For your patients with cholestatic pruritus in Alagille syndrome...

The First and Only Treatment to Provide

EARLY IMPROVEMENTS WITH LONG-TERM IMPACT[1-3]

LIVMARLI is an FDA-approved treatment for cholestatic pruritus in patients with Alagille syndrome who are ≥3 months of age.[4]

Visit **www.LIVMARLIhcp.com** to learn more.

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.

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Livmarli® (maralixibat) oral solution

BILE ACID BUILDUP MAY FUEL CHOLESTATIC PRURITUS* NOW AND IS TIED TO LIVER INJURY LATER[5,6]

Chronic Cholestasis Causes Bile Acid Buildup

In Alagille syndrome, cholestasis, which can manifest as cholestatic pruritus, leads to **bile acid buildup in the liver** and is the main driver of **ongoing liver injury, inflammation, and fibrosis.**[5,7-9]

Cholestatic Pruritus Is More Than Scratching

Cholestatic pruritus frequently leads to **wiggling, rubbing, fidgeting, and/or physical unrest, skin damage, sleep problems, irritability, and physical discomfort.**[10-14]

The Threat of Liver Transplant

Refractory cholestatic pruritus was an indication in **49% to 82% of liver transplants** in Alagille syndrome.[15,16]

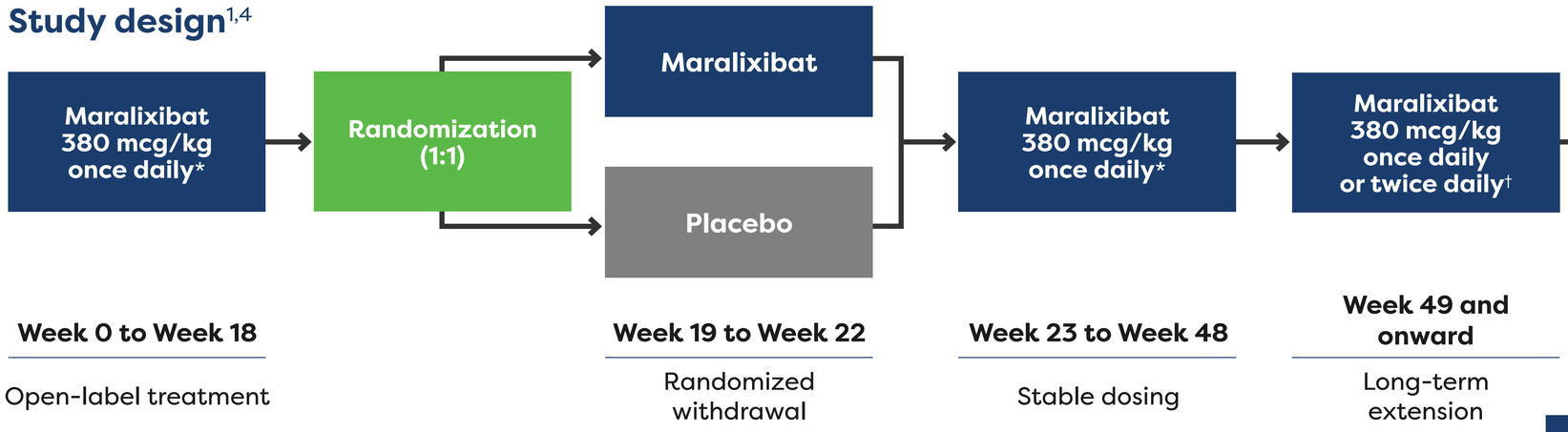
For patients with Alagille syndrome, there is a need for effective treatment options that reduce bile acid buildup, promptly relieve cholestatic pruritus, and improve long-term liver outcomes.

*The pathophysiology of cholestatic pruritus in Alagille syndrome is not completely known.

Assessing Improvements in Cholestatic Pruritus

The ICONIC study assessed efficacy and safety of treatment with LIVMARLI in patients ≥1 year old with cholestatic pruritus associated with Alagille syndrome.[1,4]

Study design[1,4]



*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 was allowed after Week 100. The approved dosage of LIVMARLI is 380 mcg/kg once daily.

Methodology: Cholestatic pruritus was assessed at baseline using the **Itch Reported Outcome (ItchRO)** scale. The ItchRO score is a **0–4 scale**, where 0 is none and 4 is very severe.[1] This scale takes itch-related symptoms into consideration, including patients' **skin damage, sleep, and irritability**.[1,14,17]

- Participants' baseline scores were calculated as the average of the daily ItchRO scores over the 2 consecutive weeks during the screening period[1]

Safety, tolerability, and pharmacokinetics of LIVMARLI in patients aged 3 months to 1 year were evaluated in **RISE, a 13-week, open-label, phase 2 study** (N=8). Participants received LIVMARLI 380 mcg/kg once daily, in addition to standard of care.[4,18]

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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Study Design

Assessing Long-Term Liver Impact

In a post hoc analysis, patients with Alagille syndrome who were treated with LIVMARLI in 3 long-term clinical trials (N=76) were followed to identify predictors of long-term, transplant-free survival. Patients with moderate-to-severe cholestatic pruritus who had a perceived benefit from LIVMARLI, remained on treatment for at least 48 weeks, and had lab results at 48 weeks were included in this analysis. No placebo arm was included.[2]

ITCH/IMAGINE II[2]
(LUM001-301/305)
10 sites
↓
n=34

IMAGO/IMAGINE[2]
(LUM001-302/303)
3 sites*
↓
n=19

ICONIC[2]
(LUM001-304)
9 sites*
↓
n=31

Inclusion criteria:

- Week 48 laboratory samples
- No prior clinical event

Alagille syndrome (N=76):

- Aged 14 months to 17.25 years
- Moderate-to-severe pruritus

Transplant-free survival was defined as time to liver transplant or death.[2]

*There was a common site in both IMAGO/IMAGINE and ICONIC trials. The total number of different sites for the overall study population (N=76) was 21.[2]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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For your patients with cholestatic pruritus in Alagille syndrome...

LIVMARLI Is the First and Only Treatment to Provide Early Improvements With Long-Term Impact

Improvements in Cholestatic Pruritus... AT THE VERY FIRST ASSESSMENT (WEEK 3)![1]

84%

(n=26/31) of patients with Alagille syndrome experienced **clinically meaningful improvements** (ie, ≥1-point reduction in ItchRO[Obs]) **in cholestatic pruritus** compared with baseline during the first year of treatment with LIVMARLI.[1]

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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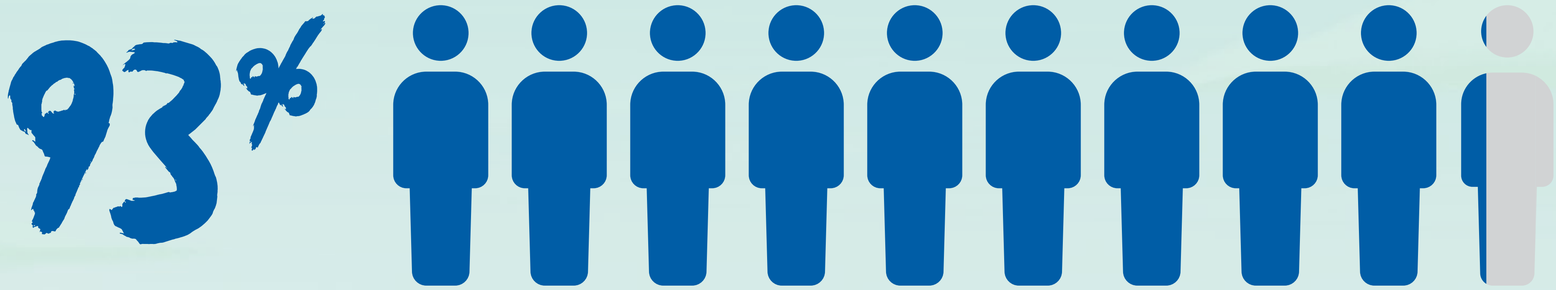
Long-Term Impact of Cholestatic Pruritus Improvements

For those who achieved a >1-point reduction in ItchRO(Obs) (n=46):



93% of patients remained transplant free 6 years after starting LIVMARLI.[2,3]*

- Only 57% of patients who did not have a >1-point reduction in ItchRO(Obs) (n=30) remained transplant free 6 years after starting LIVMARLI (*P*=0.0007)[2,3]

The impact of LIVMARLI treatment on transplant-free survival has not been established. No liver histology to assess hepatic fibrosis was collected.

*Transplant-free survival was defined as time to liver transplant or death.[2]

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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Early Improvements in Cholestatic Pruritus

WITH LIVMARLI, IMPROVEMENTS BEGIN EARLY

Significant improvements in cholestatic pruritus from baseline were seen **at the very first assessment** (Week 3), with the full effect achieved by Week 18 and maintained through 1 year with once-daily LIVMARLI ($P<0.0001$).[1,19]

CLINICALLY MEANINGFUL IMPROVEMENTS FOR MOST PATIENTS

84% of patients with Alagille syndrome experienced **clinically meaningful improvements in cholestatic pruritus** compared with baseline during the first year of treatment with LIVMARLI.[1]

- "Clinically meaningful" was defined as ≥1-point ItchRO(Obs) improvement vs baseline[1]

IMPORTANT SAFETY INFORMATION (cont'd)

DOSING INFORMATION

LIVMARLI should be taken 30 minutes before a meal in the morning. The provided oral dosing dispenser must be used to accurately measure the dose. Any remaining LIVMARLI should be discarded 100 days after first opening the bottle.

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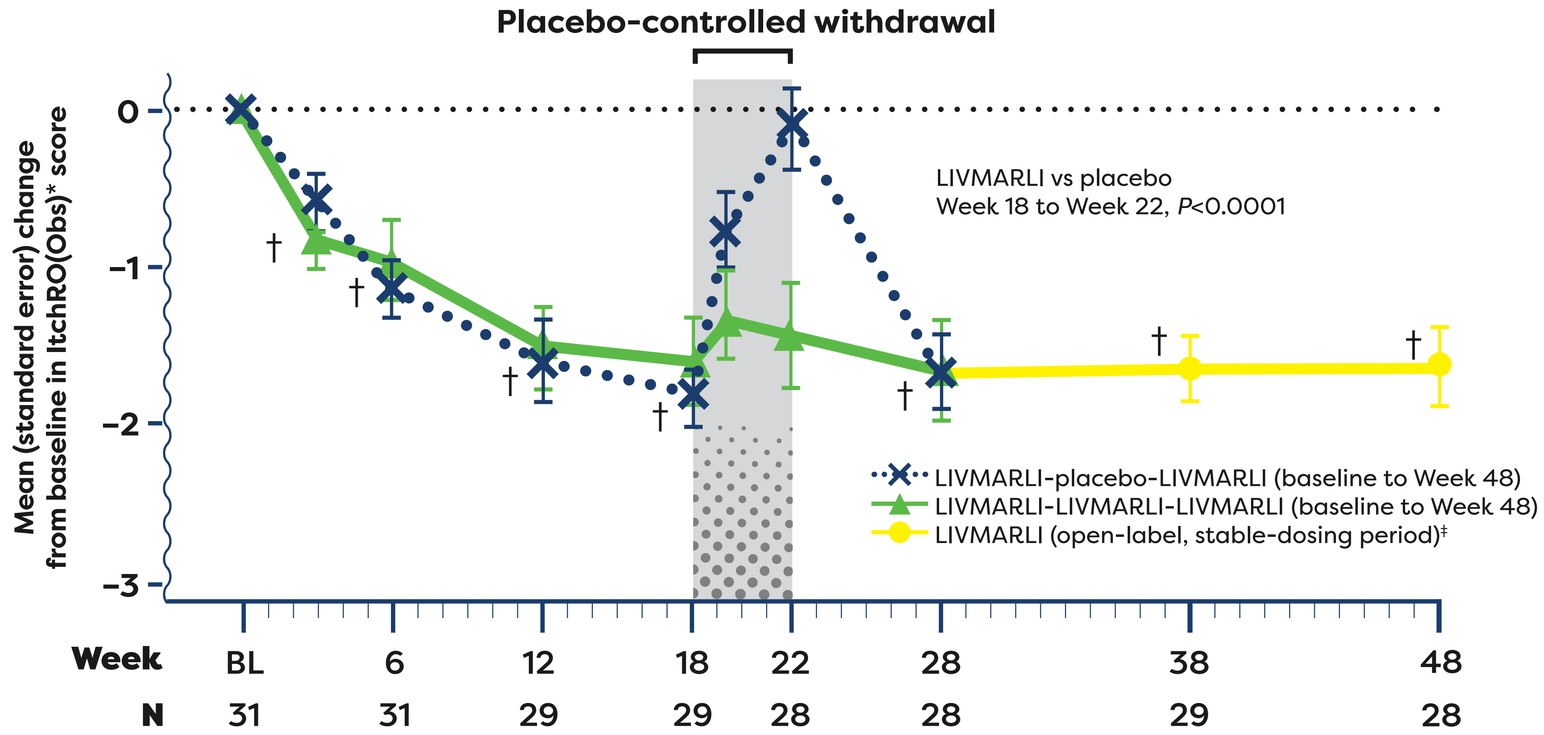
Early Improvements in Cholestatic Pruritus

DURABLE REDUCTIONS IN CHOLESTATIC PRURITUS THAT LAST OVER TIME[1,19]



*Cholestatic 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 cholestatic pruritus in people with cholestatic liver disease, including Alagille syndrome. The 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 to 8 years.[1]

†Change from baseline, *P*<0.0001.[19]

‡Included an initial 6-week dose escalation for participants previously receiving placebo.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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Long-Term Liver Impact

>1-Point Reduction in ItchRO(Obs) Was a Predictor of Transplant-Free Survival*

93% of patients who achieved a >1-point reduction in ItchRO(Obs) (n=46) remained transplant free 6 years after starting LIVMARLI.[2,3]

57% of patients who had ≤1-point reduction in ItchRO(Obs) (n=30) remained transplant free 6 years after starting LIVMARLI (*P*=0.0007).[2,3]

WHAT IS TRANSPLANT-FREE SURVIVAL?

Transplant-free survival was defined as time to[2]:

- Liver transplant
- Death

*The impact of LIVMARLI treatment on transplant-free survival has not been established. No liver histology to assess hepatic fibrosis was collected.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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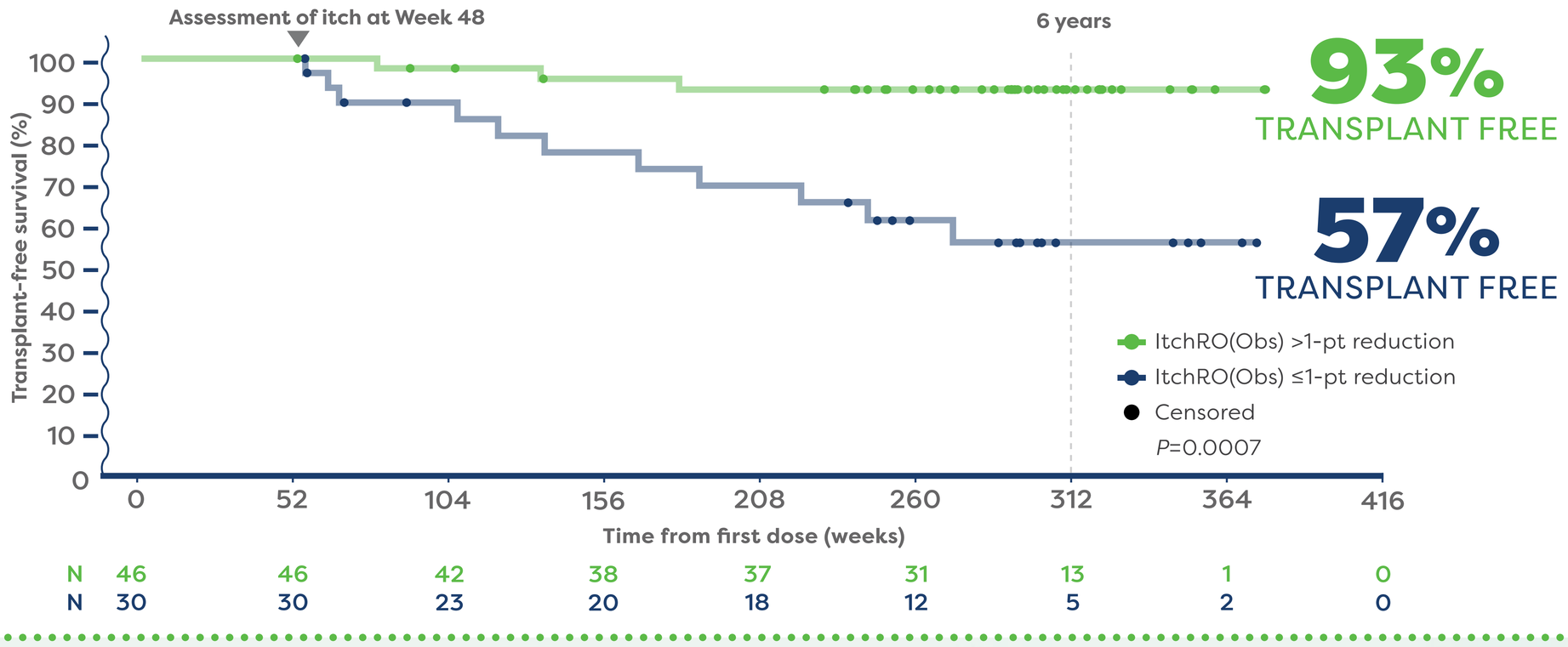
Long-Term Liver Impact

TRANSPLANT-FREE SURVIVAL OVER 6 YEARS OF TREATMENT WITH LIVMARLI[2,3]*



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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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Livmarli® (maralixibat) oral solution

Backed by >5 Years of Safety Data*

Well-Characterized Safety and Tolerability Profile

LIVMARLI has well-established safety and tolerability in patients with cholestatic pruritus in Alagille syndrome.[4,20]

Adverse reactions occurring in ≥5% of patients treated with LIVMARLI in the Alagille syndrome clinical development program (n=86)[4†]

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.[4,20]
‡Terms were defined as: FSV deficiency includes: vitamins A, D, E, and/or K deficiency, or International Normalized Ration (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, and clavicle fracture.[4]
§Exposure-adjusted incidence rate for each adverse reaction type was calculated using the first occurrence of this adverse reaction per patient.[4]

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Livmarli® (maralixibat) oral solution

Backed by >5 Years of Safety Data*

Well-Characterized Safety and Tolerability Profile

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, FSV deficiency, liver test abnormalities, gastrointestinal bleeding, and bone fractures.[4]

Five patients experienced treatment interruptions or dose reductions due to diarrhea, abdominal pain, or vomiting.[4,21] Among those taking LIVMARLI, no patients discontinued due to diarrhea, abdominal pain, or vomiting.[22]

Three patients (3%) experienced vomiting as a serious adverse event requiring hospitalization or IV fluid administration.[4]

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.[4]

- In the majority of cases, the elevations resolved or improved after discontinuation or dose modification of LIVMARLI[4]
- In some cases, the elevations resolved or improved without change in LIVMARLI dosing[4]
- Four patients experienced bilirubin increases above baseline, and LIVMARLI was subsequently withdrawn in 2 of these patients (those who had elevated bilirubin at baseline)[4]

Patients with Alagille syndrome can have FSV deficiency (vitamins A, D, E, and/or K) at baseline.[4]

- LIVMARLI may affect absorption of FSV[4]

Pediatric patients aged 3 months to <12 months had **similar safety, tolerability, and pharmacokinetic profiles** to those ≥1 year old.[4]

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

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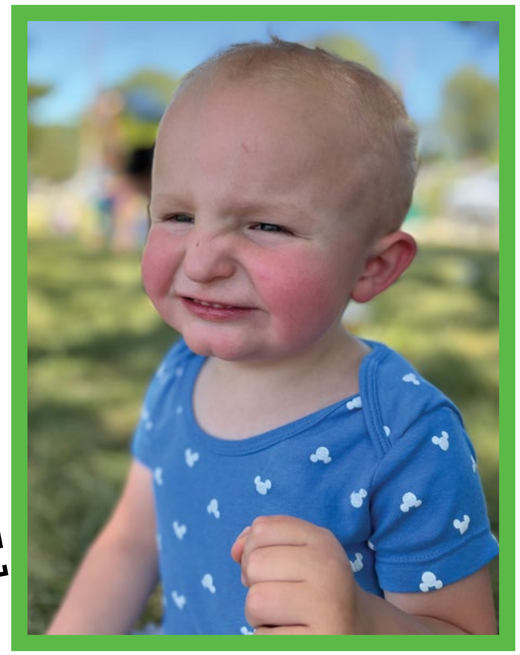
REAL PATIENTS WHO TAKE LIVMARLI

NOELLE
11 Years Old
Taking LIVMARLI since 2021

SAMMY
3 Years Old
Taking LIVMARLI since 2021



EMMA
19 Years Old
Taking LIVMARLI since 2016

Scan or tap the QR code
to get your patients started with the Patient Enrollment Form (PEF).

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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DRUG INTERACTIONS

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For your patients with cholestatic pruritus in Alagille syndrome...

The First and Only Treatment to Provide Early Improvements With Long-Term Impact

Early reductions in cholestatic pruritus that were durable over time:

84% (n=26/31) of patients with Alagille syndrome experienced **clinically meaningful improvements** (ie, ≥1-point reduction in ItchRO[Obs]) **in cholestatic pruritus**, with improvements seen as early as the very first assessment (Week 3) and maintained through 1 year (*P*<0.0001).[1,19]

For those who achieved a >1-point reduction in ItchRO(Obs) (n=46):

93% of patients remained **transplant free** 6 years after starting LIVMARLI.[2,3*]

Please see important study design information on pages 6 and 9.

The impact of LIVMARLI treatment on transplant-free survival has not been established. No liver histology to assess hepatic fibrosis was collected.

*Transplant-free survival was defined as time to liver transplant or death.[2]

IMPORTANT SAFETY INFORMATION (cont'd)

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