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)	3/2024
Dosage and Administration (2)	3/2024
Dosage and Administration (2)	7/2024
Contraindications (4)	3/2024
Warnings and Precautions (5.1)	3/2024
Warnings and Precautions (5.2)	3/2024
Warnings and Precautions (5.3)	3/2024
Warnings and Precautions (5.4)	7/2024

----------INDICATIONS AND USAGE----------

LIVMARLI is an ileal bile acid transporter (IBAT) inhibitor indicated for:

- the treatment of cholestatic pruritus in patients 3 months of age and older with Alagille syndrome (ALGS). (1.1)
- the treatment of cholestatic pruritus in patients 12 months of age and older with progressive familial intrahepatic cholestasis (PFIC). (1.2)
  - Limitations of Use:
    LIVMARLI is not recommended in a subgroup of PFIC type 2 patients with specific ABCB11 variants resulting in non-functional or complete absence of bile salt export pump (BSEP) protein. (14.2)

----------DOSAGE AND ADMINISTRATION----------

- Treatment of ALGS: Use LIVMARLI Oral Solution 9.5 mg/mL. 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 and not to exceed a maximum daily dose of 28.5 mg. (2.1)
- Treatment of PFIC: Use LIVMARLI Oral Solution 19 mg/mL. The recommended dosage is 570 mcg/kg twice daily. (2.2)
  Starting dose is 285 mcg/kg orally once daily in the morning and should be increased to 285 mcg/kg twice daily, 428 mcg/kg twice daily, and then to 570 mcg/kg twice daily, as tolerated and not to exceed a maximum daily dose of 38 mg. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Oral solution:

- 9.5 mg of maralixibat per mL: treatment of ALGS. (3)
- 19 mg of maralixibat per mL: treatment of PFIC. (3)

----------CONTRAINDICATIONS----------

Patients with prior or active hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy). (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Obtain baseline liver tests and monitor patients frequently for the first 6 to 8 months after starting therapy, and as clinically indicated thereafter during treatment. If liver test abnormalities or signs of clinical hepatitis occur, consider dose reduction or treatment interruption. For persistent or recurrent liver test abnormalities relative to baseline, discontinue LIVMARLI. Monitor patients with compensated cirrhosis frequently. Permanently discontinue LIVMARLI if hepatic decompensation event occurs. (5.1)
- Gastrointestinal Adverse Reactions: Consider reducing the dosage or interrupting LIVMARLI treatment if a patient experiences persistent diarrhea or abdominal pain, or has diarrhea with bloody stool, vomiting, dehydration requiring treatment, or fever. Consider stopping LIVMARLI treatment if diarrhea or abdominal pain persists and no alternate etiology is identified. (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)
  - Fracture: Consider interrupting LIVMARLI treatment and supplement with FSV. LIVMARLI can be restarted once FSV deficiency is corrected and maintained at corrected levels.
  - Bleeding: Interrupt treatment with LIVMARLI. Treatment can be restarted if the FSV deficiency is corrected and bleeding has resolved.
- Risk of Propylene Glycol Toxicity (Pediatric Patients Less Than 5 years of Age): Total daily intake of propylene glycol should be considered for managing the risk of propylene glycol toxicity. Monitor patients for signs of propylene glycol toxicity. Discontinue if toxicity is suspected. (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥5%) are:

- ALGS: diarrhea, abdominal pain, vomiting, fat-soluble vitamin deficiency, liver test abnormalities, and bone fractures. (6.1)
- PFIC: diarrhea, fat soluble vitamin deficiency, abdominal pain, liver test abnormalities, hematochezia, 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.

----------DRUG INTERACTIONS----------

- Bile Acid Sequestrants: Modify LIVMARLI administration schedule. (7.1)

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

Revised: 7/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Cholestatic Pruritus in Patients with Alagille Syndrome

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

1.2 Treatment of Cholestatic Pruritus in Patients with Progressive Familial Intrahepatic Cholestasis

LIVMARLI is indicated for the treatment of cholestatic pruritus in patients 12 months of age and older with progressive familial intrahepatic cholestasis (PFIC).

Limitations of Use:

LIVMARLI is not recommended in a subgroup of PFIC type 2 patients with specific ABCB11 variants resulting in non-functional or complete absence of bile salt export pump (BSEP) protein *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Alagille Syndrome

Use LIVMARLI Oral Solution **9.5 mg/mL** for the treatment of **ALGS**.

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 should not exceed 28.5 mg (3 mL) per day. Refer to the dosing by weight guidelines presented in Table 1.

Table 1: 9.5 mg/mL Solution for Patients with ALGS: Volume per Dose (mL) by Weight

Patient Weight (kg)	Days 1-7 (190 mcg/kg once daily)	Beginning Day 8 (380 mcg/kg once daily)
	9.5 mg/mL Solution (for ALGS) Volume per Dose (mL)	
5 to 6	0.1	0.2
7 to 9	0.15	0.3
10 to 12	0.2	0.45
13 to 15	0.3	0.6
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	1.25
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	2.5
70 or higher	1.5	3

2.2 Recommended Dosage for Progressive Familial Intrahepatic Cholestasis

Use LIVMARLI Oral Solution **19 mg/mL** for the treatment of **PFIC**.

The two strengths of LIVMARLI, 9.5 mg/mL and 19 mg/mL, should not be substituted for one another when treating PFIC patients. Special attention should be given to the accurate calculation of the dose volume of LIVMARLI. This is especially important for pediatric patients less than 5 years old as LIVMARLI oral solution contains the excipient propylene glycol (364.5 mg/mL) *[see Warnings and Precautions (5.4) and Overdosage (10)].*

The recommended dosage is 570 mcg/kg twice daily 30 minutes before a meal. The starting dose is 285 mcg/kg orally once daily in the morning, and should be increased to 285 mcg/kg twice daily, 428 mcg/kg twice daily, and then to 570 mcg/kg twice daily, as tolerated. The maximum daily dose should not exceed 38 mg (2 mL) per day. Refer to the dosing by weight guidelines presented in Table 2.

Table 2: 19 mg/mL Solution for Patients with PFIC: Volume per Dose (mL) by Weight

Patient Weight (kg)	285 mcg/kg (once daily titrated to twice daily)	428 mcg/kg (twice daily)	570 mcg/kg (twice daily as tolerated)
	19 mg/mL Solution (for PFIC) Volume per Dose (mL)		
5	0.1	0.1	0.15
6 to 7	0.1	0.15	0.2
8	0.1	0.2	0.25
9	0.15	0.2	0.25
10 to 12	0.15	0.25	0.3
13 to 15	0.2	0.3	0.4
16 to 19	0.25	0.4	0.5
20 to 24	0.3	0.5	0.6
25 to 29	0.4	0.6	0.8
30 to 34	0.45	0.7	0.9
35 to 39	0.6	0.8	1
40 to 49	0.6	0.9	1
50 to 59	0.8	1	1
60 or higher	0.9	1	1

2.3 Missed Dose

For once daily dosing: 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.

For twice daily dosing: If a dose is missed, it should be taken as soon as possible within 6 hours of the time it is usually taken, and the original dosing schedule should be resumed. If a dose is missed by more than 6 hours, the dose can be omitted and the original dosing schedule resumed.

2.4 Important Administration Instructions

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

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.

2.5 Dosage 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. Reduce the dosage or interrupt LIVMARLI if new onset liver test abnormalities occur. Once the liver test abnormalities either return back to baseline values or stabilize at a new baseline value, consider restarting LIVMARLI at the last tolerated dose, and increase the dose 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).

2.6 Administration Modification for Drug Interaction

Bile Acid Binding Resins

Administer LIVMARLI at least 4 hours before or 4 hours after administering the bile acid binding resins *[see Drug Interactions (7.1)]* when used concomitantly**.**

3 DOSAGE FORMS AND STRENGTHS

Oral solution:

- 9.5 mg of maralixibat per mL (for treatment of ALGS) as a clear, colorless to yellow solution.
- 19 mg of maralixibat per mL (for treatment of PFIC) as a clear, colorless to yellow solution.

4 CONTRAINDICATIONS

LIVMARLI is contraindicated in patients with prior or active hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy) *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

LIVMARLI treatment is associated with a potential for drug-induced liver injury.

In the PFIC trial, treatment-emergent hepatic decompensation events and elevations of liver tests or worsening of liver tests occurred. Two patients experienced drug-induced liver injury (DILI) attributable to LIVMARLI. Two additional patients experienced DILI in the open-label extension portion of the trial. Of these four patients, one patient required liver transplant and another patient died.

In the ALGS trial, treatment-emergent elevations of liver tests or worsening of liver tests occurred. Most abnormalities included elevations in ALT, AST, and/or TB/DB. One patient whose TB was elevated at baseline discontinued LIVMARLI after 28 weeks due to increased TB above baseline. 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 *[see Adverse Reactions (6.1)].*

Obtain baseline liver tests because some ALGS and PFIC patients have abnormal liver tests at baseline. Monitor patients frequently for the first 6 to 8 months after starting therapy and as clinically indicated thereafter during treatment with LIVMARLI. Monitor for elevations in liver tests, for the development of liver-related adverse reactions, and for physical signs of hepatic decompensation. If liver test abnormalities or signs of clinical hepatitis occur in the absence of other causes, consider dose reduction or treatment interruption.

Permanently discontinue LIVMARLI if a patient experiences the following:

- persistent or recurrent liver test abnormalities, or

- upon rechallenge, signs and symptoms consistent with clinical hepatitis, or
- a hepatic decompensation event.

The safety and effectiveness of LIVMARLI have not been established in patients with decompensated cirrhosis. Monitor patients with compensated cirrhosis frequently and discontinue LIVMARLI if hepatic decompensation occurs. LIVMARLI is contraindicated in patients with prior or active hepatic decompensation events *[see Contraindications (4)]*.

5.2 Gastrointestinal Adverse Reactions

Diarrhea and abdominal pain were reported as the most common adverse reactions in patients treated with LIVMARLI *[see Adverse Reactions (6.1)]*.

Consider reducing the dosage or interrupting LIVMARLI treatment if a patient experiences persistent diarrhea or abdominal pain, or has diarrhea with bloody stool, vomiting, dehydration requiring treatment, or fever. Consider stopping LIVMARLI treatment if diarrhea or abdominal pain persists and no alternate etiology is identified. Monitor for dehydration due to diarrhea and treat promptly. LIVMARLI was not evaluated in PFIC patients with chronic diarrhea requiring intravenous fluids.

When diarrhea or abdominal pain resolves, restart LIVMARLI at the last tolerated dose and increase the dose as tolerated. Consider stopping LIVMARLI treatment if they recur upon re-challenge with LIVMARLI.

5.3 Fat Soluble Vitamin (FSV) Deficiency

LIVMARLI may adversely affect absorption of fat-soluble vitamins (FSV). FSV include vitamins A, D, E, and K (measured using INR levels). ALGS and PFIC patients can have FSV deficiency at baseline and are frequently supplemented with FSV.

In ALGS patients in Trial 1, treatment-emergent FSV deficiency was reported in 3 (10%) patients during 48 weeks of treatment.

In PFIC patients in Trial 2, treatment-emergent FSV deficiency (assessed biochemically) was reported in 13 (28%) of LIVMARLI-treated patients versus 16 (35%) of placebo-treated patients during 26 weeks of treatment.

<u>Bone Fracture</u>

Treatment-emergent bone fracture events have been observed more frequently with LIVMARLI-treated patients compared to placebo-treated patients *[see Adverse Reactions (6.1)]*. If fracture occurs, consider interrupting LIVMARLI treatment and supplement with FSV. LIVMARLI can be restarted once FSV deficiency is corrected and maintained at corrected levels.

<u>Bleeding</u>

If bleeding occurs, interrupt treatment with LIVMARLI. LIVMARLI can be restarted if FSV deficiency is corrected and bleeding has resolved.

Obtain serum FSV levels prior to initiation of LIVMARLI and monitor the levels periodically during treatment, along with any clinical manifestations of FSV deficiency. Supplement with FSV if FSV deficiency is diagnosed. Consider discontinuing LIVMARLI if FSV deficiency persists or worsens despite adequate FSV supplementation.

If complications of FSV deficiency occur, such as fracture or bleeding, consider interrupting LIVMARLI treatment and supplement with FSV. LIVMARLI can be restarted once FSV deficiency is corrected and maintained at corrected levels.

5.4 Risk of Propylene Glycol Toxicity (Pediatric Patients Less Than 5 Years of Age)

LIVMARLI contains propylene glycol. Patients less than 5 years of age are at highest risk for propylene glycol toxicity, and a safe level for propylene glycol exposure with repeated administration has not been established for pediatric patients less than 5 years of age. When LIVMARLI is administered at the dose (380 mcg/kg once daily) for treatment of cholestatic pruritus in patients with ALGS, the exposure to propylene glycol will be 14.6 mg/kg/day. When LIVMARLI is administered at the dose (570 mcg/kg twice daily) for treatment of cholestatic pruritus in patients with PFIC, the exposure to propylene glycol will be 21.9 mg/kg/day. The total daily intake of propylene glycol from all sources should be considered for managing the risk of propylene glycol toxicity.

Monitor patients for signs of potential propylene glycol toxicity, including hemolysis, hyperosmolarity with anion gap metabolic acidosis, acute kidney injury, and CNS toxicity. Discontinue LIVMARLI if propylene glycol toxicity is suspected *[see Overdosage (10)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.2)]*
- Fat Soluble Vitamin (FSV) Deficiency *[see Warnings and Precautions (5.3)]*

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.

ALGS:

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 3 below. Treatment interruptions or dose reductions occurred in 5 (6%) patients due to diarrhea, abdominal pain, or vomiting.

Table 3: 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
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
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 26% of patients treated with LIVMARLI and increases to more than five times baseline occurred in 3%. AST increases to more than three times baseline occurred in 16% 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.

PFIC:

In Trial 2, which enrolled 93 patients, 47 patients received doses of LIVMARLI up to 570 mcg/kg BID, with a median duration of exposure of 6 months (range: 0.3-6.7 months).

The most common adverse reactions (≥5%) for PFIC patients treated with LIVMARLI at a rate greater than placebo are presented in Table 4 below. Diarrhea was the most frequent adverse reaction; the majority of episodes were mild and transient with a median duration of 5.5 days. Nineteen (40.4%) LIVMARLI-treated subjects had diarrhea greater than or equal to 7 days. Placebo-treated subjects had a median duration of 3 days of diarrhea and two subjects (4.3%) experienced diarrhea with a duration greater than or equal to 7 days. There were no severe events reported. The majority of abdominal pain events were mild based on AE grading, and associated with concurrent diarrhea.

One LIVMARLI-treated patient with an event of mild diarrhea discontinued treatment. Treatment interruptions or dose reductions occurred in 3 (6.4%) LIVMARLI-treated patients due to diarrhea or abdominal pain. No placebo-treated subjects discontinued treatment or had dose reductions or interruptions due to diarrhea.

Table 4: Adverse Reactions (any grade) Occurring in ≥5% and at a Rate Greater Than Placebo in Patients Treated with LIVMARLI in the PFIC Trial

Adverse Reaction (Any Grade)	Placebo n=46	LIVMARLI n=47
Diarrhea	9 (19.6%)	27 (57.4%)
Abdominal pain†	7 (15.2%)	13 (27.7%)
Transaminases increased (ALT or AST) †	3 (6.5%)	8 (17%)
Hematochezia or rectal hemorrhage	1 (2.2%)	4 (8.5%)
Bone Fractures†	0	3 (6.4%)

†Terms were defined as:
Abdominal Pain includes: abdominal pain, abdominal pain upper, abdominal distension
Transaminases increased includes: Hypertransaminasaemia, ALT abnormal, ALT increased, AST abnormal, AST increased, Transaminases increased, Hepatic enzyme increased.
Bone Fracture includes: upper limb fracture, lower limb fracture, radius fracture, ulna fracture, femur fracture, foot fracture

Hepatotoxicity

LIVMARLI treatment is associated with a potential for drug-induced liver injury. In PFIC patients in Trial 2, treatment-emergent elevations of liver tests or worsening of liver tests, relative to baseline values, and hepatic decompensation events were observed. Two patients experienced drug-induced liver injury (DILI) attributable to LIVMARLI; one patient received 570 mcg/kg twice daily and the second patient required dose interruption and reduction. Two additional patients experienced DILI in the open-label extension portion of the trial. Of these four patients, one patient required liver transplant and another patient died.

Biliary Complications

In the placebo-controlled portion of Trial 2, two LIVMARLI-treated patients developed cholangitis or cholecystitis within 3-weeks of drug discontinuation (after 84 days and 130 days after initiating LIVMARLI treatment, respectively). Four LIVMARLI-treated patients developed cholecystitis or cholangitis in the open-label extension portion of Trial 2; the average time to onset was 281 days.

Bone Fracture

In PFIC patients in Trial 2, treatment-emergent bone fracture events were observed. Three receiving LIVMARLI experienced bone fractures relative to none in placebo-treated patients. The median time to onset of fractures was 73 days. Two LIVMARLI-treated patients developed bone fractures in the open-label portion of Trial 2, with average time to onset of fracture was 204 days.

Bleeding

In PFIC patients in Trial 2, treatment-emergent events of hematochezia (4 [8.5%] versus 1 [2.2%]), decrease in hemoglobin greater than or equal to 2 grams/dL from baseline (8 [17%] versus 1 [2.2%]), were reported more frequently in LIVMARLI-treated patients relative to placebo-treated patients.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of LIVMARLI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: hematemesis, liver transplant, post-endoscopy hemorrhage, post-liver biopsy hemorrhage

General disorders and administration site conditions: drug ineffective

Injury, poisoning and procedural complications: off label use

Investigations: gamma-glutamyltransferase increased

Nervous system disorders: intracranial hemorrhage

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 LIVMARLI at least 4 hours before or 4 hours after administration of bile acid binding resins (e.g., cholestyramine, colesevelam, or colestipol).

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 ALGS is higher than the general population because ALGS is an autosomal dominant condition. The background risk of miscarriage for ALGS is unknown. The background risk of birth defects and miscarriage for PFIC 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 or PFIC 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

ALGS

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 (14.1)]*. 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 with ALGS less than 3 months of age.

PFIC

The safety and effectiveness of LIVMARLI for the treatment of cholestatic pruritus in PFIC have been established in pediatric patients aged 12 months of age and older. Use of LIVMARLI in this population is supported by evidence from Trial 2 in patients 1 to <18 years of age that included 26 weeks of placebo-controlled safety and efficacy data *[see Adverse Reactions (6) and Clinical Studies (14.2)]*.

The 19 mg/mL formulation of LIVMARLI should be used in patients with PFIC in order to minimize exposure to excipients, including propylene glycol. Patients less than 5 years of age are at highest risk for propylene glycol toxicity. The total daily intake of propylene glycol from all sources should be considered for managing the risk of propylene glycol toxicity *[see Warnings and Precautions (5.4)]*.

The safety and effectiveness of LIVMARLI have not been established in patients with PFIC younger than 12 months of age.

8.5 Geriatric Use

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

8.6 Hepatic impairment

Clinical studies of LIVMARLI included ALGS or PFIC patients with impaired hepatic function at baseline. The efficacy and safety in ALGS or PFIC patients with clinically significant portal hypertension and in patients with decompensated cirrhosis have not been established. LIVMARLI is contraindicated in patients with prior or active hepatic decompensation events *[see Dosage and Administration (2.5), Contraindications (4), Warnings and Precautions (5.1), and Clinical Studies (14)]*.

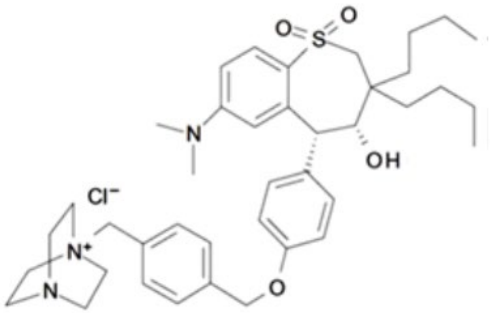
10 OVERDOSAGE

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 as an excipient. In cases of suspected overdose, monitor for signs of propylene glycol toxicity, including hemolysis, hyperosmolarity with anion gap metabolic acidosis, acute kidney injury, and CNS toxicity. Discontinue LIVMARLI if propylene glycol toxicity is suspected.

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 $C_{40}H_{56}ClN_3O_4S$ 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), or containing 19 mg of maralixibat per mL (equivalent to 20 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 or PFIC and the pathophysiology of pruritus in patients with ALGS or PFIC is not completely understood. Although the complete mechanism by which maralixibat improves pruritus in ALGS or PFIC 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

ALGS

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 (14.1)]*. 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.

PFIC

In Trial 2, pediatric patients with PFIC were administered LIVMARLI 570 mcg/kg or placebo twice daily for up to 22 weeks after an initial 4–6-week dose escalation period *[see Clinical Studies (14.2)]*. At baseline, serum bile acids concentrations were highly variable among patients ranging from 4 to 504 µmol/L and mean (SD) serum bile acid level was 253 (136) µmol/L. Serum bile acid concentrations decreased from baseline in the majority of patients as early as at Week 2; while the concentrations fluctuated, 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 and PFIC patients were below the limit of quantification (0.25 ng/mL) in the majority of plasma samples.

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 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.

12.5 Pharmacogenomics

PFIC is a heterogenous disease caused by homozygous or compound heterozygous variants, with different PFIC subtypes occurring in the general population. PFIC1 is caused by variants in the

aminophospholipid flippase (ATP8B1) gene, which encodes the Familial Intrahepatic Cholestasis 1 (FIC1) protein, while PFIC2 results from variants in the ABCB11 gene, which encodes the Bile Salt Export Pump (BSEP) protein. PFIC2 is further categorized into BSEP subgroups based on specific variants. The BSEP-1 subgroup includes patients with at least one p.D482G (c.1445A>G) or p.E297G (c.890A>G) variant, BSEP-2 includes patients with at least one missense variant other than p.D482G or p.E297G (non BSEP-1), and BSEP-3 includes patients with variants that are predicted to encode a non-functional protein. PFIC3 is caused by variants in the ABCB4 gene, which encodes multidrug resistance protein 3 (MDR3). PFIC4 is caused by variants in the tight junction protein 2 gene (TJP2), which encodes TJP2. PFIC6 is caused by variants in myosin 5B (MYO5B), which encodes MYO5B. Patients can be clinically diagnosed with PFIC without a known pathogenic variant.

PFIC2 is the most common subtype accounting for 37-90% of patients with PFIC. The prevalence of BSEP-1, BSEP-2, and BSEP-3 subgroups are approximately 27.3%, 51.5%, and 21.2%, respectively, based on data from a global consortium characterizing the natural history of severe BSEP deficiency.

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* (rat 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

14.1 Alagille Syndrome

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 5. 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 5: 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

14.2 Progressive Familial Intrahepatic Cholestasis

The efficacy of LIVMARLI was assessed in Trial 2 (NCT03905330), a 26-week randomized, placebo-controlled trial.

Efficacy was evaluated in 64 patients with documented molecular diagnosis of PFIC with presence of biallelic known pathogenic variants; this included 31 non-truncated PFIC2 patients (i.e., excluding patients with BSEP3) and 33 patients with PFIC1 (n=13), PFIC3 (n=9), PFIC4 (n=7), or PFIC6 (n=4) *[see Clinical Pharmacology (12.5)]*. Additional patients with BSEP3 (n=9), prior surgical diversion (n=8), heterozygous subjects (n=2), or no variants associated with cholestasis (n=8) were included for evaluation in a supplemental cohort *[see Adverse Reactions (6.1)].*

Patients were randomized to receive maralixibat orally 570 mcg/kg (n=33) or placebo (n=31) twice daily. 53% of pediatric patients were females. Most patients were on stable ursodeoxycholic acid (89.1%) or rifampicin (51.6%) therapy at baseline. The baseline mean (standard deviation [SD]) of liver test parameters were as follows: serum bile acid levels 263 (143) µmol/L, AST 113 (82) U/L, ALT 107 (87) U/L, and TB 4.1 (4.1) mg/dL, DB 3.0 (3.1) 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 2 if their average pruritus score was greater than or equal to 1.5 in the 4 weeks prior to baseline.

Table 6 presents the results of the comparison between LIVMARLI and placebo on the mean change in the average morning ItchRO(Obs) severity score between baseline and Weeks 15–26. For the outcome summarized over Weeks 15-26, the average morning ItchRO(Obs) severity score for each patient was calculated by: (Step 1) averaging the morning scores within a week; (Step 2) averaging 4 weekly morning scores to yield a single 4-week score; and finally (Step 3) averaging the three 4-week average morning scores (Weeks 15-18, Weeks 19-22, Weeks 23-26). The baseline average itching scores for each patient was calculated by averaging the morning ItchRO(Obs) score obtained in Step 2 across the 4 weeks prior to the first dose of the study. Patients treated with LIVMARLI demonstrated greater improvement in pruritus compared with placebo.

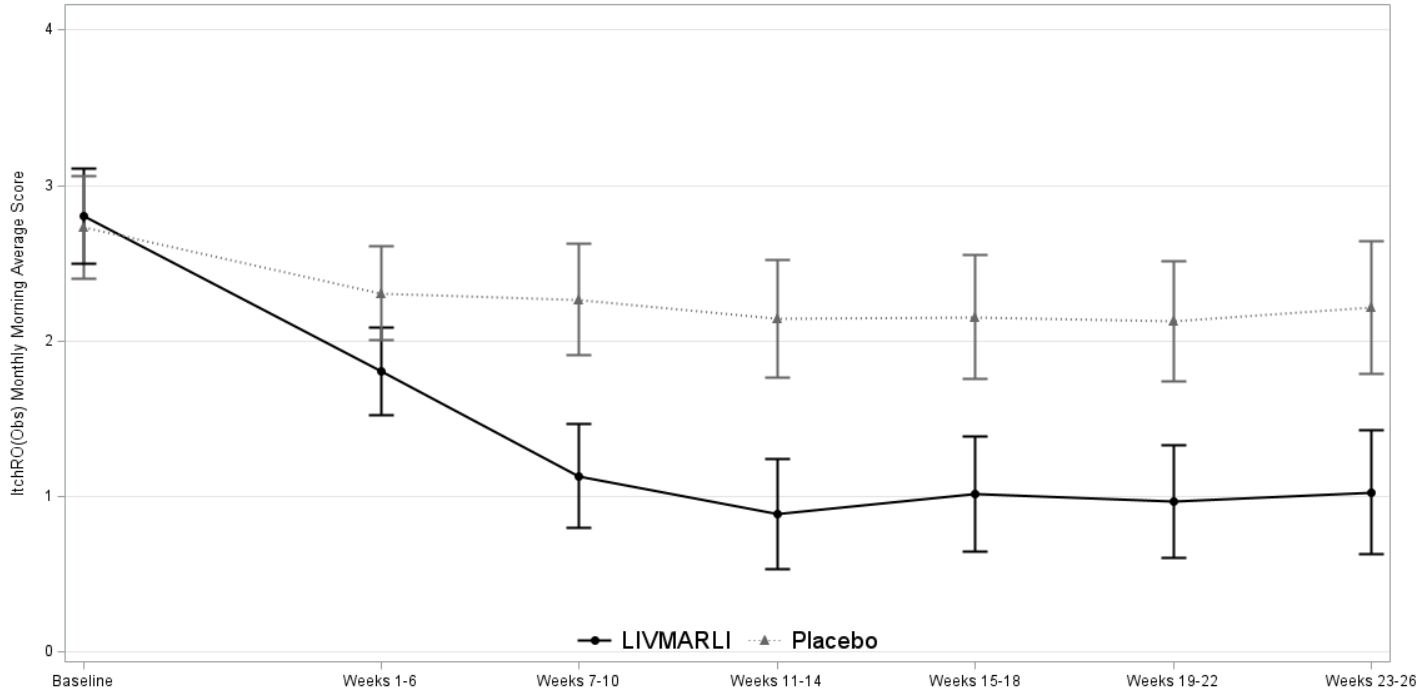
Table 6: Average Morning ItchRO(Obs) Pruritus Severity Scores in Trial 2

	Maralixibat (N=33)	**Placebo (N=31)**
Baseline Mean	2.9	2.7
Change from baseline to Weeks 15-26[a]		
Mean (95% CI)	-1.8 (-2.2, -1.4)	-0.6 (-1.0, -0.2)
Mean difference from Placebo (95% CI) p-value	-1.2 (-1.7, -0.7) <0.0001	

[a]Results based on least squares means from an analysis of a mixed-effect model for repeated measures (MMRM). Model adjusts for treatment group, visit, treatment group-by-visit interaction, baseline 4-week average morning ItchRO(Obs) severity score, baseline score-by-visit interaction, and PFIC type.

Figure 1 displays the means (95% confidence intervals) of patients' average morning ItchRO(Obs) severity scores in each treatment group for each 4-6 week time period.

Figure 1. **Mean of the Average Morning ItchRO(Obs) Pruritus Severity Scores Over Time in PFIC 1, 2, 3, 4, and 6**



Note: Figure 1 presents least squares mean (95% CI) estimates from a mixed model for repeated measures (MMRM) with observed value as the dependent variable and fixed categorical effects of treatment group, time period, treatment-by-time period interaction, and PFIC type.

Although the number of patients with BSEP3 in Trial 2 were limited, improvement in pruritus was not observed in 5 patients with BSEP3 who received LIVMARLI compared to 4 patients with BSEP3 who received placebo for 26 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING

Oral Solution

LIVMARLI is a clear, colorless to yellow oral solution.

ALGS: 9.5 mg per mL

- 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

PFIC: 19 mg per mL

- Each amber plastic bottle contains LIVMARLI oral solution at a concentration of 19 mg per mL.
- One 30 mL amber plastic bottle: NDC 79378-111-01

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) and discard any remaining LIVMARLI after 100 days *[see Dosage and Administration (2.4)]*.

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 once or twice daily as prescribed using a calibrated measuring device (0.5 mL, 1 mL or 3 mL oral dispenser) provided by the pharmacist to measure and deliver the prescribed dose accurately *[see Dosage and Administration (2.1, 2.2 2.4)]*.
- 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 30ºC (86ºF). Discard any unused LIVMARLI 100 days after opening the bottle *[see How Supplied/Storage and Handling (16)]*.

Hepatotoxicity

Advise patients or their caregiver(s) that liver tests should be obtained before starting LIVMARLI and periodically during LIVMARLI therapy. Inform patients or their caregiver(s) of the risk of hepatotoxicity that could be fatal and that they will need to undergo monitoring for liver injury. Instruct patients or their caregiver(s) to immediately report any signs or symptoms of severe liver injury to their healthcare provider *[see Warnings and Precautions (5.1)].*

Gastrointestinal Adverse Reactions

Advise patients or their caregiver(s) to notify their healthcare provider if they experience a new onset or worsening of gastrointestinal symptoms (abdominal pain, vomiting, bloody stool, and diarrhea) *[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 treatment and periodically during treatment to assess for FSV deficiency *[see Warnings and Precautions (5.3)].* Inform patients or their caregiver(s) that they may bleed more easily, may bleed longer, or have a bone fracture. Advise patients or their caregiver(s) to call their healthcare provider for any signs or symptoms of bleeding or report any fractures.

Rx only

Manufactured for:
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