HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LIVMARLI safely and effectively. See full prescribing information for LIVMARLI.

LIVMARLI® (maralixibat) oral solution

Initial U.S. Approval: 2021

RECENT MAJOR CHANGES

Indications and Usage (1)	3/2023
Dosage and Administration (2.1, 2.3)	3/2023

INDICATIONS AND USAGE

LIVMARLI is an ileal bile acid transporter (IBAT) inhibitor indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 3 months of age and older. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage is 380 mcg/kg once daily, taken 30 minutes before a meal in the morning. (2.1)
- Starting dose is 190 mcg/kg orally once daily, and should be increased to 380 mcg/kg once daily after one week, as tolerated. (2.1)

DOSAGE FORMS AND STRENGTHS

Oral solution: 9.5 mg of maralixibat per mL. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Liver Test Abnormalities: Obtain baseline liver tests and monitor during treatment. Dose reduction or treatment interruption may be considered if abnormalities occur. For persistent or recurrent liver test abnormalities, consider LIVMARLI discontinuation. (5.1)
- Gastrointestinal Adverse Reactions: Consider interrupting LIVMARLI treatment if a patient experiences persistent diarrhea, abdominal pain, vomiting, or has diarrhea with bloody stool, vomiting, dehydration requiring treatment, or fever. If diarrhea, abdominal pain, or vomiting persists and no alternate etiology is identified, consider stopping LIVMARLI treatment. (5.2)
- Fat-Soluble Vitamin (FSV) Deficiency: Obtain baseline levels and monitor during treatment. Supplement if deficiency is observed. If FSV deficiency persists or worsens despite FSV supplementation, consider discontinuing LIVMARLI treatment. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (≥5%) are diarrhea, abdominal pain, vomiting, fat-soluble vitamin deficiency, liver test abnormalities, gastrointestinal bleeding, and bone fractures (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Mirum Pharmaceuticals at 1-855-MRM-4YOU or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LIVMARLI® is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 3 months of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

The recommended dosage is 380 mcg/kg once daily, taken 30 minutes before a meal in the morning. Start dosing at 190 mcg/kg administered orally once daily; after one week, increase to 380 mcg/kg once daily, as tolerated. The maximum daily dose volume for patients above 70kg is 3 mL or 28.5 mg per day. Refer to the dosing by weight guidelines presented in Table 1.

Table 1: Individual Dose Volume by Patient Weight

Patient Weight (kg)	Days 1-7 (190 mcg/kg once daily)		Beginning Day 8 (380 mcg/kg once daily)	
	Volume QD (mL)	Dosing dispenser size (mL)	Volume QD (mL)	Dosing dispenser size (mL)
5 to 6	0.1	0.5	0.2	0.5
7 to 9	0.15		0.3	
10 to 12	0.2		0.45	
13 to 15	0.3		0.6	1
16 to 19	0.35		0.7	
20 to 24	0.45		0.9	
25 to 29	0.5		1	
30 to 34	0.6	1	1.25	3
35 to 39	0.7		1.5	
40 to 49	0.9		1.75	
50 to 59	1		2.25	
60 to 69	1.25	3	2.5	
70 or higher	1.5		3	

2.2 Missed Dose

If a dose is missed, it should be taken as soon as possible within 12 hours of the time it is usually taken, and the original dosing schedule should be resumed. If a dose is missed by more than 12 hours, the dose can be omitted and the original dosing schedule resumed.

2.3 Important Administration Instructions

Administer LIVMARLI 30 minutes before a meal in the morning *[see Clinical Pharmacology (12.3)]*.

For patients taking bile acid binding resins, take LIVMARLI at least 4 hours before or 4 hours after taking a bile acid binding resin *[see Drug Interactions (7.1)]*.

A calibrated measuring device (0.5 mL, 1 mL or 3 mL oral dosing dispenser) will be provided by the pharmacy to measure and deliver the prescribed dose accurately.

After opening the LIVMARLI bottle, store below 30°C (86°F) and discard any remaining LIVMARLI after 100 days.

2.4 Dose Modification for Management of Adverse Events

Establish the baseline pattern of variability of liver tests prior to starting LIVMARLI, so that potential signs of liver injury can be identified. Monitor liver tests (e.g., ALT [alanine aminotransferase], AST [aspartate aminotransferase], TB [total bilirubin]), DB [direct bilirubin] and International Normalized Ratio [INR]) during treatment with LIVMARLI. Interrupt LIVMARLI if new onset liver test abnormalities occur in the absence of other causes. Once the liver test abnormalities either return back to baseline values or stabilize at a new baseline value, consider restarting LIVMARLI at 190 mcg/kg, and increase to 380 mcg/kg as tolerated. Consider discontinuing LIVMARLI permanently if liver test abnormalities recur or symptoms consistent with clinical hepatitis are observed *[see Warnings and Precautions (5.1)]*.

LIVMARLI has not been studied in patients with hepatic decompensation. Discontinue LIVMARLI permanently if a patient experiences a hepatic decompensation event (e.g., variceal hemorrhage, ascites, hepatic encephalopathy).

3 DOSAGE FORMS AND STRENGTHS

Oral solution: 9.5 mg of maralixibat per mL as a clear, colorless to yellow solution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Liver Test Abnormalities

Patients enrolled in Trial 1 had abnormal liver tests at baseline. During Trial 1, treatment-emergent elevations of liver tests or worsening of liver tests, relative to baseline values, were observed. Most abnormalities included elevation in ALT, AST, or T/DB. In Trial 1, one patient (TB elevated at baseline) discontinued LIVMARLI due to increased TB above baseline after 28 weeks. Four patients had ALT increases that led to dose modification (n=1), dose interruption (n=2), or permanent discontinuation (n=2) of LIVMARLI during the long-term, open-label extension period of Trial 1 *[see Adverse Reactions (6.1)]*.

Obtain baseline liver tests and monitor during treatment. Dose reduction or treatment interruption may be considered if abnormalities occur in the absence of other causes. For persistent or recurrent liver test abnormalities, consider treatment discontinuation.

LIVMARLI was not evaluated in ALGS patients with cirrhosis. Monitor patients during treatment with LIVMARLI for elevations in liver tests and for the development of liver-related adverse reactions. Weigh the potential risks against the benefits of continuing treatment with LIVMARLI in patients who have experienced persistent or recurrent liver tests abnormalities. Discontinue LIVMARLI permanently if a patient progresses to portal hypertension or experiences a hepatic decompensation event.

5.2 Gastrointestinal Adverse Reactions

Diarrhea, abdominal pain, and vomiting were reported as the most common adverse reactions in patients treated with LIVMARLI *[see Adverse Reactions (6.1)]*. Three patients (3%) experienced vomiting as a serious adverse event requiring hospitalization or intravenous fluid administration.

If diarrhea, abdominal pain, and/or vomiting occur and no other etiologies are found, consider reducing the dose of LIVMARLI or interrupting LIVMARLI dosing. For diarrhea or vomiting, monitor for dehydration and treat promptly. Consider interrupting LIVMARLI dosing if a patient experiences persistent diarrhea or has diarrhea with accompanying signs and symptoms such as bloody stool, vomiting, dehydration requiring treatment, or fever.

When diarrhea, abdominal pain, and/or vomiting resolve, restart LIVMARLI at 190 mcg/kg/day and increase the dose as tolerated. If they recur upon re-challenge with LIVMARLI, then consider stopping LIVMARLI treatment.

5.3 Fat Soluble Vitamin (FSV) Deficiency

Fat-soluble vitamins (FSV) include vitamin A, D, E, and K (measured using INR levels). ALGS patients can have FSV deficiency at baseline. LIVMARLI may affect absorption of fat-soluble vitamins. In Trial 1, treatment emergent FSV deficiency was reported in 3 (10%) patients during 48 weeks of treatment.

Obtain serum FSV levels at baseline and monitor during treatment, along with any clinical manifestations. If FSV deficiency is diagnosed, supplement with FSV. Consider discontinuing LIVMARLI if FSV deficiency persists or worsens despite adequate FSV supplementation.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the Alagille syndrome clinical development program, which includes five clinical studies comprising 86 patients, patients received doses of LIVMARLI up to 760 mcg/kg per day with a median duration of exposure of 32.3 months (range: 0.03 - 60.9 months). In Trial 1, the 4-week placebo control period occurred after 18 weeks of LIVMARLI treatment. In two supportive studies that included long-term open-label extensions, only 13 weeks of placebo-controlled treatment occurred which evaluated doses lower than 380 mcg/kg/day. The majority of LIVMARLI exposure in the development program occurred without a placebo control in open-label trial extensions.

The most common adverse reactions (≥5%) for ALGS patients treated with LIVMARLI are presented in Table 2 below. Treatment interruptions or dose reductions occurred in 5 (6%) patients due to diarrhea, abdominal pain, or vomiting.

Table 2: Adverse Reactions Occurring in ≥ 5% of Patients Treated with LIVMARLI in the ALGS Clinical Development Program

	LIVMARLI (n=86)	
Adverse Reaction	**Any Grade n (%)**	**Number of events per 100 person-years[1]**
Diarrhea	48 (55.8%)	41.6
Abdominal pain*	46 (53.5%)	38.6
Vomiting	35 (40.7%)	19.8
Nausea	7 (8.1%)	2.9
Fat-Soluble Vitamin deficiency*	22 (25.6%)	11.1
Transaminases increased (ALT, AST)*	16 (18.6%)	6.9
Gastrointestinal Bleeding*	9 (10.4%)	3.8
Bone Fractures*	8 (9.3%)	3.3

*Terms were defined as:

Fat-Soluble Vitamin deficiency includes: A, D, E, or K deficiency, or INR increase

Abdominal Pain includes: abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper

Transaminases increased includes: ALT abnormal, ALT increased, AST abnormal, AST increased

Gastrointestinal Bleeding includes: hematochezia, hematemesis, gastrointestinal hemorrhage, melena

Bone Fracture includes: tibia fracture, rib fracture, hand fracture, humerus fracture, pathological fracture, forearm fracture, clavicle fracture

[1] Exposure adjusted incidence rate for each adverse reaction type was calculated using the first occurrence of this adverse reaction per patient

Liver Test Abnormalities

Increase in Transaminases

In a pooled analysis of patients with ALGS (N=86) administered LIVMARLI, increases in hepatic transaminases (ALT) were observed. Seven (8.1%) patients discontinued LIVMARLI due to ALT increases. Three (3.5%) patients had a decrease in dose or interruption of LIVMARLI in response to ALT increases. In the majority of cases, the elevations resolved or improved after discontinuation or dose modification of LIVMARLI. In some cases, the elevations resolved or improved without change in LIVMARLI dosing. Increases to more than three times baseline in ALT occurred in 24% of patients treated with LIVMARLI and increases to more than five times baseline occurred in 2%. AST increases to more than three times baseline occurred in 14% of patients treated with LIVMARLI, and an increase to more than five times baseline occurred in one patient. Elevations in transaminases were asymptomatic and not associated with bilirubin elevations or other laboratory abnormalities.

Increases in Bilirubin

Four (4.6%) patients in the pooled analysis experienced bilirubin increases above baseline, and LIVMARLI was subsequently withdrawn in two of these patients, who had elevated bilirubin at baseline.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on LIVMARLI

Bile acid binding resins

Bile acid binding resins may bind to maralixibat in the gut. Administer bile acid binding resins (e.g., cholestyramine, colesevelam, or colestipol) at least 4 hours before or 4 hours after administration of LIVMARLI.

7.2 Effects of LIVMARLI on Other Drugs

OATP2B1 substrates

Maralixibat is an OATP2B1 inhibitor based on in vitro studies. A decrease in the oral absorption of OATP2B1 substrates (e.g., statins) due to OATP2B1 inhibition in the GI tract cannot be ruled out. Consider monitoring the drug effects of OATP2B1 substrates (e.g. statins) as needed *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Maternal use at the recommended clinical dose of LIVMARLI is not expected to result in measurable fetal exposure because systemic absorption following oral administration is low *[see Clinical Pharmacology (12.3)]*. Maralixibat may inhibit the absorption of fat-soluble vitamins *[see Warnings and Precautions (5.3) and Clinical Considerations]*. In animal reproduction studies, no developmental effects were observed *(see Data)*.

The estimated background risk of major birth defects for the indicated population is higher than the general population because Alagille syndrome is an autosomal dominant condition. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Maralixibat may inhibit the absorption of fat-soluble vitamins (FSV). Monitor for FSV deficiency and supplement as needed. Increased supplementation of FSVs may be needed during pregnancy *[see Warnings and Precautions (5.3)]*.

Data

Animal Data

No effects on embryo-fetal development were observed in pregnant rats treated orally with up to 1000 mg/kg/day (approximately 3300 to 12000 times the maximum recommended dose based on AUC [area under the plasma concentration-time curve]) or in pregnant rabbits treated orally with up to 250 mg/kg/day (approximately 1200 to 4700 times the maximum recommended dose based on AUC) during the period of organogenesis. No effects on postnatal development were observed in a pre- and postnatal development study, in which female rats were treated orally with up to 750 mg/kg/day during organogenesis through lactation. Maternal systemic exposure to maralixibat at the maximum dose tested was approximately 2500 to 9400 times the maximum recommended dose based on AUC.

8.2 Lactation

Risk Summary

LIVMARLI has low absorption following oral administration, and breastfeeding is not expected to result in exposure of the infant to LIVMARLI at the recommended dose *[see Clinical Pharmacology (12.3)]*. There are no data on the presence of LIVMARLI in human milk, the effects on the breastfed infant, or the effects on milk production. Patients with ALGS can have FSV deficiency as part of their disease. Maralixibat may reduce absorption of fat-soluble vitamins *[see Warnings and Precautions (5.3)]*. Monitor FSV levels and supplement FSV intake, if FSV deficiency is observed during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's need for LIVMARLI and any potential adverse effects on the breastfed child from LIVMARLI or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of LIVMARLI for the treatment of cholestatic pruritus in Alagille syndrome have been established in pediatric patients aged 3 months of age and older. Use of LIVMARLI in this population is supported by evidence from a study of patients 1 to 15 years of age (N=31) that included 18 weeks of open-label treatment followed by a 4 week placebo-controlled randomized withdrawal period and a subsequent 26-week open-label treatment period. Additional safety information was obtained from four studies in patients up to 21 years of age (N=55) *[see Adverse Reactions (6) and Clinical Studies (14)]*. Use of LIVMARLI in patients 3 to <12 months of age is supported by an open-label, multicenter study of LIVMARLI which showed a similar safety, tolerability and pharmacokinetic profile to patients with ALGS ≥12 months of age.

The safety and effectiveness of LIVMARLI have not been established in patients less than 3 months of age.

8.5 Geriatric Use

The safety and effectiveness of LIVMARLI for the treatment of pruritus in ALGS in adult patients, 65 years of age and older, have not been established.

8.7 Hepatic Impairment

Clinical studies of LIVMARLI included ALGS patients with impaired hepatic function at baseline. The efficacy and safety in ALGS patients with clinically significant portal hypertension and in patients with decompensated cirrhosis have not been established *[see Clinical Studies (14), Dosage and Administration (2.4), and Warnings and Precautions (5.1)]*.

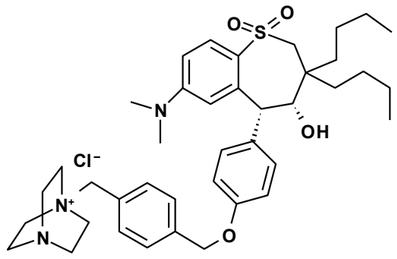
10 OVERDOSAGE

Single doses of maralixibat up to 500 mg, approximately 18-fold higher than the recommended dose, have been administered in healthy adults and were tolerated without a meaningful increase in adverse effects when compared to lower doses. If an overdose occurs, discontinue LIVMARLI, monitor the patient for any signs and symptoms and institute general supportive measures if needed.

LIVMARLI contains propylene glycol (364.5 mg/mL) as an excipient. Oral doses of propylene glycol up to 50 mg/kg/day (1 month to <5 years of age) and 500 mg/kg/day (≥5 years of age) are generally considered safe. Overdoses of propylene glycol may manifest with hyperosmolality, CNS, cardiovascular, and/or respiratory effects and may subside with the elimination of propylene glycol.

11 DESCRIPTION

LIVMARLI (maralixibat) oral solution is an ileal bile acid transporter (IBAT) inhibitor. Maralixibat is present as a chloride salt with the chemical name 1-[[4-[[4-[(4*R*,5*R*)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride. The molecular formula of maralixibat chloride is $C_{40}H_{59}ClN_2O_4S$ with a molecular weight of 710.42. It has the following chemical structure:



LIVMARLI is supplied in a multiple-dose bottle containing 9.5 mg of maralixibat per mL (equivalent to 10 mg of maralixibat chloride per mL). The oral solution contains the following inactive ingredients: edetate disodium, grape flavor, propylene glycol, purified water, and sucralose. The pH of the oral solution is 3.8 – 4.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Maralixibat is a reversible inhibitor of the ileal bile acid transporter (IBAT). It decreases the reabsorption of bile acids (primarily the salt forms) from the terminal ileum.

Pruritus is a common symptom in patients with ALGS and the pathophysiology of pruritus in patients with ALGS is not completely understood. Although the complete mechanism by which maralixibat improves pruritus in ALGS patients is unknown, it may involve inhibition of the IBAT, which results in decreased reuptake of bile salts, as observed by a decrease in serum bile acids *[see Clinical Pharmacology (12.2)]*.

12.2 Pharmacodynamics

In Trial 1, pediatric patients with ALGS were administered open-label treatment with LIVMARLI 380 mcg/kg once daily for 13 weeks after an initial 5-week dose-escalation period *[see Clinical Studies (14)]*. At baseline, serum bile acids were highly variable among patients ranging from 20 to 749 µmol/L and mean (SD) serum bile acid level was 283 (210.6) µmol/L. Serum bile acid levels decreased from baseline in the majority of patients as early as at Week 12 and the reduction in serum bile acids was generally maintained for the treatment period.

12.3 Pharmacokinetics

Because of the low systemic absorption of maralixibat, pharmacokinetic parameters cannot be reliably calculated at the recommended dose. Concentrations of maralixibat in the pediatric ALGS patients were below the limit of quantification (0.25 ng/mL) in the majority of plasma samples. In Trial 1, the highest concentration of maralixibat in pediatric ALGS patients following treatment with LIVMARLI 380 mcg/kg once daily was 5.93 ng/mL.

Following single oral administration of maralixibat in healthy adults at doses ranging from 1 mg to 500 mg, plasma concentrations of maralixibat were below the limit of quantification (0.25 ng/mL) at doses less than 20 mg and PK parameters could not be reliably estimated.

Following a single dose administration of 30 mg under fasted condition, median Tmax was 0.75 and mean (SD) Cmax and AUClast were 1.65 (1.10) ng/ml and 3.43 (2.13) ng-h/mL, respectively.

Absorption

Maralixibat is minimally absorbed and plasma concentrations are often below the limit of quantification (0.25 ng/mL) after single or multiple doses at recommended doses. Following a single oral administration of maralixibat 30, 45, and 100 mg liquid formulation under fasted condition, AUClast and Cmax increased in a dose-dependent manner with increase of 4.6- and 2.4-fold, respectively, following a 3.3-fold dose increase from 30 to 100 mg.

No accumulation of maralixibat was observed following repeated oral administration of administration of maralixibat in healthy adults at doses up to 100 mg once-daily.

Effect of Food

Concomitant administration of a high-fat meal with a single oral dose of maralixibat decreased both the rate and extent of absorption. AUC and Cmax of maralixibat values in the fed state were 64.8% to 85.8% lower relative to oral administration of 30 mg in fasted conditions. The effect of food on the changes of systemic exposures to maralixibat is not clinically significant *[see Dosage and Administration (2.1, 2.3)]*.

Distribution

Maralixibat shows high binding (91%) to human plasma proteins in vitro.

Elimination

Following a single oral dose of 30 mg maralixibat in healthy adults, the mean half-life ($t_{1/2}$) was 1.6 hours.

Metabolism

No maralixibat metabolites have been detected in plasma. Three minor metabolites, accounting for <3% of maralixibat-associated fecal radioactivity in total, were identified following oral administration of [^{14}C]maralixibat.

Excretion

Fecal excretion was found to be the major route of elimination. Following a single oral dose of 5 mg ^{14}C-maralixibat, 73% of the dose was excreted in the feces with 0.066% excreted in the urine. 94% of the fecal excretion was as unchanged maralixibat.

Specific Populations

Patients with Renal Impairment

The pharmacokinetics of maralixibat were not studied in patients with impaired renal function, including those with end-stage renal disease (ESRD) or those on hemodialysis.

Drug Interaction Studies

Effect of Other Drugs on Maralixibat

Maralixibat is not a substrate of the drug transporters MDR1 (P-gp), BCRP, OATP1B1, OATP1B3, or OATP2B2; therefore, concomitant drug products are not predicted to affect the disposition of maralixibat.

Effect of Maralixibat on Other Drugs

In vitro, maralixibat did not induce CYP isoforms 1A2, 2B6, or 3A4, nor inhibit CYP isoforms 1A2, 2B6, 2C8, 2C9, 2C19 or 2D6 at clinically relevant concentrations. Maralixibat inhibits CYP3A4 in vitro, however clinically relevant effects on the pharmacokinetics of CYP3A4 substrates are unlikely. In vitro, maralixibat did not inhibit the transporters MDR1 (P-gp), BCRP, OAT1, OAT3, OATP1B1, OATP1B3, PEPT1, OCT1, OCT2, OCT3, OCTN1, OCTN2, MRP2, MATE1, or MATE2-K at clinically relevant concentrations.

Maralixibat inhibits the drug transporter OATP2B1 in vitro, which can potentially result in reduced absorption of drugs that rely on OATP2B1-mediated uptake in the GI tract. In clinical studies coadministration of 4.75 mg maralixibat (once daily in the morning) with daily doses of either simvastatin, or lovastatin in the evening, did not have a clinically relevant effect on the pharmacokinetics of these statins and their metabolites. Coadministration of 4.75 mg maralixibat did not affect pharmacokinetics of atorvastatin. However, the effect of maralixibat on the pharmacokinetics of OATP2B1 substrates at higher doses has not been evaluated in a clinical study.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No drug-related tumors were observed following oral administration of maralixibat chloride to TgRasH2 mice at doses of up to 25 (males) or 75 (females) mg/kg/day for 26 weeks.

Mutagenesis

Maralixibat chloride was negative in *in vitro* (bacterial reverse mutation, chromosomal aberration in mammalian cells) and *in vivo* (mouse bone marrow micronucleus) assays.

Impairment of Fertility

No effects on fertility were observed in female rats treated orally with up to 2000 mg/kg/day or in male rats treated orally with up to 750 mg/kg/day.

14 CLINICAL STUDIES

The efficacy of LIVMARLI was assessed in Trial 1 (NCT02160782), which consisted of an 18-week open-label treatment period; a 4-week randomized, double-blind, placebo-controlled drug-withdrawal period; a subsequent 26-week open-label treatment period; and a long-term open-label extension period.

Thirty-one pediatric ALGS patients with cholestasis and pruritus were enrolled, with 90.3% of patients receiving at least one medication to treat pruritus at study entry. All patients had JAGGED1 mutation. Patients were administered open-label treatment with LIVMARLI 380 mcg/kg once daily for 13 weeks after an initial 5-week dose-escalation period; two patients discontinued treatment during this first 18 weeks of open-label treatment. The 29 patients who completed the open-label treatment phase were then randomized to continue treatment with LIVMARLI or receive matching placebo during the 4-week drug withdrawal period at Weeks 19-22 (n=16 placebo, n=13 LIVMARLI). All 29 patients completed the randomized, blinded drug withdrawal period; subsequently, patients received open-label LIVMARLI at 380 mcg/kg once daily for an additional 26 weeks.

Randomized patients had a median age of 5 years (range: 1 to 15 years) and 66% were male. The baseline mean (standard deviation [SD]) of liver test parameters were as follows: serum bile acid levels 280 (213) µmol/L, AST 158 (68) U/L, ALT 179 (112) U/L, Gamma Glutamyl Transferase (GGT) 498 (399) U/L, and TB 5.6 (5.4) mg/dL.

Given the patients' young age, a single-item observer-reported outcome was used to measure patients' pruritus symptoms as observed by their caregiver twice daily (once in the morning and once in the evening) on the Itch Reported Outcome Instrument (ItchRO[Obs]). Pruritus symptoms were assessed on a 5-point ordinal response scale, with scores ranging from 0 (none observed or reported) to 4 (very severe). Patients were included in Trial 1 if their average pruritus score was greater than 2.0 (moderate) in the 2 weeks prior to baseline.

The average of the worst daily ItchRO(Obs) pruritus scores was computed for each week. For randomized patients, the mean (SD) at baseline (pre-treatment) was 3.1 (0.5) and the mean (SD) at Week 18 (pre-randomized withdrawal period) was 1.4 (0.9). On average, patients administered LIVMARLI for 22 weeks maintained pruritus reduction whereas those in the placebo group who were withdrawn from LIVMARLI after Week 18 returned to baseline pruritus scores by Week 22. Results from the placebo-controlled period are presented in Table 3. After re-entering the open-label treatment phase, both randomized treatment groups had similar mean pruritus scores by Week 28, the first week placebo patients received the full dosage of LIVMARLI after withdrawal. These observer-rated pruritus results are supported by similar results on patient-rated pruritus in patients 5 years of age and older who were able to self-report their itching severity.

Table 3: Weekly Average of Worst Daily ItchRO(Obs) Pruritus Severity Scores in Trial 1

	Maralixibat (N=13)	Placebo (N=16)	Mean Difference
Week 22, Mean (95% CI)	1.6 (1.1, 2.1)	3.0 (2.6, 3.5)	
Change from Week 18 to Week 22, Mean (95% CI)	0.2 (-0.3, 0.7)	1.6 (1.2, 2.1)	-1.4 (-2.1, -0.8)

Results based on an analysis of covariance model with treatment group and Week 18 average worst daily pruritus score as covariates

16 HOW SUPPLIED/STORAGE AND HANDLING

Oral Solution

LIVMARLI is a clear, colorless to yellow oral solution.

Each amber plastic bottle contains LIVMARLI oral solution at a concentration of 9.5 mg per mL.

One 30 mL amber plastic bottle: NDC 79378-110-01

Storage and Handling

Store unopened LIVMARLI between 20°C and 25°C (68°F and 77°F), excursion permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. After opening the LIVMARLI bottle, store below 30°C (86°F) *[see Dosage and Administration (2.3)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient or their caregiver(s) to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Administration Instructions

Advise patients or their caregivers(s) to:

- Take LIVMARLI 30 minutes prior to a meal in the morning using a calibrated measuring device (0.5 mL, 1 mL or 3 mL oral dispenser) to measure and deliver the prescribed dose accurately *[see Dosage and Administration (2.1, 2.3)]*.
- Take LIVMARLI at least 4 hours before or 4 hours after taking a bile acid binding resin (e.g., cholestyramine, colesevelam, or colestipol) *[see Drug Interactions (7.1)]*.
- Store the opened bottle below 30°C (86°F). Discard any unused LIVMARLI 100 days after opening the bottle *[see How Supplied/Storage and Handling (16)]*.

Liver Test Abnormalities

Advise patients or their caregiver(s) that liver tests should be obtained before starting LIVMARLI and periodically during LIVMARLI therapy, due to the risk of elevation in liver tests and development of liver-related adverse reactions *[see Dosage and Administration (2.4) and Warnings and Precautions (5.1, 5.2)]*.

Gastrointestinal Adverse Reactions

Advise patients or their caregiver(s) to notify their healthcare provider if they experience new onset or worsening of gastrointestinal symptoms *[see Warnings and Precautions (5.2)]*.

Fat Soluble Vitamin (FSV) Deficiency

Advise patients or their caregiver(s) that INR (for vitamin K) and serum levels of vitamins A, D, E will be obtained before starting and periodically during treatment to assess for FSV deficiency *[see Warnings and Precautions (5.3)]*.

Rx only

Manufactured for:
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FPI-0011