FIRST AND ONLY FDA-APPROVED TREATMENT

For patients with
Alagille syndrome

AIM TO DITCH THE ITCH

LIVMARLI is the first and only FDA-approved treatment for cholestatic pruritus in patients with Alagille syndrome who are ≥1 year old[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Liver Test Abnormalities: Patients enrolled in clinical trials had abnormal liver tests at baseline. In the main clinical trial, treatment-emergent elevations or worsening of liver tests (ALT, AST or T/DB) relative to baseline were observed. 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. Discontinue permanently if a patient progresses to portal hypertension or experiences a hepatic decompensation event.

LIVMARLI helps keep itch at bay[1,2]**—**
visit **www.LIVMARLIhcp.com** to learn more.

Please see Important Safety Information throughout and full Prescribing Information for LIVMARLI.

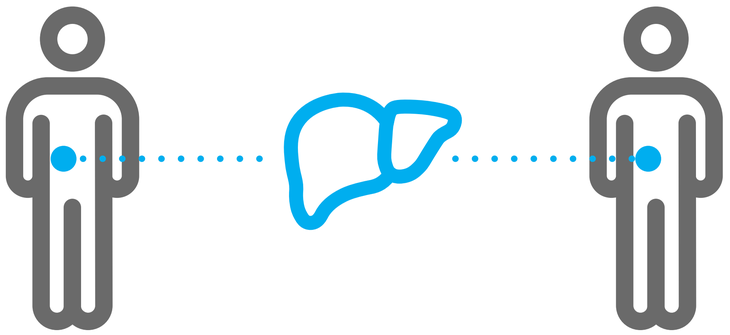
Livmarli®
(maralixibat) oral solution

THE BURDEN OF CHOLESTATIC PRURITUS IN ALAGILLE SYNDROME

Related to elevated serum bile acid (sBA), cholestatic pruritus in Alagille syndrome is among the worst of any cholestatic liver disease.[3-6]

As a result of this insufferable itch, cholestatic pruritus in Alagille syndrome frequently leads to cutaneous mutilation and scarring.[7-9]

REFRACTORY CHOLESTATIC PRURITUS HAS BEEN REPORTED TO BE A LEADING INDICATION FOR LIVER TRANSPLANT.[10]



With burdensome symptoms such as cholestatic pruritus, and a lack of response to off-label, unapproved agents, Alagille syndrome is often managed by surgery, including surgical biliary diversion or liver transplant.[6,8]

However, issues such as the presence of a stoma, the need for lifelong immunosuppression, and other complications may limit the use of surgical treatment and liver transplant.[6]

In Alagille syndrome, it has been reported that only

24% TO 41%

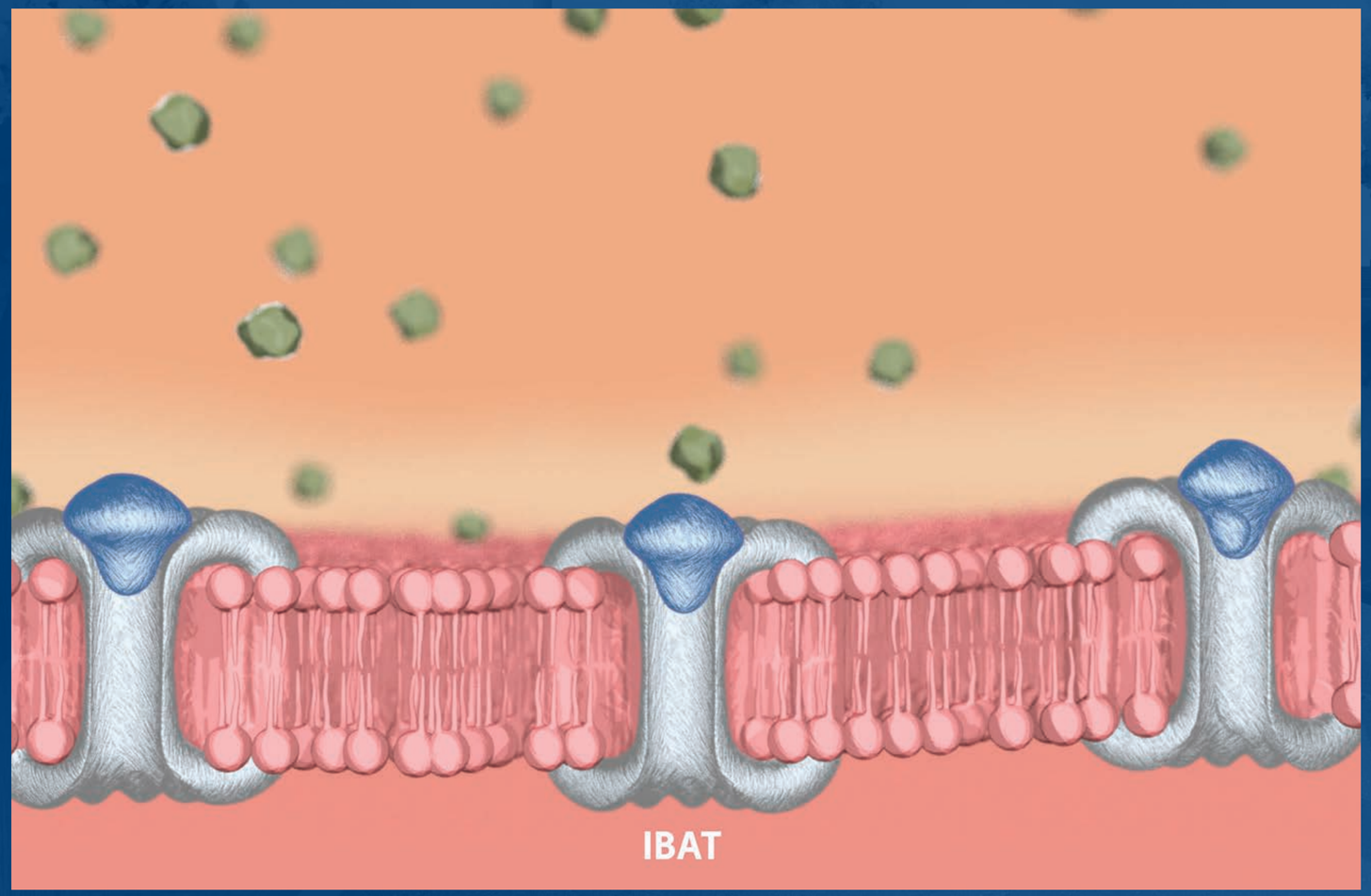
OF CHILDREN ARE ALIVE AND HAVE THEIR NATIVE LIVER BY ADULTHOOD.[11,12]

Mechanism of action (MOA)

The first and only approved treatment for cholestatic pruritus in Alagille syndrome

BATTLE BILE BUILDUP!

LIVMARLI helps battle bile acid buildup.



IBAT=ileal bile acid transporter.

LIVMARLI interrupts recirculation of bile acids to the liver and increases fecal excretion of bile acids to **reduce serum bile acid (sBA) levels in the body**, with minimal systemic absorption.[1,2,13]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

GI Adverse Reactions: Diarrhea, abdominal pain and vomiting were reported as the most common adverse reactions. If diarrhea, abdominal pain and/or vomiting occur and no other etiologies are found, consider reducing the dose or interrupting LIVMARLI. 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. Restart LIVMARLI at 190 mcg/kg/day when diarrhea, abdominal pain or vomiting resolve, and increase the dose as tolerated. If they recur upon re-challenge, consider stopping LIVMARLI treatment.

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Mechanism of action (MOA)

The first and only approved treatment for cholestatic pruritus in Alagille syndrome

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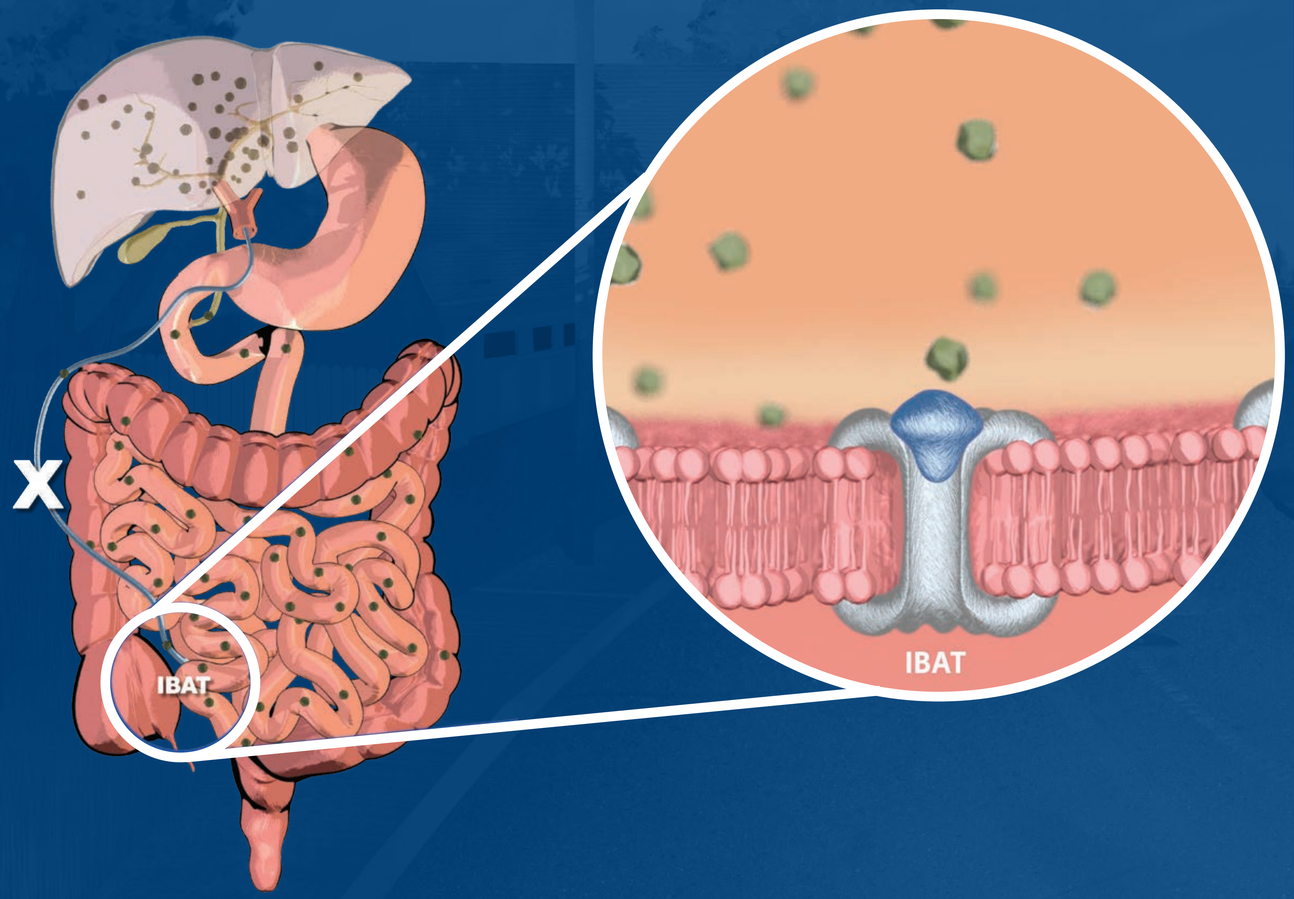

During the first year of treatment, 83% (n=24/29) of patients with Alagille syndrome in the ICONIC study experienced a ≥20% reduction in serum bile acid (sBA) levels vs baseline with LIVMARLI.[2,14]

Although the complete mechanism by which LIVMARLI improves cholestatic pruritus in patients with Alagille syndrome is unknown, it may involve inhibition of the ileal bile acid transporter (IBAT), which results in decreased reuptake of bile salts, as observed by a decrease in sBA.[1]

- In the ICONIC pivotal study for LIVMARLI, sBA reductions correlated with reductions in cholestatic pruritus intensity, further supporting the potential causal relationship between the two[15]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Fat-Soluble Vitamin Deficiency: ALGS patients can have fat-soluble vitamin (FSV) deficiency (vitamins A, D, E, and K) at baseline, and LIVMARLI may affect absorption of FSV. In the main clinical trial, treatment emergent FSV deficiency was reported in 3 (10%) patients during 48 weeks of treatment. Obtain baseline serum levels and monitor during treatment, along with any clinical manifestations. Supplement if deficiency is observed. Consider discontinuing LIVMARLI if FSV deficiency persists or worsens despite adequate FSV supplementation.

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Study design

ICONIC is the first and only pivotal study of an IBAT* inhibitor in Alagille syndrome to demonstrate significant improvement in cholestatic pruritus[1,2†]

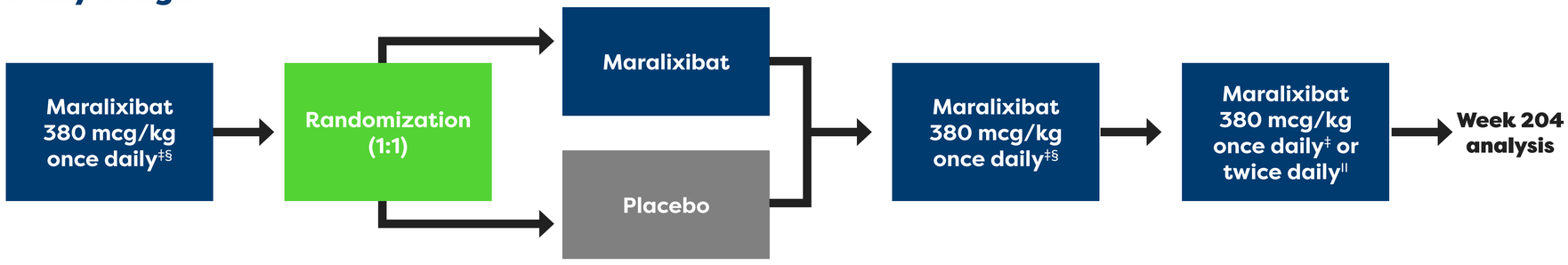
LIVER LEAGUE STUDY HALL

The ICONIC study assessed efficacy and safety of treatment with LIVMARLI in children ≥1 year old with cholestatic pruritus associated with Alagille syndrome.[1,2]

This study 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.[1,2]

*IBAT=ileal bile acid transporter.
†Mean difference −1.4 points [95% CI, −2.1, −0.8].[1]
‡Equivalent to maralixibat chloride 400 mcg/kg.
§Included a 6-week dose escalation period for all participants during the first 6 weeks of the open-label treatment period and for participants who received placebo during the randomized withdrawal design (RWD).
‖Twice per day dosing (started after Week 100) was equivalent to maralixibat chloride 800 mcg/kg.

Study design[1,2]



Cholestatic pruritus responses to LIVMARLI were assessed through approximately 4 years.[2]

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

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

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Study design

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Select baseline characteristics[2]

	All Participants (N=31)
Mean age at baseline visit, years (SD)	5.4 (4.2)
Sex, n (%)	–
Female	12 (39)
Male	19 (61)
Genotyped mutation within *JAG1*, n (%)	31 (100)

	All Participants (N=31)
History of receiving treatment for pruritus, n (%)	–
Any medication	29 (94)
Ursodeoxycholic acid	25 (81)
Rifampicin	23 (74)
Naltrexone	1 (3)
Sertraline	1 (3)
Trial parameter, mean (SD)	–
ItchRO(Obs) weekly morning average severity score‡	2.9 (0.5)
CSS score	3.3 (0.9)
sBA, µmol/L	283 (211)

FSV supplements were available as SOC throughout the study. No changes beyond SOC in supplementation occurred during the study.[2]

*IBAT=ileal bile acid transporter.
†Mean difference −1.4 points [95% CI, −2.1, −0.8].[1]
‡Average ItchRO(Obs) scores are based on the 7 days prior to baseline visit.
CSS=Clinician Scratch Scale; FSV=fat-soluble vitamin; ItchRO=Itch Reported Outcome; JAG1=jagged canonical Notch ligand 1; sBA=serum bile acid; SD=standard deviation; SOC=standard of care.

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

Administer bile acid binding resins at least 4 hours before or 4 hours after administration of LIVMARLI.

A decrease in the absorption of OATP2B1 substrates (eg, statins) due to OATP2B1 inhibition by LIVMARLI in the GI tract cannot be ruled out. Consider monitoring the drug effects of OATP2B1 substrates as needed.

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Help keep itch at bay with significant improvements in cholestatic pruritus

Significant improvements in cholestatic pruritus from baseline were achieved as early as Week 3 and maintained through 1 year in patients with Alagille syndrome taking once-daily LIVMARLI.[2]

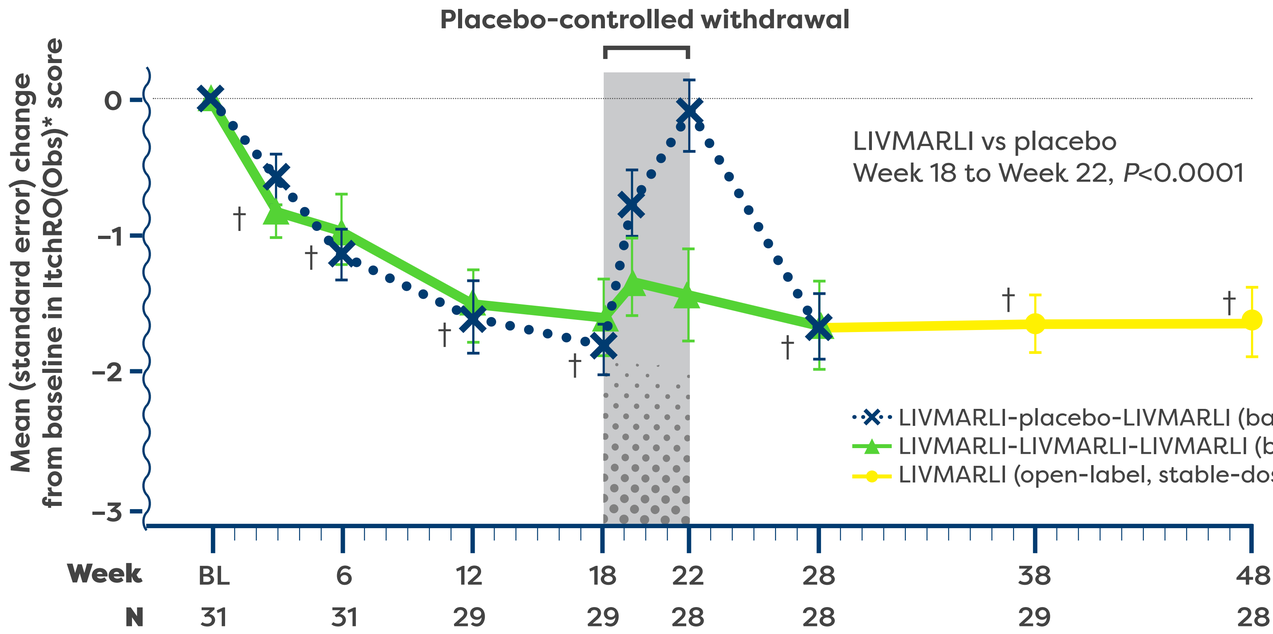
- For patients who remained on treatment with LIVMARLI in the open-label extension (n=15), cholestatic pruritus responses compared with baseline were durable through nearly 4 years[2]

*Pruritus was assessed each day, in the morning and evening, using the Itch Reported Outcome (ItchRO) scale—a validated tool designed to assess the impact of itching in children with cholestatic liver disease, including Alagille syndrome. The Itch Reported Outcome (ItchRO) score is a 0–4 scale, where 0 is none, 1 is mild, 2 is moderate, 3 is severe, and 4 is very severe. Changes in ItchRO score of 1.0 or more have been shown to be clinically meaningful. ItchRO(Obs) was completed by caregivers and was the basis for the key pruritus endpoint. The patient-rated ItchRO (ItchRO[Pt]) was completed independently by participants aged 9 years or older and with caregiver assistance for participants aged 5–8 years.[2]

†Change from baseline, *P*<0.0001.

‡Included an initial 6-week dose escalation for participants previously receiving placebo.

Improvements in Cholestatic Pruritus Over Time[2,16]



IMPORTANT SAFETY INFORMATION (cont'd)

DOSING INFORMATION

LIVMARLI should be taken 30 minutes before the first meal of the day. The provided oral dosing dispenser must be used to accurately measure the dose. Any remaining LIVMARLI should be discarded 45 days after first opening the bottle.

Livmarli® (maralixibat) oral solution

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Cholestatic pruritus efficacy

Help keep itch at bay with significant improvements in cholestatic pruritus

During the first year of treatment, 84% (n=26/31) of patients with Alagille syndrome experienced clinically meaningful improvements in cholestatic pruritus compared with baseline with once-daily LIVMARLI.[2]

- "Clinically meaningful" was defined as ≥1-point Itch Reported Outcome (ItchRO [Obs]) improvement vs baseline (caregiver-reported pruritus score)[2]

At 1 year, improvements in cholestatic pruritus were correlated with decreases in serum bile acid (sBA) (r=0.47).[15]

*Based on mean daily morning ItchRO(Obs) scores across all patients through 4 years.

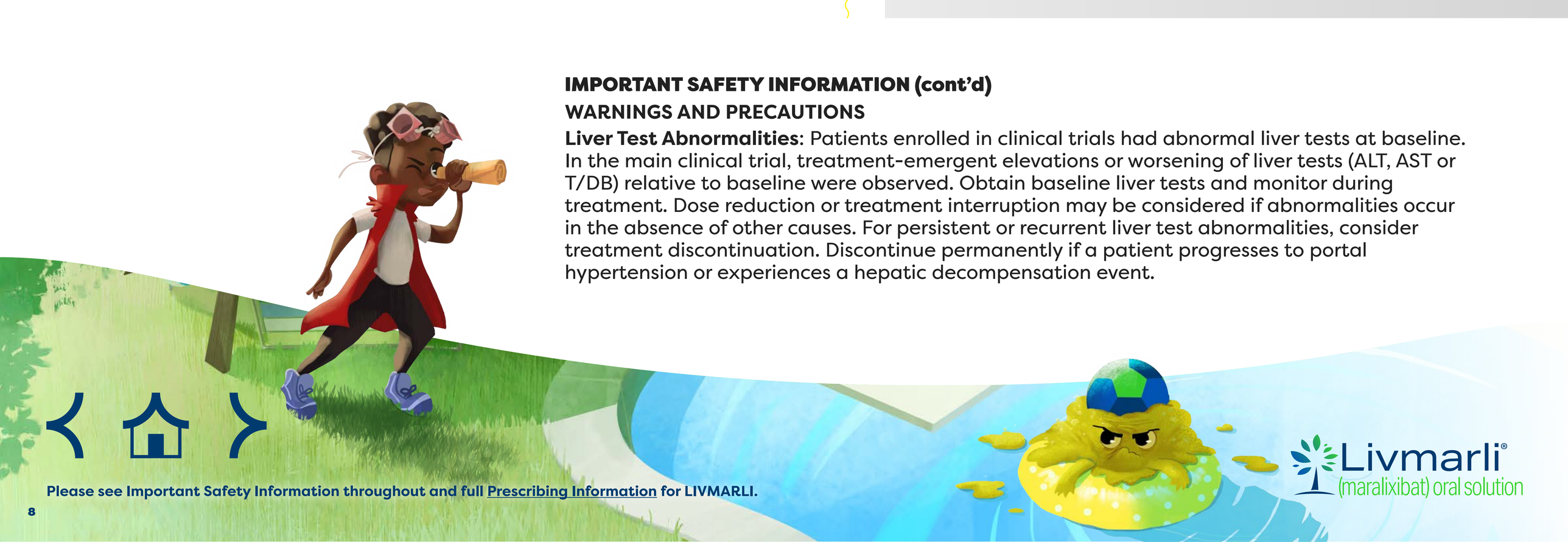
POST HOC ANALYSIS:
During the first year, patients receiving LIVMARLI in the pivotal ICONIC study had an increasing proportion of days with minimal to no itch.[17]

- In patients who remained on LIVMARLI (n=21) during the open-label extension (beyond 48 weeks), the median proportion of days with minimal to no itch was 95%[17]*

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Liver Test Abnormalities: Patients enrolled in clinical trials had abnormal liver tests at baseline. In the main clinical trial, treatment-emergent elevations or worsening of liver tests (ALT, AST or T/DB) relative to baseline were observed. 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. Discontinue permanently if a patient progresses to portal hypertension or experiences a hepatic decompensation event.



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Livmarli® (maralixibat) oral solution

Backed by >5 years of safety data,* LIVMARLI has a

Well-characterized safety and tolerability profile for cholestatic pruritus in patients with Alagille syndrome who are ≥1 year old[1,18]

Adverse reactions occurring in ≥5% of patients treated with LIVMARLI in the Alagille syndrome clinical development program (n=86)[1,18†]

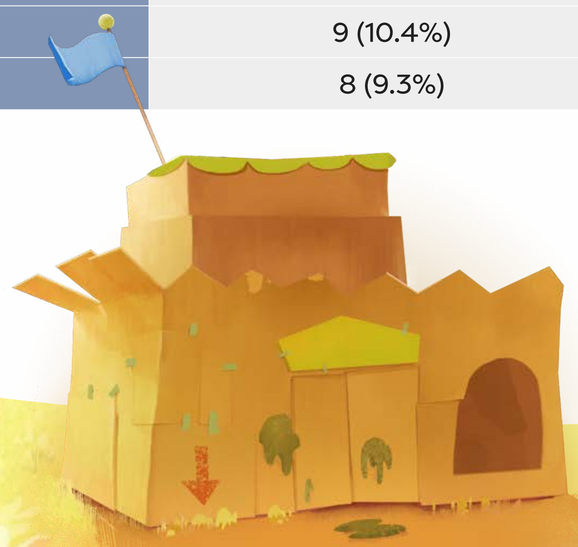
Adverse reaction	Any grade n (%)	Number of events per 100 person-years[§]
Diarrhea	48 (55.8%)	41.6
Abdominal pain[‡]	46 (53.5%)	38.6
Vomiting	35 (40.7%)	19.8
Nausea	7 (8.1%)	2.9
Fat-soluble vitamin (FSV) deficiency[‡]	22 (25.6%)	11.1
Transaminases increased (alanine aminotransferase [ALT], aspartate aminotransferase [AST])[‡]	16 (18.6%)	6.9
Gastrointestinal bleeding[‡]	9 (10.4%)	3.8
Bone fractures[‡]	8 (9.3%)	3.3

*The majority of exposure occurred without a placebo control in open-label extensions.

†Integrated safety profile from multiple clinical trials, including the ICONIC study.[1,18]

‡Terms were defined as: FSV deficiency includes A, D, E, and/or K deficiency, or International Normalized Ratio (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 fractures include 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.[1]



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The most common adverse reactions seen with LIVMARLI in the Alagille syndrome clinical development program, which included 5 clinical studies comprising 86 patients, were diarrhea, abdominal pain, vomiting, fat-soluble vitamin (FSV) deficiency, liver test abnormalities, gastrointestinal bleeding, and bone fractures.[1]

Five patients experienced treatment interruptions or dose reductions due to diarrhea, abdominal pain, or vomiting.[1,19] Among those taking LIVMARLI, no patients discontinued due to diarrhea, abdominal pain, or vomiting.[20]

Three patients (3%) experienced vomiting as a serious adverse event requiring hospitalization or IV fluid administration.[1]

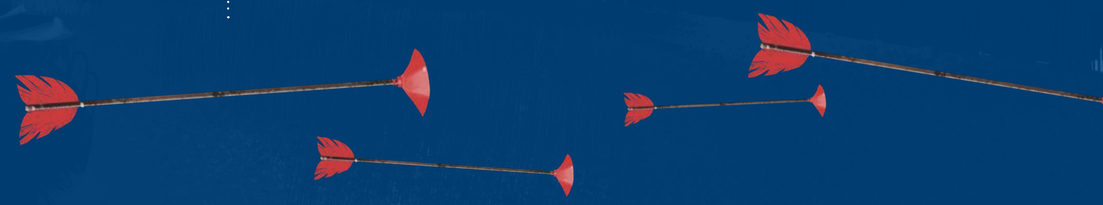
In a pooled analysis of patients with Alagille syndrome (n=86), 7 patients discontinued LIVMARLI due to increases in hepatic transaminases (ALT), and 3 patients had a decrease in dose or interruption of LIVMARLI in response to these increases; elevations in transaminases were asymptomatic and not associated with bilirubin or other laboratory abnormalities.[1]

- In the majority of cases, the elevations resolved or improved after discontinuation or dose modification of LIVMARLI[1]
- In some cases, the elevations resolved or improved without change in LIVMARLI dosing[1]
- Four patients experienced bilirubin increases, and LIVMARLI was subsequently withdrawn in 2 of these patients (those who had elevated bilirubin at baseline)[1]

Patients with Alagille syndrome can have FSV deficiency (vitamins A, D, E, and/or K) at baseline.[1]

- LIVMARLI may affect absorption of FSV[1]

*The majority of exposure occurred without a placebo control in open-label extensions.



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Livmarli® (maralixibat) oral solution

Oral liquid. Grape flavored.

A once-daily medicine for cholestatic pruritus in Alagille syndrome

Individual dose volume by patient weight[1]

Patient Weight (kg)	Days 1 to 7 (190 mcg/kg once daily)	Beginning Day 8 (380 mcg/kg once daily)
	Volume QD (mL)	Volume QD (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

The recommended dosage of LIVMARLI is 380 mcg/kg administered orally (PO) once daily (QD), taken approximately 30 minutes before the first meal of the day.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

GI Adverse Reactions: Diarrhea, abdominal pain and vomiting were reported as the most common adverse reactions. If diarrhea, abdominal pain and/or vomiting occur and no other etiologies are found, consider reducing the dose or interrupting LIVMARLI. 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. Restart LIVMARLI at 190 mcg/kg/day when diarrhea, abdominal pain or vomiting resolve, and increase the dose as tolerated. If they recur upon re-challenge, consider stopping LIVMARLI treatment.

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Livmarli® (maralixibat) oral solution

Visit www.LIVMARLIhcp.com to learn more.

References: 1. LIVMARLI® (maralixibat) oral solution. Prescribing Information. Mirum Pharmaceuticals, Inc. **2.** Gonzales E, Hardikar W, Stormon M, et al. Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study. *Lancet.* 2021;398(10311):1581-1592. doi:10.1016/S0140-6736(21)01256-3 **3.** Krantz ID, Piccoli DA, Spinner NB. Alagille syndrome. *J Med Genet.* 1997;34(2):152-157. doi:10.1136/jmg.34.2.152 **4.** Jesina D. Alagille syndrome: an overview. *Neonatal Netw.* 2017;36(6):343-347. doi:10.1891/0730-0832.36.6.343 **5.** Hartley JL, Gissen P, Kelly DA. Alagille syndrome and other hereditary causes of cholestasis. *Clin Liver Dis.* 2013;17(2):279-300. doi:10.1016/j.cld.2012.12.004 **6.** Kamath BM, Stein P, Houwen RHJ, Verkade HJ. Potential of ileal bile acid transporter inhibition as a therapeutic target in Alagille syndrome and progressive familial intrahepatic cholestasis. *Liver Int.* 2020;40(8):1812-1822. doi:10.1111/liv.14553 **7.** Elisofon SA, Emerick KM, Sinacore JM, Alonso EM. Health status of patients with Alagille syndrome. *J Pediatr Gastroenterol Nutr.* 2010;51(6):759-765. doi:10.1097/MPG.0b013e3181ef3771 **8.** Kamath BM, Baker A, Houwen R, Todorova L, Kerkar N. Systematic review: the epidemiology, natural history, and burden of Alagille syndrome. *J Pediatr Gastroenterol Nutr.* 2018;67(2):148-156. doi:10.1097/MPG.0000000000001958 **9.** Kamath BM, Chen Z, Romero R, et al. Quality of life and its determinants in a multicenter cohort of children with Alagille syndrome. *J Pediatr.* 2015;167(2):390-396.e3. doi:10.1016/j.jpeds.2015.04.077 **10.** Lykavieris P, Hadchouel M, Chardot C, Bernard O. Outcome of liver disease in children with Alagille syndrome: a study of 163 patients. *Gut.* 2001;49(3):431-435. doi:10.1136/gut.49.3.431 **11.** Kamath BM, Ye W, Goodrich NP, et al. Outcomes of childhood cholestasis in Alagille syndrome: results of a multicenter observational study. *Hepatol Commun.* 2020;4(3):387-398. doi:10.1002/hep4.1468 **12.** Vandriel SM, Liting L, She H, et al. Clinical features and natural history of 1154 Alagille syndrome patients: results from the international multicenter GALA study group. *J Hepatol.* 2020;73(1):S554-S555. **13.** Martin P, Apostol G, Smith W, Jennings L, Vig P. Dose-dependent fecal bile acid excretion with apical sodium-dependent bile acid transporter inhibitors maralixibat and volixibat in a dose-ranging phase 1 study in overweight and obese adults. Poster presented at: American Association for the Study of Liver Diseases: The Liver Meeting; November 8-12, 2019; Boston, MA. **14.** Data on file. REF-00106. Mirum Pharmaceuticals, Inc. **15.** Gonzales E, Vig P, Tucker E, Jaecklin T, et al. Pruritus intensity is associated with cholestasis biomarkers and quality of life measures after maralixibat treatment in children with Alagille syndrome. Poster presented at: American Association for the Study of Liver Diseases: The Liver Meeting Digital Experience™ (TLMdX); November 13-16, 2020. **16.** Gonzales E, Sturm E, Stormon E, et al. Durability of treatment effect with long-term maralixibat in children with Alagille syndrome: 4-year safety and efficacy. Presented at: American Association for the Study of Liver Diseases Annual Meeting: The Liver Meeting; November 8-12, 2019; Boston, MA. **17.** Data on file. REF-00100. Mirum Pharmaceuticals, Inc. **18.** Raman RK, Garner W, Vig P, Tucker E. An integrated analysis of long-term clinical safety in maralixibat-treated participants with Alagille syndrome. Poster presented at: European Association for the Study of the Liver (EASL): International Liver Congress; June 23-26, 2021. **19.** Kamath BM, Raman RK, Garner W, Tucker E, Vig P, Gonzales E. Gastrointestinal tolerability of maralixibat in patients with Alagille syndrome: an integrated analysis of short- and long-term treatment. Poster presented at: The 6th World Congress of Pediatric Gastroenterology, Hepatology and Nutrition; June 2-5, 2021; Vienna, Austria. **20.** Data on file. REF-00180. Mirum Pharmaceuticals, Inc.

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Livmarli® (maralixibat) oral solution

For patients with Alagille syndrome

Aim to ditch the itch

FDA APPROVED

Once-daily LIVMARLI is the first and only agent to demonstrate clinically meaningful improvements in cholestatic pruritus associated with Alagille syndrome.[2]

Proven mechanism of action

LIVMARLI is an ileal bile acid transporter (IBAT) inhibitor that reduces serum bile acid (sBA) levels in the body by interrupting recirculation of bile acids to the liver and increasing their excretion in feces.[1,2,13]

Significant improvements in cholestatic pruritus

Significant improvements in cholestatic pruritus from baseline were achieved as early as Week 3 and maintained through 1 year (*P*<0.0001); for patients who remained on treatment with LIVMARLI in the open-label extension (n=15), cholestatic pruritus responses compared with baseline were durable through nearly 4 years.[2,16]

Backed by >5 years of safety data*

LIVMARLI has a well-characterized safety and tolerability profile for cholestatic pruritus in patients with Alagille syndrome who are ≥1 year old.[1,18]

*The majority of exposure occurred without a placebo control in open-label extensions.

Once-daily dosing

The recommended dosage of LIVMARLI (380 mcg/kg) is administered orally once daily approximately 30 minutes before the first meal of the day.[1]

Streamlined, steady support

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Learn more by calling
1-855-MRM-4YOU
(1-855-676-4968)
Monday to Friday,
8:00 AM to 8:00 PM ET.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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