy of maralixibat can be expected in Japanese patients with PFIC.

(v) Efficacy in patients with PFIC aged <1 year

Although patients with PFIC aged ≥1 month were eligible for Study 3002, patients with PFIC <1 year were not enrolled. Table 65 shows changes of the fasting sBA concentration, CSS score, and average morning ItchRO (Obs) severity score in patients with PFIC enrolled in Study 801 for which patients with ALGS and those with PFIC aged <1 year were eligible. After administration of maralixibat, a decreasing trend of the fasting sBA concentration was observed, but no definitive improving trend was observed in pruritus assessment. This discrepancy was considered largely attributable to the infant subjects in whom observer-reported pruritus assessment might have not been adequately performed because of their underdeveloped motor functions. Actually, investigation of the data in 7 subjects with baseline ItchRO (Obs) scores available showed that baseline sBA concentrations and total bilirubin did not largely differ between subjects aged <5 months[44)] and those aged ≥5 months (sBA, 289.33 μmol/L in subjects aged <5 months and 179.51 μmol/L in those aged ≥5 months; total bilirubin 49.77 μmol/L in subjects aged <5 months and 35.19 μmol/L in those aged ≥5 months), but baseline average morning ItchRO (Obs) severity score was <2 in all of the 4 subjects aged <5 months, compared to ≥2 in 2 of 3 subjects aged ≥5 months; the baseline score in subjects aged <5 months tended to be lower than that in those aged ≥5 months. In 3 subjects aged ≥5 months with baseline ItchRO (Obs) scores available, changes in average morning ItchRO (Obs) severity score from baseline to Week 6 and Week 10 (individual value or mean) were −1.85 (in 1 subject) and −1.71 (in 2 subjects), respectively, and at most of the other timepoints, a decreasing trend from baseline was observed. These findings support the possibility that observer-reported pruritus assessment might have not been adequately performed in subjects aged <5 months. In view of the results in subjects aged ≥5 months, maralixibat can be expected

44) In infants whose motor functions are being developed, observable signs related to pruritus are generally limited. Especially the hand's motor functions needed for scratching develop around 5 to 6 months of age, and in infants younger than that age, scratching is not generally observed (*Cells.* 2021;10:2788). Therefore, data on the baseline ItchRO (Obs) score were discussed by age category (<5 and ≥5 months of age).

to improve symptoms of pruritus in patients with PFIC aged <1 year as well. A decreasing trend of fasting sBA concentration after administration of maralixibat is also observed in patients with PFIC aged <1 year including those aged <5 months, and thus the pharmacological effect of maralixibat was shown and maintained until Week 29 (Table 65). The long-term efficacy of maralixibat was evaluated in Study 801. In patients with PFIC, the fasting sBA concentration (mean ± SD) at Week 61 was 90.44 ± 136.70 μmol/L (in 3 subjects) and CSS (mean ± SD) at Week 61 was 1.33 ± 1.16 (in 3 subjects). Although the number of patients was limited, the results of assessment of pruritus were not largely different from those until Week 29 (Table 65), and a decreasing trend of the fasting sBA concentration was also maintained until Week 61.

In view of results on the efficacy in patients with PFIC aged <1 year in Study 801, the efficacy of maralixibat can be expected in patients with PFIC aged <1 year as in those aged ≥1 year, including the long-term efficacy.

Table 65. Changes of fasting sBA concentration, CSS score, and average morning ItchRO (Obs) severity score over time (Study 801, patients with PFIC, OC)

	Baseline	Week 6[a)]	Week 10	Week 13	Week 29[b)]
Fasting sBA concentration (μmol/L)	228.32 ± 107.53 (9)	179.24 ± 137.14 (8)	196.58 ± 145.21 (9)	130.33 ± 88.20 (8)	170.43 ± 109.39 (8)
CSS	1.55 ± 1.21 (10)	1.40 ± 1.35 (10)	-	1.70 ± 1.57 (10)	1.56 ± 1.42 (9)
Average morning ItchRO (Obs) severity score	1.010 ± 0.908 (7)	0.217 ± 0.349 (5)	0.200 ± 0.313 (5)	1.600 ± 1.287 (5)	1.027 ± 1.061 (4)

Mean ± SD (number of subjects); -, Not applicable
a) Week 3 for the fasting sBA concentration
b) Week 21 for the average morning ItchRO (Obs) severity score

PMDA's view on the efficacy of maralixibat in patients with PFIC based on descriptions in the above Subsections (i) to (v):
In Study 502, a statistically significant difference was observed in change in average morning ItchRO (Obs) severity score from baseline to Weeks 15 to 26, the primary endpoint, between the maralixibat group and placebo group, and results on the fasting sBA concentration suggest the efficacy of maralixibat. Thus, at least in the region where the concerned study was conducted, maralixibat has been shown to be effective in the treatment of pruritus and cholestasis in patients with PFIC.

Results on changes in average morning ItchRO (Obs) severity score and fasting sBA concentration from Study 3002 were similar to those from Study 502, and ethnic factors are unlikely to affect the efficacy of maralixibat in view of its pharmacokinetics and mechanism of action. In addition, in view of the pathology of PFIC, the efficacy of maralixibat can be expected in Japanese patients with PFIC as well, and data from individual subjects in Study 3002 also suggest the efficacy. Therefore, results obtained so far support the efficacy of maralixibat in Japanese patients with PFIC.

For the efficacy in patients with PFIC aged <1 year, a decreasing trend of the fasting sBA concentration was observed after administration of maralixibat in patients with PFIC aged <1 year enrolled in Study 801, although Study 3002 did not enroll patients with PFIC aged <1 year. No improving trend was observed for either CSS score or average morning ItchRO (Obs) severity score, but the lack of improvement was potentially attributable to inadequate pruritus assessment in subjects aged <5 months.

Actually, in 3 subjects aged ≥5 months with baseline ItchRO (Obs) scores available, these scores showed an improving trend after administration of maralixibat. In addition to the above findings, considering that the efficacy of maralixibat in patients with PFIC aged ≥1 year can be similarly expected for both Japanese and non-Japanese patients, the efficacy can be expected in Japanese patients with PFIC aged <1 year as well.

Given that the response to maralixibat measured as the fasting sBA concentration and average morning ItchRO (Obs) severity score was maintained during the long-term treatment with maralixibat in Studies 503 and 3002, the long-term efficacy of maralixibat can be also expected.

As shown above, changes of assessment score for symptoms of pruritus and the fasting sBA concentration over time in Study 3002 were similar to those in Study 502. In addition to this finding, the impact of ethnic factors, mechanism of action of maralixibat, and pathology of PFIC, the efficacy was comprehensively evaluated taking account of results for each of the subjects in Study 3002, results from Study 801, and results on the long-term efficacy from multiple studies. In conclusion, the efficacy of maralixibat can be expected in the treatment of pruritus and cholestasis in Japanese patients with PFIC, including the long-term efficacy and efficacy in those aged <1 year.

7.R.2 Safety

As a result of the review in Sections 7.R.2.1 to 7.R.2.3 below, PMDA considers that the safety of maralixibat in patients with ALGS and those with PFIC is manageable and clinically acceptable in view of its observed efficacy as long as maralixibat is used in compliance with the cautions raised. However, hepatotoxicity that may affect a risk-benefit balance of maralixibat has not been adequately investigated in clinical studies, and thus the incidence of hepatotoxicity should be monitored in post-marketing settings as well.

7.R.2.1 Summary of safety in clinical studies in and outside Japan

The applicant's explanation about the safety of maralixibat in patients with ALGS and those with PFIC:
Table 66 shows the summary of incidences of adverse events in the foreign phase II study (Study 304) and Japanese phase III study (Study 3001) both in patients with ALGS by period. In both studies, adverse events occurred in all subjects who received maralixibat [see Sections 7.1.1 and 7.2.1].

In Study 304, the incidence of adverse drug reactions tended to be higher during the run-in period than during the RWD period and stable-dosing period, and the most common events were abdominal pain, diarrhoea, and vomiting, which were mostly mild or moderate. During the RWD period, incidences of adverse events, adverse drug reactions, and serious adverse events in the maralixibat group were not clearly higher than those in the placebo group, and neither deaths nor serious adverse drug reactions occurred throughout the entire period. During the stable-dosing period, the incidence of adverse drug reactions tended to be lower than that during any of the other periods. The incidence of adverse drug reactions during the long-term treatment period tended to be higher than that during the stable-dosing period, but the most common adverse drug reactions were abdominal pain, diarrhoea, and vomiting, which were mostly mild or moderate and allowed continuation of the study drug.

In Study 3001, of which the very limited sample size precludes adequate comparisons, no trend clearly different from that in Study 304 was observed.

In view of the above, the safety of maralixibat in patients with ALGS, including the long-term safety and safety in Japanese patients, has no large problems.

Table 66. Summary of incidences of adverse events in clinical studies in patients with ALGS by period (Studies 304 and 3001, safety analysis set)

	Study 304					Study 3001		
	Run-in period Weeks 1-18 (n = 31)	RWD period Weeks 19-22		Stable-dosing period Weeks 23-48 (n = 29)	Long-term treatment period Weeks 49-100[a] (n = 23)	Ascending-dose period Weeks 1-2 (n = 7)	Stable-dosing period Weeks 3-24 (n = 7)	Stable-dosing period Weeks 25-48 (n = 7)
		Placebo (n = 16)	Maralixibat (n = 13)					
All adverse events	96.8 (30)	75.0 (12)	53.8 (7)	86.2 (25)	100.0 (23)	0	71.4 (5)	71.4 (5)
All adverse drug reactions	38.7 (12)	18.8 (3)	7.7 (1)	3.4 (1)	34.8 (8)	0	14.3 (1)	0
Death	0	0	0	0	0	0	0	0
Serious adverse events	12.9 (4)	6.3 (1)	7.7 (1)	17.2 (5)	26.1 (6)	0	14.3 (1)	14.3 (1)
Serious adverse drug reactions	0	0	0	0	0	0	0	0
Adverse events leading to treatment discontinuation	6.5 (2)	0	0	6.9 (2)	8.7 (2)	0	0	0

Incidence (%) (number of subjects with events)
a) Including patients who received maralixibat for longer than 100 weeks

Table 67 and Table 68 show the summaries of incidences of adverse events in the foreign phase III studies (Studies 502 and 503) and Japanese phase III study (Study 3002) all in patients with PFIC by period, respectively. In all the studies, adverse events occurred in the majority (96.5%[45]-100%) of the patients who received maralixibat [see Sections 7.2.2 and 7.2.3].

In Study 502, the incidence of adverse events in the maralixibat group was similar to that in the placebo group during either period (Weeks 1-12, Weeks 13-22). The most common adverse drug reaction which tended to more frequently occur in the maralixibat group than in the placebo group was diarrhoea, which was mild or moderate in any affected patient and allowed continuation of the study drug in most of the affected patients. During the stable-dosing period, the incidence of serious adverse events tended to be higher in the maralixibat group than in the placebo group, but there were no events reported by ≥2 subjects. Throughout the treatment period, a serious adverse drug reaction occurred only in 1 subject (blood bilirubin increased), was mild in severity, and led to interruption of the study drug but the outcome was reported as "resolved." For the safety by period, the incidence of adverse events per unit of the treatment period did not tend to increase clearly with the increasing treatment period in Studies 502 and 503.

In Study 3002, of which the very limited sample size precludes adequate comparisons, no trend clearly different from that in Studies 502 and 503 was observed.

In view of the above, the safety of maralixibat in patients with PFIC, including the long-term safety and safety in Japanese patients, has no large problems.

[45] Adverse events occurred in 96.5% (82 of 85) of the patients who received maralixibat in Study 503.

Table 67. Summary of incidences of adverse events in clinical studies in patients with PFIC by period (Studies 502 and 3002, safety analysis set)

	Study 502				Study 3002		
	Dose-escalation and stable-dosing periods Weeks 1-12		Stable-dosing period Weeks 13-26		Ascending-dose period Weeks 1-4 (n = 5)	Stable-dosing period Weeks 5-28 (n = 5)	Stable-dosing period Weeks 29-48 (n = 5)
	Placebo (n = 46)	Maralixibat (n = 47)	Placebo (n = 45)	Maralixibat (n = 45)			
All adverse events	76.1 (35)	89.4 (42)	84.4 (38)	75.6 (34)	60.0 (3)	80.0 (4)	100 (5)
All adverse drug reactions	4.3 (2)	34.0 (16)	0	6.7 (3)	20.0 (1)	0	0
Death	0	0	0	0	0	0	0
Serious adverse events	6.5 (3)	6.4 (3)	0	6.7 (3)	0	0	0
Serious adverse drug reactions	0	2.1 (1)	0	0	0	0	0
Adverse events leading to treatment discontinuation	0	2.1 (1)	0	0	0	0	0

Incidence (%) (number of subjects with events)

Table 68. Summary of incidences of adverse events in clinical study in patients with PFIC by period (Study 503, safety analysis set)

	Weeks 0-12 (n = 85)	Weeks 13-24 (n = 77)	Weeks 25-36 (n = 68)	Weeks 37-48 (n = 51)	Weeks 49-72 (n = 41)	Weeks 73-96 (n = 17)	Weeks 97-120 (n = 8)
All adverse events	89.4 (76)	71.4 (55)	72.1 (49)	68.6 (35)	63.4 (26)	58.8 (10)	50.0 (4)
All adverse drug reactions	27.1 (23)	6.5 (5)	8.8 (6)	5.9 (3)	0	0	0
Death	0	0	0	0	0	0	0
Serious adverse events	4.7 (4)	7.8 (6)	1.5 (1)	5.9 (3)	2.4 (1)	11.8 (2)	0
Serious adverse drug reactions	1.2 (1)	0	0	0	0	0	0
Adverse events leading to treatment discontinuation	1.2 (1)	0	0	3.9 (2)	0	0	0

Incidence (%) (number of subjects with events)

PMDA's view:

In clinical studies in patients with ALGS and those with PFIC, diarrhoea and abdominal pain occurred with maralixibat irrespective of the target disease, but the events were mostly mild or moderate in severity and allowed continuation of maralixibat. During the stable-dosing period in Study 502, the incidence of serious adverse events tended to be higher in the maralixibat group than in the placebo group, but throughout the treatment period, a serious adverse drug reaction occurred only in 1 subject and was mild in severity. The outcome was reported as "resolved" after interruption of the study drug.

For the incidence of adverse events by period, the incidence of diarrhoea and abdominal pain tended to be high not only during the run-in period but also during the long-term treatment period in Study 304, and thus these events warrant caution throughout the treatment period. The incidence of other adverse events by period does not show any increasing trend with an increase in the period of the treatment with maralixibat in any clinical study in patients with ALGS or those with PFIC, and the other adverse events do not warrant particular caution for the long-term treatment at present.

Furthermore, in either Japanese phase III study in patients with ALGS or those with PFIC, of which the sample size was very limited, no trend of the safety results clearly different from that in foreign clinical studies was observed.

In conclusion, the safety of maralixibat in patients with ALGS and those with PFIC has no large problems. The adverse events of special interest including diarrhoea-related events, which were mainly observed in clinical studies, are separately reviewed in Section 7.R.2.2.

7.R.2.2 Adverse events of special interest

The applicant specified diarrhoea-related events, fat-soluble vitamin deficiency, and hepatotoxicity as adverse events of special interest for maralixibat and explained data on these events based on results from Studies 304, 3001, 502, 503, and 3002, as described below.

7.R.2.2.1 Diarrhoea-related events

The applicant's explanation about diarrhoea-related events:
Table 69 and Table 70 show incidences of diarrhoea-related events in Studies 304, 3001, 502, 503, and 3002,[46)] The diarrhoea-related events observed were mostly diarrhoea in all the studies.

In Study 304 in patients with ALGS, the incidence of diarrhoea-related events in the maralixibat group during the RWD period was lower than that in the placebo group. Among diarrhoea-related events occurring in 17 subjects during the entire period, events in 10 subjects were considered causally unrelated to the study drug, and remaining events in 7 subjects were thus classified as adverse drug reactions but all mild or moderate. A causal relationship to the study drug was both ruled out for serious diarrhoea-related events occurring in 2 subjects (diarrhoea and gastroenteritis in 1 subject each). The events resolved without changing the dose of maralixibat. In Study 3001, diarrhoea occurred in 1 subject as a diarrhoea-related event, which was mild and for which a causal relationship to the study drug was ruled out.

In Study 502 in patients with PFIC, the incidence of diarrhoea-related events in the maralixibat group was higher than that in the placebo group, but no serious events occurred. All the events except for one moderate event were mild and for most of them, a causal relationship to the study drug was ruled out. A diarrhoea-related event leading to treatment discontinuation occurred in 1 subject and was assessed as the adverse drug reaction, which did not require additional treatment and resolved after discontinuation of the study drug. The pooled data from the maralixibat group in Study 502 and Study 503 included diarrhoea-related events in 47 subjects, and of them, events in 3 subjects (gastroenteritis in 3 subjects) were serious, but a causal relationship to the study drug was ruled out for all the serious events. No diarrhoea-related events leading to discontinuation occurred in Study 503. In Study 3002, diarrhoea-related events occurred in 2 subjects (diarrhoea and gastroenteritis in 1 subject each). Diarrhoea was assessed as an adverse drug reaction, but both diarrhoea and gastroenteritis were mild.

46) Definition in Studies 304, 3001, and 3002: Events coded into the following MedDRA PTs: Diarrhoea and Gastroenteritis
Definition in Studies 502 and 503: Events coded into the following MedDRA PTs: Diarrhoea, Intermittent diarrhoea, Frequent bowel movements, and Gastroenteritis

Table 69. Incidences of diarrhoea-related events in clinical studies in patients with ALGS (Studies 304 and 3001, safety analysis set)

	Study 304					Study 3001
	Run-in period 18 weeks (n = 31)	RWD period 4 weeks		Stable-dosing period 26 weeks (n = 29)	Entire period[a)] (n = 31)	Entire period (n = 7)
		Placebo (n = 16)	Maralixibat (n = 13)			
Diarrhoea-related events	41.9 (13)	12.5 (2)	7.7 (1)	24.1 (7)	71.0 (22)	14.3 (1)
Diarrhoea	41.9 (13)	6.3 (1)	7.7 (1)	17.2 (5)	54.8 (17)	14.3 (1)
Gastroenteritis	0	6.3 (1)	0	6.9 (2)	22.6 (7)	0

Incidence (%) (number of subjects with events); MedDRA ver.26.0 (Study 304) and ver.27.0 (Study 3001)
a) Events in the placebo group during the placebo treatment period in the RWD period were removed.

Table 70. Incidences of diarrhoea-related events in clinical studies in patients with PFIC (Studies 502, 503, and 3002, safety analysis set)

	Study 502 Week 22		Pooled from Studies 502 and 503[a)] Entire period (n = 85)	Study 3002 Entire period (n = 5)
	Placebo (n = 46)	Maralixibat (n = 47)		
Diarrhoea-related events	19.6 (9)	61.7 (29)	55.3 (47)	40.0 (2)
Diarrhoea	19.6 (9)	57.4 (27)	50.6 (43)	20.0 (1)
Gastroenteritis	4.3 (2)	6.4 (3)	8.2 (7)	20.0 (1)

Incidence (%) (number of subjects with events); MedDRA ver.26.0 (Study 502, Study 503) and ver.26.1 (Study 3002)
a) Pooled data from the maralixibat group in Study 502 and Study 503

Although diarrhoea-related events deemed as serious adverse drug reactions did not occur, diarrhoea occurred after administration of maralixibat at a certain incidence and thus warrants caution. The applicant will raise caution in the package insert with a statement to the effect that (1) if abdominal pain or diarrhoea persists during maralixibat treatment, and no other causes are identified, dose reduction or interruption should be considered; and (2) the patient should be monitored for dehydration resulting from diarrhoea; and if any abnormality is observed, appropriate treatment should be given promptly.

PMDA's view:
In view of the obtained clinical study results and the applicant's explanation about diarrhoea-related events, there are no safety concerns that could significantly impair the benefits of maralixibat at present. However, considering that diarrhoea occurred at a certain incidence after administration of maralixibat and diarrhoea leading to treatment discontinuation was reported as an adverse drug reaction, adequate attention should be paid to the onset of diarrhoea during maralixibat treatment. Therefore, the applicant's policy is appropriate to provide the cautionary statement in the package insert.

7.R.2.2.2 Fat-soluble vitamin deficiency

The applicant's explanation about fat-soluble vitamin deficiency:
Maralixibat inhibits reabsorption of bile acids in the ileum, and its long-term use may affect absorption of fat-soluble vitamins by reducing circulating bile acids. In patients with ALGS or PFIC, fat-soluble vitamin concentrations in blood could be low even before administration of maralixibat, and thus fat-soluble vitamin deficiency and its accompanying symptoms may be caused or worsened by maralixibat.

Table 71 and Table 72 show incidences of fat-soluble vitamin deficiency[47)] in Studies 304, 3001, 502, 503, and 3002, respectively.

In Study 304 in patients with ALGS, no fat-soluble vitamin deficiency occurred during the RWD period, and of the events of fat-soluble vitamin deficiency that occurred in 11 subjects during the entire period, events for which a causal relationship to the study drug could not be ruled out were limited to 1 subject. The 2 events of fat-soluble vitamin deficiency occurring in the concerned subject, epistaxis and visual acuity reduced, were moderate and mild. A serious fat-soluble vitamin deficiency (seizure) occurred in 1 subject, but a causal relationship to the study drug was ruled out for the event, and it resolved without changing the dose of maralixibat. In Study 3001, no fat-soluble vitamin deficiency occurred.

In Study 502 in patients with PFIC, the incidence of fat-soluble vitamin deficiency in the maralixibat group was lower than that in the placebo group. Of the events of fat-soluble vitamin deficiency that occurred in 12 subjects in the maralixibat group, event for which a causal relationship could not be ruled out was limited to 1 subject (Vitamin E deficiency) and mild. A serious fat-soluble vitamin deficiency was limited to 1 subject (Vitamin K deficiency) in the placebo group, and no fat-soluble vitamin deficiency leading to treatment discontinuation occurred. The pooled data from the maralixibat group in Study 502 and Study 503 included the events of fat-soluble vitamin deficiency in 23 subjects, of which none were serious ones or ones leading to treatment discontinuation. In Study 3002, no fat-soluble vitamin deficiency occurred.

[47)] Definition in Study 304: Events coded into the following MedDRA PTs: Vitamin A deficiency, Vitamin A abnormal, Vitamin A decreased, Vitamin A deficiency related corneal disorder, Night blindness, Keratomalacia, Haemorrhagic disease of newborn, Xerophthalmia, Growth retardation, Nail disorder, Dry skin, Eye disorder, Eye irritation, Eye pruritus, Vitamin D deficiency, Vitamin D abnormal, Vitamin D decreased, Rickets, Osteomalacia, Osteoporosis, Osteopenia, Heart rate abnormal, Heart rate increased, Heart rate irregular, Tachycardia, Arrhythmia, Hypocalcaemia, Tetany, Tremor, Irritability, Hunger, Seizure, Confusional state, Anxiety, Fatigue, Calcium deficiency, Pallor, Palpitations, Hyperhidrosis, Paraesthesia oral, Tooth demineralisation, Bone deformity, Bone density abnormal, Bone density decreased, Fracture, Vitamin E deficiency, Vitamin E decreased, Hyporeflexia, Ataxia, Nystagmus, Areflexia, Ophthalmoplegia, Visual acuity reduced, Visual impairment, Abnormal behaviour, Personality disorder, Personality change, Muscle atrophy, Muscle disorder, Muscle spasms, Hair disorder, Alopecia, Alopecia areata, Vitamin K deficiency, Vitamin K decreased, Mean platelet volume abnormal, Mean platelet volume decreased, Platelet count abnormal, Platelet count decreased, Cold feet, Cold hands, Cold hands & feet, Cold extremities, Coldness of lower extremities, Blood glucose increased, Bleeding time abnormal, Bleeding time prolonged, Coagulation time abnormal, Coagulation time prolonged, International normalised ratio increased, International normalised ratio abnormal, Haemorrhage, Melaena, Epistaxis, Haematochezia, and Haemoptysis.
Definition in Study 502: Events coded into the following MedDRA PTs: Vitamin A deficiency, Vitamin A abnormal, Vitamin A decreased, Vitamin D deficiency, Vitamin D abnormal, Vitamin D decreased, Vitamin E deficiency, Vitamin E abnormal, Vitamin E decreased, Vitamin K deficiency, Vitamin K abnormal, Vitamin K decreased, International normalised ratio increased, and International normalised ratio abnormal.
Definition in Study 503: Events coded into the following MedDRA PTs: Vitamin A deficiency, Vitamin A abnormal, Vitamin A decreased, Vitamin D deficiency, Vitamin D abnormal, Vitamin D decreased, Vitamin E deficiency, Vitamin E decreased, Vitamin K deficiency, Vitamin K abnormal, Vitamin K decreased, International normalised ratio increased, International normalised ratio abnormal, Blood 1,25-dihydroxycholecalciferol decreased, and Blood 25-hydroxycholecalciferol decreased.
Definition in Studies 3001 and 3002: Events deemed as ones of fat-soluble vitamin deficiency by the investigator.

Table 71. Incidences of fat-soluble vitamin deficiency in clinical studies in patients with ALGS (Studies 304 and 3001, safety analysis set)

	Study 304					Study 3001
	Run-in period 18 weeks (n = 31)	RWD period 4 weeks		Stable-dosing period 26 weeks (n = 29)	Entire period[a)] (n = 31)	Entire period (n = 7)
		Placebo (n = 16)	Maralixibat (n = 13)			
Fat-soluble vitamin deficiency	22.6 (7)	0	0	3.4 (1)	35.5 (11)	0
Visual acuity reduced	0	0	0	0	3.2 (1)	0
Haematochezia	3.2 (1)	0	0	0	6.5 (2)	0
Fatigue	3.2 (1)	0	0	3.4 (1)	9.7 (3)	0
International normalised ratio increased	3.2 (1)	0	0	0	3.2 (1)	0
Vitamin D decreased	3.2 (1)	0	0	0	3.2 (1)	0
Vitamin A deficiency	3.2 (1)	0	0	0	3.2 (1)	0
Growth retardation	0	0	0	0	3.2 (1)	0
Seizure	3.2 (1)	0	0	0	3.2 (1)	0
Epistaxis	3.2 (1)	0	0	0	6.5 (2)	0
Alopecia	3.2 (1)	0	0	0	3.2 (1)	0

Incidence (%) (number of subjects with events); MedDRA ver.26.0 (Study 304) and ver.27.0 (Study 3001)
a) Events in the placebo group during the placebo treatment period in the RWD period were removed.

Table 72. Incidences of fat-soluble vitamin deficiency in clinical studies in patients with PFIC (Studies 502, 503, and 3002, safety analysis set)

	Study 502 Week 22		Pooled from Studies 502 and 503[a)] Entire period (n = 85)	Study 3002 Entire period (n = 5)
	Placebo (n = 46)	Maralixibat (n = 47)		
Fat-soluble vitamin deficiency	32.6 (15)	25.5 (12)	27.1 (23)	0
Vitamin E decreased	6.5 (3)	8.5 (4)	7.1 (6)	0
Vitamin D decreased	4.3 (2)	8.5 (4)	8.2 (7)	0
International normalised ratio increased	8.7 (4)	2.1 (1)	5.9 (5)	0
Vitamin A decreased	2.2 (1)	0	0	0
Vitamin D deficiency	8.7 (4)	8.5 (4)	9.4 (8)	0
Vitamin E deficiency	8.7 (4)	6.4 (3)	4.7 (4)	0
Vitamin A deficiency	4.3 (2)	4.3 (2)	5.9 (5)	0
Vitamin K deficiency	2.2 (1)	0	2.4 (2)	0

Incidence (%) (number of subjects with events); MedDRA ver.26.0 (Study 502, Study 503) and ver.26.1 (Study 3002)
a) Pooled data from the maralixibat group in Study 502 and Study 503

As shown above, most of the events of fat-soluble vitamin deficiency in the clinical studies were non-serious and a causal relationship to the study drug was ruled out for most of them; and the incidence of fat-soluble vitamin deficiencies in the maralixibat group were not clearly higher than those in the placebo group. Therefore, fat-soluble vitamin deficiency is currently unlikely to be related to maralixibat. However, patients with ALGS or PFIC may be in an underlying condition of decreased fat-soluble vitamins even before the start of treatment with maralixibat. The applicant thus will raise caution in the package insert with a statement to the effect that before the start of and during treatment with maralixibat, the patients should be carefully monitored for their condition by measuring fat-soluble vitamins and prothrombin-time international normalized ratio, and where necessary supplementation with fat-soluble vitamins should be considered.

PMDA's view:
In view of the obtained clinical study results and the applicant's explanation about fat-soluble vitamin deficiency, no clinically relevant safety concerns were identified in the range evaluated in clinical studies. However, maralixibat may affect absorption of fat-soluble vitamins given its pharmacological action, and patients with ALGS and those with PFIC can be in a condition of decreased fat-soluble vitamins

even before administration of maralixibat in clinical settings. In view of these points, the applicant's policy is appropriate to provide the cautionary statement in the package insert.

7.R.2.2.3 Hepatotoxicity

The applicant's explanation about hepatotoxicity:

Table 73 shows incidences of abnormal liver function test values (transaminase increased[48)] and bilirubin increased[49)]) in Studies 304 and 3001, and Table 74 shows such data from Studies 502, 503, and 3002.

In Study 304 in patients with ALGS, no transaminase increased occurred until the end of the stable-dosing period (Week 48), but transaminase increased occurred in 4 subjects (ALT increased in 4 subjects, AST increased in 2 subjects) after Week 48, and a causal relationship to the study drug could not be ruled out for any of these events. Although the events in these 4 subjects were all non-serious, events in 2 subjects (ALT increased in 2 subjects) were severe in severity and life-threatening or resulting in motor disability/incapacity, and the severe event in 1 subject led to treatment discontinuation. No bilirubin increased occurred until the end of the RWD period (Week 22). Bilirubin increased (blood bilirubin increased) that occurred in 1 subject during the stable-dosing period was serious and led to treatment discontinuation, but its causal relationship to the study drug was ruled out. In Study 3001, transaminase increased (ALT increased) occurred in 1 subject, but the event, which was mild, was considered causally unrelated to the study drug.

In Study 502 in patients with PFIC, the incidence of transaminase increased in the maralixibat group was higher than that in the placebo group, but all events were mild or moderate, and none of them were serious or led to treatment discontinuation. Transaminase increased for which a causal relationship to the study drug could not be ruled out occurred in 2 subjects (ALT increased and transaminases increased), and both were mild or moderate. Bilirubin increased did not occur more frequently in the maralixibat group than in the placebo group. However, serious bilirubin increased occurred in 1 subject in the maralixibat group (blood bilirubin increased), was classified as an adverse drug reaction, and led to treatment discontinuation, but it was mild. The pooled data from the maralixibat group in Study 502 and Study 503 included the events of transaminase increased in 13 subjects and bilirubin increased in 11 subjects. Of these, events in 1 subject (ALT increased and blood bilirubin increased [the subject had more than 1 event]) were classified as adverse drug reactions and led to treatment discontinuation. In the concerned subject, ALT increased was non-serious and blood bilirubin increased was serious, but both were moderate. In Study 3002, transaminase increased occurred in 1 subject (ALT increased and AST increased [the subject had more than 1 event]), and bilirubin increased occurred in 1 subject (blood bilirubin increased), but all were mild or moderate, and a causal relationship to the study drug was ruled out for all of them.

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48) Definition in Study 304: Events coded into the following MedDRA PTs: ALT increased and AST increased
Definition in Studies 502 and 503: Events coded into the following MedDRA PTs: Hepatic enzyme increased, Transaminases abnormal, Transaminases increased, ALT increased, AST increased, AST abnormal, and ALT abnormal.
Definition in Studies 3001 and 3002: Events deemed as liver function parameter abnormal by the investigator

49) Definition in Study 304: Event coded into MedDRA PT, Blood bilirubin increased
Definition in Studies 502 and 503: Events coded into the following MedDRA PTs: Blood bilirubin increased, Blood bilirubin abnormal, and Hyperbilirubinaemia
Definition in Studies 3001 and 3002: Events deemed as liver function parameter abnormal by the investigator

Table 73. Incidences of abnormal liver function test values in clinical studies in patients with ALGS (Studies 304 and 3001, safety analysis set)

	Study 304					Study 3001
	Run-in period 18 weeks (n = 31)	RWD period 4 weeks		Stable-dosing period 26 weeks (n = 29)	Entire period[a)] (n = 31)	Entire period (n = 7)
		Placebo (n = 16)	Maralixibat (n = 13)			
Transaminase increased	0	0	0	0	12.9 (4)	14.3 (1)
ALT increased	0	0	0	0	12.9 (4)	14.3 (1)
AST increased	0	0	0	0	6.5 (2)	0
Bilirubin increased	0	0	0	3.4 (1)	3.2 (1)	0
Blood bilirubin increased	0	0	0	3.4 (1)	3.2 (1)	0

Incidence (%) (number of subjects with events); MedDRA ver.26.0 (Study 304) and ver.27.0 (Study 3001)
a) Events in the placebo group during the placebo treatment period in the RWD period were removed.

Table 74. Incidences of abnormal liver function test values in clinical studies in patients with PFIC (Studies 502, 503, and 3002, safety analysis set)

	Study 502 Week 22		Study 503 Entire period (n = 85)	Study 3002 Entire period (n = 5)
	Placebo (n = 46)	Maralixibat (n = 47)		
Transaminase increased	6.5 (3)	14.9 (7)	15.3 (13)	20.0 (1)
ALT increased	6.5 (3)	12.8 (6)	11.8 (10)	20.0 (1)
AST increased	2.2 (1)	4.3 (2)	2.4 (2)	20.0 (1)
Transaminases increased	0	2.1 (1)	3.5 (3)	0
Bilirubin increased	19.6 (9)	14.9 (7)	12.9 (11)	20.0 (1)
Hyperbilirubinaemia	10.9 (5)	0	0	0
Blood bilirubin increased	8.7 (4)	14.9 (7)	12.9 (11)	20.0 (1)

Incidence (%) (number of subjects with event); MedDRA ver.26.0 (Study 502) and ver.26.1 (Study 3002)

As shown above, most of the events were non-serious. However, in clinical studies of maralixibat, liver function test values changed, and serious blood bilirubin increased and transaminases increased that led to treatment discontinuation were reported as adverse drug reactions. In view of these findings, hepatotoxicity is considered as an important potential risk of maralixibat. The applicant thus will raise caution in the package insert with a statement to the effect that before the start of and during treatment with maralixibat, the patients should undergo liver function test and be carefully monitored for their condition.

PMDA's view:

Findings on hepatotoxicity included the following findings: (1) Transaminase increased occurred in a certain proportion of the subjects in Study 304; (2) the incidence of transaminase increased tended to be higher in the maralixibat group than in the placebo group in Study 502; and (3) severe events and serious events leading to treatment discontinuation occurred, although the number of the events was limited. In view of these findings, hepatotoxicity is an important potential risk of maralixibat. Therefore, the applicant's policy is appropriate to provide the cautionary statement about conduct of liver function test in the package insert. The risk-benefit balance of maralixibat in the treatment of ALGS and PFIC may be affected depending on the severity of its hepatotoxicity, but it has not been investigated adequately in clinical studies. Hepatotoxicity thus should be investigated in post-marketing settings as well.

7.R.2.3 Foreign post-marketing safety information

The applicant's explanation about the foreign post-marketing safety information about maralixibat:
Maralixibat was first approved for the indication of ALGS in the US on September 29, 2021 and, as of November 2024, it has been approved for the indication of ALGS or PFIC in 41 countries or regions. The foreign safety information up to the data lock date of the latest periodic safety update report (reporting period from September 29, 2023 to March 28, 2024; estimated cumulative exposure, 618 patients) did not show any trend largely different from that of adverse events in the clinical studies, raising no additional safety concerns about maralixibat.

PMDA's view:
The applicant's explanation is reasonable in that the post-marketing safety information about maralixibat did not include the events suggestive of additional safety concerns different from those identified in the clinical studies at present.

7.R.3 Indications and clinical positioning

The applicant's explanation about the indications and clinical positioning of maralixibat:
ALGS and PFIC are both very rare cholestatic liver diseases and classified as a designated intractable disease in Japan. No drugs indicated for the treatment of ALGS or PFIC are approved in Japan. Oral ursodeoxycholic acid and bile acid adsorbent, supplementation with fat-soluble vitamins and essential fatty acids as well as, for pruritus, the main symptom, antihistamines and phenobarbital are used, but their effects are all limited. In patients affected by either disease, if internal treatment does not improve pruritus or growth disorder, biliary diversion surgery will be performed, and if the disease progresses to hepatic cirrhosis, liver transplant will be indicated.

Maralixibat is an IBAT inhibitor. By inhibiting absorption of bile acids from the intestine, it reduces bile acids in enterohepatic circulation, increases excretion of bile acids into feces, and consequently decreases sBA concentrations. Maralixibat is therefore expected to be used as a drug for the treatment of cholestasis in patients with ALGS or PFIC.

Based on results from Studies 304 and 3001 in patients with ALGS, maralixibat can be expected to have the efficacy in the treatment of cholestasis and pruritus associated with ALGS [see Section 7.R.1.1.2], and the safety was found to have no clinically relevant problems [see Section 7.R.2]. Based on results from Studies 502 and 3002 in patients with PFIC, maralixibat can be expected to have the efficacy in the treatment of cholestasis and pruritus associated with PFIC [see Section 7.R.1.2.2], and the safety was found to have no clinically relevant problems [see Section 7.R.2]. The long-term efficacy outcome for maralixibat treatment of ALGS and PFIC has not been investigated in controlled studies. However, comparison of outcome data in the cohort of 84 patients with ALGS who were enrolled in Study 304 and followed up for up to 6 years with those in an external control cohort (natural history in 1438 patients with ALGS collected in The Global ALagille Alliance Study) revealed that the time to onset of the event[50)] was longer in the maralixibat dose cohort than in the control cohort, although the result warrants careful interpretation because (1) there was an imbalance in baseline fasting sBA concentration between the cohorts; and (2) the control cohort included many patients with missing baseline fasting sBA

[50)] Liver transplant, biliary diversion surgery, decompensated hepatic cirrhosis, or death was handled as an event.

concentrations, precluding adjustment for the concerned patient characteristic (*Hepatology.* 2024;79:1279-92). In Study 501, of 18 patients with PFIC who did not achieve improvement of the fasting sBA concentration, 15 subjects underwent liver transplant by Week 260, but all of 7 subjects who achieved improvement of the fasting sBA concentration during the study period (decreased to <102 μmol/L or decreased from baseline by >75%) continued maralixibat until Week 312 and survived without undergoing biliary diversion surgery or liver transplant.

As described above, maralixibat is expected to be used as a new drug for the treatment of ALGS and PFIC. In addition to a decrease in fasting sBA concentration and improvement of symptoms of pruritus, the long-term outcome can be expected to be improved if the sBA concentration is reduced. Therefore, the applicant proposes that maralixibat should be indicated for "Alagille syndrome" and "progressive familial intrahepatic cholestasis (PFIC)."

PMDA's view:
In Study 304 in patients with ALGS, changes in fasting sBA concentration and results in the ItchRO-based pruritus assessment suggested the efficacy of maralixibat [see Section 7.R.1.1.2]. In Study 502 in patients with PFIC, results in the ItchRO-based pruritus assessment demonstrated the efficacy of maralixibat, and changes in fasting sBA concentration also suggested the efficacy of maralixibat [see Section 7.R.1.2.2]. Based on results from Study 3001 in Japanese patients with ALGS and Study 3002 in Japanese patients with PFIC, the efficacy of maralixibat can be expected for the treatment of pruritus and cholestasis in Japanese patients with ALGS and those with PFIC as well. The safety of maralixibat in any of the studies is considered acceptable in view of the observed efficacy [see Section 7.R.2]. However, whether maralixibat can be expected to improve the long-term outcome in patients with ALGS and those with PFIC remains unknown at present because no controlled clinical studies that would enable the investigation of such outcome are conducted. In conclusion, maralixibat will offer a new option for the treatment of cholestasis and its associated pruritus in patients with ALGS and those with PFIC, and the indications should be specified as "cholestatic pruritus associated with alagille syndrome" and "cholestatic pruritus associated with progressive familial intrahepatic cholestasis."

The detailed description of the indications will be finalized in view of comments raised in the Expert Discussion.

7.R.4 Dosage and administration

7.R.4.1 Dosage and administration in patients with ALGS

The applicant's explanation about the dosage regimen of maralixibat in patients with ALGS:
As for the initial dose and titration scheme in Study 304, maralixibat was administered QD at 6 ascending doses. The initial dose was 14 μg/kg, and the dose was titrated to 35, 70, 140, 280, and 400 μg/kg in this order at a 1-week interval, because the safety data at high doses had not adequately accrued at the time of study planning. During the run-in period, no safety concerns were raised. In Study 304, a favorable safety profile was obtained even at 400 μg/kg QD, and during the long-term treatment period (Period 2), the dose was increased from 400 μg/kg QD to 400 μg/kg BID using a 2-step titration scheme,[27)] with the evidence of favorable tolerability. Furthermore, favorable safety of maralixibat was confirmed with regimens of 14 μg/kg QD to 400 μg/kg BID in Study 304 as shown above, but

administration at 6 ascending doses might pose an increased risk of medication error in clinical settings. In light of these points, maralixibat was started at 200 μg/kg QD, followed by an increase to 400 μg/kg QD after 1week in the Expanded Access Program in patients with ALGS aged ≥1 year, which was conducted mainly in the US. As of the data cut-off date of [redacted], 24 patients received maralixibat, and none of the deaths, serious adverse events, and adverse events leading to treatment discontinuation occurred. In Study 3001, a simplified titration scheme was adopted in view of the above data and convenience of patients, and maralixibat was started at 200 μg/kg QD and, followed by an increase to 400 μg/kg QD after 1 week. In Study 3001, all subjects successfully received the increased dose of 400 μg/kg QD and continued the treatment, and no safety problems were observed during the dose-escalation period. In Study 801 in patients aged <1 year, the same 2-step titration scheme as that in Study 3001 was also adopted, and all subjects successfully received the increased dose of 400 μg/kg QD with no safety problems during the dose-escalation period.

In Study 304, the stable dose of 400 μg/kg QD was specified based on results from the foreign phase I study (Study SHP625-101[51)] [Study 101]) and foreign phase II studies (Studies 301 and 302). More specifically, a dose-fBA excretion relationship observed within the dose range evaluated in Study 101 (maralixibat 10 mg, 20 mg, 50 mg or 100 mg QD or 50 mg BID) indicated that a dose of 400 μg/kg QD (corresponding to approximately 30 mg/day in patients weighing 70 kg) would have higher efficacy than the dose of 70 to 280 μg/kg QD, used as the stable dose in Studies 301 and 302 (approximately 5-20 mg/day in patients weighing 70 kg). The same stable dose of 400 μg/kg QD was specified in Study 3001 as well. Both studies demonstrated the efficacy of maralixibat at 400 μg/kg QD [see Section 7.R.1.1.2], and no safety problems were raised during the stable-dosing period [see Section 7.R.2].

Based on the above, the applicant proposes the following dosage regimen of maralixibat in patients with ALGS: An initial oral dose of maralixibat 200 μg/kg QD, followed by an increase to 400 μg/kg QD after 1 week.

PMDA's view:
While the 6-step titration scheme was adopted in Study 304, the 2-step titration scheme was adopted in Studies 3001 and 801, and no safety problems were raised during the dose-escalation period. In addition, Studies 304 and 3001 demonstrated the efficacy at 400 μg/kg QD and raised no particular safety problems during the stable-dosing period. In view of the above results, PMDA accepts the following applicant's proposed dosage and administration of maralixibat in patients with ALGS, as done in Study 3001: An initial oral dose of maralixibat 200 μg/kg QD, followed by an increase to 400 μg/kg QD after 1 week. In view of the review in Section 6.R.1, administration before a meal should be specified in the Dosage and Administration section.

The detailed description of the Dosage and Administration will be finalized in view of comments raised in the Expert Discussion.

[51)] A placebo-controlled, randomized, single-blind, parallel-group study in overweight and obese non-Japanese adults to evaluate an effect of 7-day treatment with maralixibat (10 mg, 20 mg, 50 mg, or 100 mg QD or 50 mg BID) relative to that with volixibat (10 mg or 20 mg QD) based on data on fBA excretion

7.R.4.2 Dosage and administration in patients with PFIC

The applicant's explanation about the dosage regimen of maralixibat in patients with PFIC:
The initial dose and titration scheme in Study 502 were specified based on results from Study 304, which included patients with a different disease. More specifically, during the long-term treatment period (Period 2) in Study 304, the dose was gradually increased from 400 μg/kg QD to 400 μg/kg BID in increments up to 260 μg/kg/day, but no tolerability problems were raised. In view of the above finding, a 4-step titration scheme using similar increments was adopted, and maralixibat was administered BID at 4 ascending doses. The initial dose was 150 μg/kg, and the dose was titrated to 300, 450, and 600 μg/kg (in increments up to 300 μg/kg/day). In Study 3002, the same titration scheme as that in Study 502 was adopted. During the dose-escalation period, no safety problems were raised in either Study 502 or 3002. In Study 502, most of the subjects reached 600 μg/kg BID, and the safety information obtained up to that timepoint indicated that a slow, multiple-step titration scheme, which could pose a potential risk of medication error, was unnecessary. In Study 801, a 3-step titration scheme was adopted in view of findings in preceding Study 502, which are described above, and maralixibat was administered at 3 ascending doses from an initial 300 μg/kg QD to 300 μg/kg BID and 600 μg/kg BID (for 1 week each). The dose was successfully increased to 600 μg/kg BID in all subjects, and during the dose-escalation period, adverse events occurred in 3 of 4 subjects but all were mild or moderate. A serious adverse event (gastroenteritis adenovirus) occurred in 1 subject, but its causal relationship to the study drug was ruled out, and the outcome was reported as "resolved." In view of the above data and convenience for patients, the applicant considered it possible to specify a simple and practical dosing scheme, 3-step titration scheme starting at 300 μg/kg QD, which is similar to the initial dose and titration scheme in Study 801.

In Study 502, the stable dose of 600 μg/kg BID was specified based on the following findings: (1) In Study 501, a foreign phase II study, the titration of the stable dose from 280 μg/kg QD to 280 μg/kg BID led to a decrease in fasting sBA concentration in some subjects; and (2) in a foreign phase I study in overweight and obese adults (Study 101), the dose of 100 mg/day (corresponding to approximately 1,400 μg/kg/day in adults weighing 70 kg) was tolerated. In Study 3002, the same stable dose as that in Study 502 was adopted. Study 502 demonstrated the efficacy of maralixibat at 600 μg/kg BID, and Study 3002 also showed similar results [see Section 7.R.1.2.2], and no safety problems were observed in either study.

Based on the above, the applicant proposes the following dosage regimen of maralixibat in patients with PFIC: An initial oral dose of maralixibat 300 μg/kg QD, followed by an increased to 300 μg/kg BID after 1 week, and then to 600 μg/kg BID after another week.

PMDA's view:
As for the initial dose and titration scheme in Studies 502 and 3002, the 4-step titration scheme starting at 150 μg/kg BID was adopted, and the efficacy and safety of maralixibat were demonstrated. The safety trend did not differ between Study 502 and Study 3002, and in Study 801, the 3-step titration scheme starting at 300 μg/kg QD was used, raising no particular safety concerns. Thus, the 3-step titration scheme is acceptable. In Studies 502 and 3002, the efficacy of maralixibat at 600 μg/kg BID was demonstrated, and no major safety problems were raised. In view of these findings, the stable dose may be specified as done in the clinical studies. In conclusion, PMDA accepts the following applicant's

proposed dosage and administration of maralixibat in patients with PFIC: Maralixibat should be started at 300 μg/kg QD and, followed by an increase to 300 μg/kg BID after 1 week, and then to 600 μg/kg BID after another week, which should be continued as a stable dose. In view of the review in Section 6.R.1, administration before a meal should be specified in the Dosage and Administration section.

The detailed description of the Dosage and Administration will be finalized in view of comments raised in the Expert Discussion.

7.R.5 Post-marketing investigations

The applicant explanation:
The applicant plans to conduct post-marketing surveillance with the safety specification of the incidence of "hepatotoxicity" during maralixibat treatment in post-marketing clinical settings. More specifically, the surveillance is planned as a post-marketing database survey using the registry established through a multi-center prospective registry study targeting childhood-onset cholestatic liver diseases (Comprehensive and Informative Registry system for Childhood Liver disease) run by Delta Compass.

PMDA's view:
Although the policy of using the database to investigate the events of hepatotoxicity proposed by the applicant in the post-marketing surveillance is appropriate, details of the surveillance plan should be further examined.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-5, CTD 5.3.5.2-9) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that maralixibat has efficacy in the treatment of cholestatic pruritus associated with Alagille syndrome and progressive familial intrahepatic cholestasis, and that maralixibat has acceptable safety in view of its benefits. The drug substance is classified as a poisonous drug. The drug product is not classified as a poisonous drug or a powerful drug.

Maralixibat is clinically meaningful because it offers a new treatment option for patients with Alagille syndrome and those with progressive familial intrahepatic cholestasis. PMDA also considers that the indications and dosage and administration should be further examined.

PMDA has concluded that maralixibat may be approved if maralixibat is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 20, 2025

Product Submitted for Approval

Brand Name	Livmarli Oral Solution 10 mg/mL
Non-proprietary Name	Maralixibat Chloride
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	June 27, 2024

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy and safety

At the Expert Discussion, the expert advisors supported all PMDA's conclusions presented in Sections "7.R.1 Efficacy" and "7.R.2 Safety" in the Review Report (1).

1.2 Indications

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.3 Indications and clinical positioning" in the Review Report (1).

In view of the comments raised in the Expert Discussion, PMDA concluded that the indications should be as shown below, and the Precautions Concerning Indications section should be specified as shown below in view of the mechanism of action of maralixibat. The applicant responded appropriately.

Indications
Cholestatic pruritus in patients with the following diseases:
○ Alagille syndrome
○ Progressive familial intrahepatic cholestasis

Precautions Concerning Indications

Progressive familial intrahepatic cholestasis

- Maralixibat is not expected to be effective in patients harboring *ABCB11* mutation that results in complete absence of bile salt export pump (BSEP) function.

1.3 Dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.4 Dosage and administration" in the Review Report (1).

In view of the comments raised in the Expert Discussion, PMDA concluded that the dosage and administration should be as shown below, and the Precautions Concerning Dosage and Administration section should be specified as shown below. The applicant responded appropriately.

Dosage and Administration

Alagille syndrome

The usual dosage is 200 μg/kg of maralixibat chloride orally administered once daily before a meal. After 1 week of the treatment, the dose should be increased to 400 μg/kg administered once daily.

Progressive familial intrahepatic cholestasis

The usual dosage is 300 μg/kg of maralixibat chloride orally administered once daily before a meal. After 1 week of the treatment, the dose should be increased to 300 μg/kg administered twice daily. After another week of the treatment, the dose should be further increased to 600 μg/kg administered twice daily.

Precautions Concerning Dosage and Administration

For both indications

- Whether maralixibat is continued should be considered if no response is achieved after 3 months of treatment with maralixibat.

Alagille syndrome

- The dose of maralixibat should be determined based on the table below, which provides the dose in mL of solution to be given for each body weight range.

Body weight	200 μg/kg	400 μg/kg
	Volume per dose	Volume per dose
4 kg	0.1 mL	0.15 mL
5-6 kg	0.1 mL	0.2 mL
7-9 kg	0.15 mL	0.3 mL
10-12 kg	0.2 mL	0.45 mL
13-15 kg	0.3 mL	0.6 mL
16-19 kg	0.35 mL	0.7 mL
20-24 kg	0.45 mL	0.9 mL
25-29 kg	0.5 mL	1 mL
30-34 kg	0.6 mL	1.25 mL
35-39 kg	0.7 mL	1.5 mL
40-49 kg	0.9 mL	1.75 mL
50-59 kg	1 mL	2.25 mL
60-69 kg	1.25 mL	2.5 mL
≥70 kg	1.5 mL	3 mL

Progressive familial intrahepatic cholestasis

- The dose of maralixibat should be determined based on the table below, which provides the dose in mL of solution to be given for each body weight range.

Body weight	300 μg/kg	600 μg/kg
	Volume per dose	Volume per dose
3 kg	0.1 mL	0.2 mL
4 kg	0.1 mL	0.25 mL
5 kg	0.15 mL	0.3 mL
6-7 kg	0.2 mL	0.4 mL
8-9 kg	0.25 mL	0.5 mL
10-12 kg	0.35 mL	0.6 mL
13-15 kg	0.4 mL	0.8 mL
16-19 kg	0.5 mL	1 mL
20-24 kg	0.6 mL	1.25 mL
25-29 kg	0.8 mL	1.5 mL
30-34 kg	0.9 mL	2 mL
35-39 kg	1.25 mL	2.25 mL
40-49 kg	1.25 mL	2.75 mL
50-59 kg	1.5 mL	3 mL
60-69 kg	2 mL	3 mL
70-79 kg	2.25 mL	3 mL
≥80 kg	2.5 mL	3 mL

1.4 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.5 Post-marketing investigations" in the Review Report (1).

PMDA has concluded that the risk management plan (draft) for maralixibat should include the safety specification presented in Table 75, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 76. The applicant is required to continue examining the post-marketing database survey plan in detail and implement the survey according to an appropriate plan.

Table 75. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• None	• Liver disorders	• None
Efficacy specification		
• None		

Table 76. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing database survey	• Disseminate data gathered during early post-marketing phase vigilance

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following approval condition. Since the product is designated as an orphan drug, the re-examination period is 10 years.

Indications

Cholestatic pruritus in patients with the following diseases:

○ Alagille syndrome

○ Progressive familial intrahepatic cholestasis

Dosage and Administration

Alagille syndrome

The usual dosage is 200 μg/kg of maralixibat chloride orally administered once daily before a meal. After 1 week of the treatment, the dose should be increased to 400 μg/kg administered once daily.

Progressive familial intrahepatic cholestasis

The usual dosage is 300 μg/kg of maralixibat chloride orally administered once daily before a meal. After 1 week of the treatment, the dose should be increased to 300 μg/kg administered twice daily. After another week of the treatment, the dose should be further increased to 600 μg/kg administered twice daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

List of Abbreviations

ALGS	Alagille syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
$AUC_{0\text{-last}}$	AUC from time zero to the last measurable time
$AUC_{0\text{-t}}$	AUC from time zero to 't' (where t = the time of detection)
AUC_{inf}	AUC from time zero to infinity
BCRP	Breast cancer resistance protein
BID	bis in die
BHK cells	Baby hamster kidney cell
BSEP	Bile salt export pump
7αC4	7alpha-hydroxy-4-cholesten-3-one
Caco-2 cells	Human colon cancer cells
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum concentration
CPP	Critical process parameter
CQA	Critical quality attribute
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
ED_{50}	Effective dose for 50% of the animals
fBA	Fecal bile acid
FIC1 protein	Familial intrahepatic cholestasis 1 protein
FOB	Functional observational battery
$f_{u,gut}$	Fraction unbound in gut
GC	Gas chromatography
GGT	Gamma-glutamyl transpeptidase
HEK293 cells	Human embryonic kidney cell line 293
hERG	Human ether-à-go-go-related gene
HPLC	High performance liquid chromatography
IBAT	Ileal bile acid transporter
IC_{50}	50% inhibitory concentration
IR	Infrared absorption spectroscopy
ItchRO	Itch reported outcome
ITT	Intent-to-treat
K_I	Inhibitor concentration at 50% of maximum inhibition rate
K_i	Inhibition constant
LC-MS	Liquid chromatography-mass spectrometry
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LOCF	Last observation carried forward
Maralixibat	Maralixibat Chloride
MATE	Multidrug and toxin extrusion
MDCK cells	Mardin-Darby canine kidney cells
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA PT	MedDRA preferred term
MITT	Modified intent-to-treat
MRP2	Multidrug resistance protein 2
MMRM	Mixed-effects model for repeated measures
NMR	Nuclear magnetic resonance spectroscopy

NZW	New Zealand White
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OC	Observed cases
OCT	Organic cation transporter
OCTN	Organic cation/carnitine transporter
P_{app}	Apparent permeability coefficient
pBDL	Partial bile duct ligation
PBPK	Physiologically based pharmacokinetic
PEPT1	Peptide transporter 1
PFIC	Progressive familial intrahepatic cholestasis
P-gp	P-glycoprotein
pKa	Acid dissociation constant
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Prothrombin time
QD	quaque die
QOL	Quality of life
QT	QT interval
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
RH	Relative humidity
RWD	Randomized withdrawal
sBA	Serum bile acid
SD	Sprague Dawley
$t_{1/2}$	Elimination half-life
t_{max}	Time to reach maximum concentration
UV-VIS	Ultraviolet-visible spectroscopy