

CHOLESTATIC PRURITUS RESPONSE DATA: PATIENTS WITH PFIC TAKING LIVMARLI

MARCH-PFIC was a 26-week, Phase 3, randomized, placebo-controlled study that assessed efficacy and safety of treatment with LIVMARLI in patients who were 12 months to <18 years old with cholestatic pruritus in progressive familial intrahepatic cholestasis (PFIC).^{1,2}

MARCH-ON is an open-label, long-term extension study for patients who completed the MARCH-PFIC study and continued treatment with LIVMARLI.³

An exploratory analysis of the MARCH-PFIC and MARCH-ON studies analyzed bilirubin levels in patients who achieved a cholestatic pruritus response with LIVMARLI.⁴



INDICATION

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 nonfunctional or complete absence of bile salt export pump (BSEP) protein.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

LIVMARLI is contraindicated in patients with prior or active hepatic decompensation events (eg, variceal hemorrhage, ascites, or hepatic encephalopathy).

WARNINGS AND PRECAUTIONS

Hepatotoxicity: LIVMARLI treatment is associated with a potential for drug-induced liver injury (DILI).

In the PFIC trial, treatment-emergent hepatic decompensation events and elevations of liver tests or worsening of liver tests occurred. Two patients experienced DILI attributable to LIVMARLI. Two additional patients experienced DILI in the open-label extension portion of the trial. Of these 4 patients, 1 patient required liver transplant and another patient died.

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STUDY DESIGN

MARCH-PFIC

In the pivotal MARCH-PFIC study, the primary endpoint was met²:

- In the BSEP cohort, patients treated with LIVMARLI (n=14) had statistically significantly greater reductions in Itch Reported Outcome (Observer) (ItchRO[Obs]) scores from baseline vs placebo (n=17) at 6 months (-1.7 vs -0.6, least squares [LS] mean change -1.1 [95% CI, -1.8 to -0.3]; $P=0.0063$)^{2*} –Similar results were observed in the All-PFIC cohort⁵
- In the MARCH-PFIC study, 64% of patients saw improvement in their cholestatic pruritus and were considered LIVMARLI responders²
- LIVMARLI has well-established safety and tolerability for cholestatic pruritus in patients with progressive familial intrahepatic cholestasis (PFIC).^{1,2} The most common adverse reactions ($\geq 5\%$) in the MARCH-PFIC clinical study were diarrhea, fat-soluble vitamin (FSV) deficiency, abdominal pain, liver test abnormalities, hematochezia, and bone fractures.¹ No new safety signals were observed in the exploratory analysis

EXPLORATORY ANALYSIS

This exploratory analysis of the MARCH-PFIC study and MARCH-ON open-label extension study evaluated the association between cholestatic pruritus response and bilirubin levels in patients with PFIC who received LIVMARLI in MARCH/MARCH-ON.⁴

LIVMARLI responders were those who saw improvement in their cholestatic pruritus. This was defined as either an improvement of ≥ 1 point from baseline or a score of ≤ 1 on the ItchRO(Obs) scale.²

Selected baseline characteristics of the All-PFIC, All-LIVMARLI cohort included in this analysis:

- LIVMARLI responders (n=37) had an average ItchRO(Obs) score of 2.5 (1.3), total bilirubin of 3.04 (3.04) mg/dL, and direct bilirubin of 2.17 (2.31) mg/dL^{4**†}
- Nonresponders (n=22) had an average ItchRO(Obs) score of 2.5 (0.8), total bilirubin of 6.28 (4.91) mg/dL, and direct bilirubin of 4.68 (3.52) mg/dL^{4**†}

In PFIC, elevated bilirubin is a common clinical finding and has been shown to be associated with worse long-term outcomes. **Bilirubin and pruritic response in patients with PFIC warrants further investigation.**^{4,6,7}

*All data are mean (standard deviation).

†Baseline ItchRO(Obs) score is the 4-week morning average severity score.

‡Combines LIVMARLI-LIVMARLI and Placebo-LIVMARLI treatment groups in MARCH-ON. Baseline for LIVMARLI-LIVMARLI is from the MARCH-PFIC study and Placebo-LIVMARLI is from MARCH-ON. LIVMARLI responders are defined as a patient having a 4-week average morning ItchRO(Obs) severity change from baseline of ≤ -1.0 OR an average severity score of ≤ 1.0 . For the purpose of determining response, the average severity score from the three 4-week periods (Weeks 15 to 18, 19 to 22, and 23 to 26) are used. A patient is defined as a LIVMARLI nonresponder if the 4-week average baseline score is missing OR all three 4-week average (post-baseline) scores are missing.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

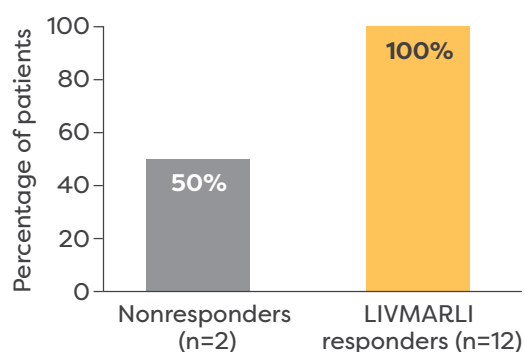
Hepatotoxicity: Obtain baseline liver tests and monitor during treatment. Liver-related adverse reactions and physical signs of hepatic decompensation should also be monitored. Dose reduction or treatment interruption may be considered if abnormalities occur in the absence of other causes. Permanently discontinue LIVMARLI if a patient experiences the following: persistent or recurrent liver test abnormalities, clinical hepatitis upon rechallenge, or a hepatic decompensation event.

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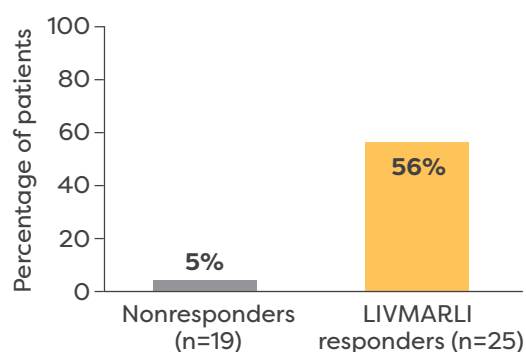


BILIRUBIN LEVELS IN CHOLESTATIC PRURITUS RESPONDERS⁴

Patients with normal bilirubin levels (≤ 1.2 mg/dL) at baseline that remained within normal range^{4§}



Patients with abnormal bilirubin levels (> 1.2 mg/dL) at baseline that shifted to normal (≤ 1.2 mg/dL) levels^{4§}



[§]Based on average total bilirubin value at Weeks 18, 22, and 26.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Gastrointestinal (GI) Adverse Reactions: Diarrhea and abdominal pain were reported as the most common adverse reactions. Monitor for dehydration and treat promptly. Consider reducing the dosage or interrupting LIVMARLI dosing if a patient experiences persistent diarrhea or diarrhea with bloody stool, vomiting, dehydration requiring treatment, or fever.

Fat-Soluble Vitamin (FSV) Deficiency: Patients can have FSV deficiency (vitamins A, D, E, and K) at baseline, and LIVMARLI may adversely affect absorption of FSVs. Treatment-emergent bone fracture events have been observed more frequently with patients treated with LIVMARLI compared with patients treated with placebo. If bone fractures or bleeding occur, consider interrupting LIVMARLI and supplement with FSVs. LIVMARLI can be restarted once FSV deficiency is corrected and maintained at corrected levels.

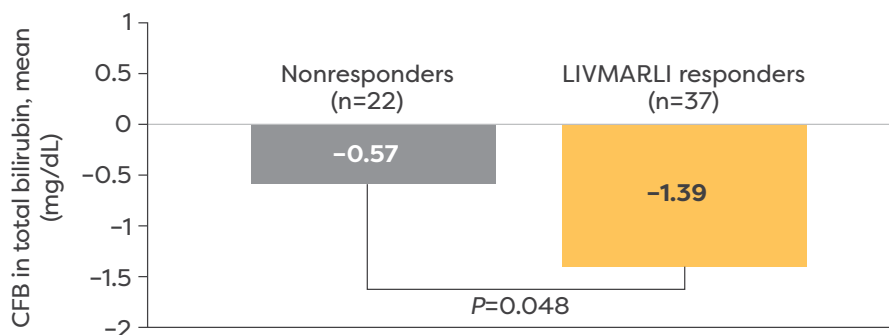
Risk of Propylene Glycol Toxicity (Pediatric Patients Less Than 5 Years of Age): Total daily intake of propylene glycol should be considered for managing the risk of propylene glycol toxicity. Monitor patients for signs of propylene glycol toxicity. Discontinue LIVMARLI if toxicity is suspected.

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BILIRUBIN LEVELS IN CHOLESTATIC PRURITUS RESPONDERS⁴

Mean change from baseline (CFB) in total bilirubin (mg/dL)^{4||}



^{||}Based on average total bilirubin value at Weeks 18, 22, and 26.

These data are based on an ongoing, exploratory analysis of MARCH-PFIC/MARCH-ON. Visit mirumpharma.com/our-science for the latest publications and presentations.



IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

The most common adverse reactions are diarrhea, FSV deficiency, abdominal pain, liver test abnormalities, hematochezia, and bone fractures.

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.

References: 1. LIVMARLI[®] (maralixibat) oral solution. Prescribing Information. Mirum Pharmaceuticals, Inc. 2. Miethke AG, Moukarzel A, Porta G, et al. Maralixibat in progressive familial intrahepatic cholestasis (MARCH-PFIC): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Gastroenterol Hepatol*. 2024;9(7):620-631. doi:10.1016/S2468-1253(24)00080-3 3. Miethke A, Moukarzel A, Porta G, et al. Long-term maintenance of response and improved liver health with maralixibat in patients with progressive familial intrahepatic cholestasis (PFIC): 2-year data from the MARCH-ON study. Presented at: American Association for the Study of Liver Diseases (AASLD) The Liver Meeting: November 10-14, 2023; Boston, MA. 4. Data on file. REF-01712. Mirum Pharmaceuticals, Inc. 5. Miethke A, Moukarzel A, Porta G, et al. Efficacy and safety of maralixibat in patients with progressive familial intrahepatic cholestasis (MARCH-PFIC): A randomized placebo-controlled Phase 3 study. Presented at: European Society For Pediatric Gastroenterology, Hepatology, and Nutrition. May 17-20, 2023; Vienna, Austria. 6. Amirneni S, Haep N, Gad MA, et al. Molecular overview of progressive familial intrahepatic cholestasis. *World J Gastroenterol*. 2020;26(47):7470-7484. doi:10.3748/wjg.v26.i47.7470 7. Verkade HJ, Thompson RJ, Arnell H, et al. Systematic review and meta-analysis: partial external biliary diversion in progressive familial intrahepatic cholestasis. *J Pediatr Gastroenterol Nutr*. 2020;71(2):176-183. doi:10.1097/MPG.0000000000002789

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