

PATIENTS WITH PFIC WHO ACHIEVED A CHOLESTATIC PRURITUS RESPONSE WITH LIVMARLI

Growth Data: Height and Weight

MARCH-PFIC was a 26-week, Phase 3, randomized, placebo-controlled study that assessed efficacy and safety of treatment with LIVMARLI in patients 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 height and weight 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.

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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PRURITUS AND GROWTH

Research has shown that pruritus may contribute to systemic issues that impair growth, including sleep disruptions, nutritional challenges, and increased inflammatory burden. Reducing pruritus severity has been associated with improved linear growth in children with chronic pruritic conditions.⁵⁻⁸

MARCH-PFIC

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

- In the bile salt export pump (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 cohort⁹
- In the MARCH-PFIC study, 64% of patients saw improvements 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 (≥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 height and weight in patients with PFIC who received LIVMARLI in MARCH-PFIC/MARCH-ON (N=60).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 Itch Reported Outcome (Observer) (ItchRO[Obs]) scale.²

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

- LIVMARLI responders (n=37) had an average ItchRO(Obs) score of 2.5, height Z-score of -1.8, and weight Z-score of -1.2^{4*†}
- LIVMARLI nonresponders (n=23) had an average ItchRO(Obs) score of 2.6, height Z-score of -2.6, and weight Z-score of -1.8^{4*†}

CI=confidence interval.

*Baseline for the LIVMARLI-LIVMARLI group is from MARCH-PFIC and baseline for the Placebo-LIVMARLI group is from MARCH-ON, respectively. All data are mean unless otherwise indicated. Values are based on non-missing assessments. ItchRO(Obs) is the 4-week morning average severity score.

†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

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.

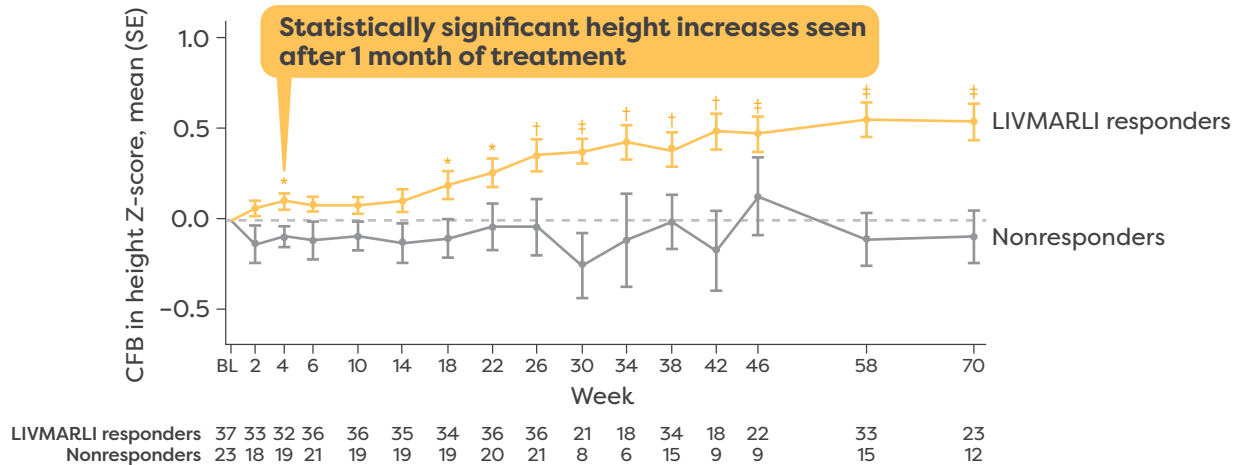
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HEIGHT INCREASES IN PATIENTS WHO ACHIEVED A CHOLESTATIC PRURITUS RESPONSE WITH LIVMARLI

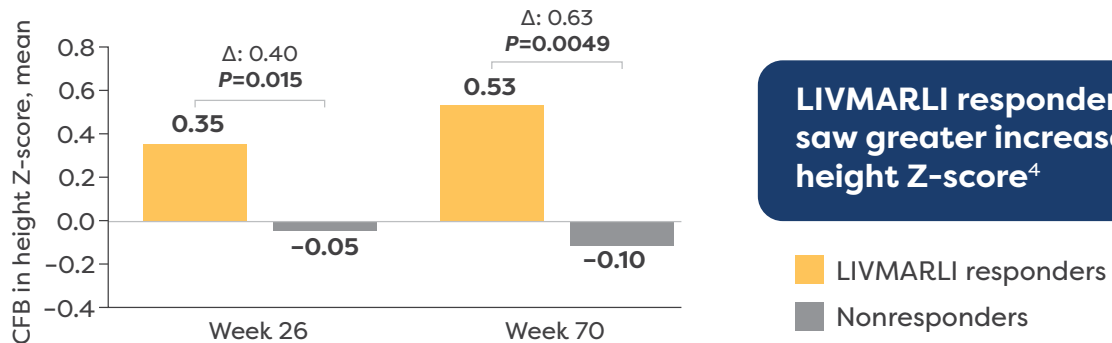
LIVMARLI responders were those who saw relief from their cholestatic pruritus. This was defined as an improvement of ≥ 1 point from baseline or a score of ≤ 1 on the Itch Reported Outcome (Observer) (ItchRO[Obs]) scale.²

Mean change from baseline (CFB) in height Z-score over time⁴



LIVMARLI responders experienced significant increases through 70 weeks ($P < 0.0001$).⁴

Mean CFB in height Z-score by analysis timepoints⁴



LIVMARLI responders saw greater increases in height Z-score⁴

* $P \leq 0.05$.
[†] $P \leq 0.001$.
[‡] $P \leq 0.0001$.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

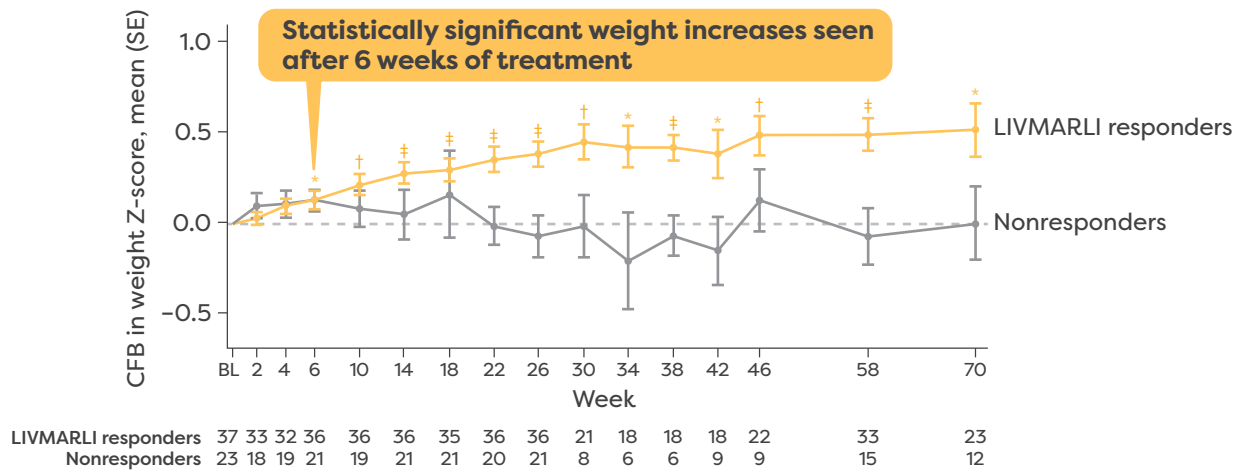
Fat-Soluble Vitamin (FSV) Deficiency: Patients can have FSV deficiency (vitamins A, D, E, and K) at baseline, and LIVMARLI may adversely affect absorption of FSVs. Treatment-emergent bone fracture events have been observed more frequently with patients treated with LIVMARLI compared with patients treated 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.

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WEIGHT INCREASES IN PATIENTS WHO ACHIEVED A CHOLESTATIC PRURITUS RESPONSE WITH LIVMARLI

Mean CFB in weight Z-score over time⁴

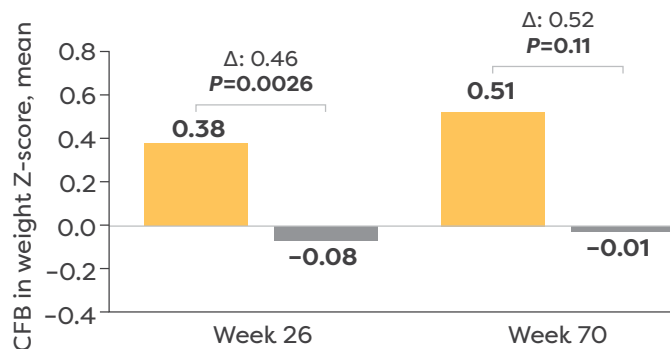


LIVMARLI responders had elevations in weight Z-score over 70 weeks of treatment ($P < 0.0001$).⁴

Mean CFB in weight Z-score by analysis timepoints⁴

LIVMARLI responders saw greater increases in weight Z-score⁴

■ LIVMARLI responders
■ Nonresponders



BL=baseline; SE=standard error.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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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PATIENTS WITH PFIC WHO SAW IMPROVEMENTS IN CHOLESTATIC PRURITUS WITH LIVMARLI ALSO SHOWED INCREASES IN HEIGHT AND WEIGHT



Additional research is needed to better understand the relationship between cholestatic pruritus response and increases in growth for patients with progressive familial intrahepatic cholestasis (PFIC).⁴

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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. Miethke AG, Aqul AA, Lin C-H, et al. Improvements in pruritus are associated with improvements in growth in patients with progressive familial intrahepatic cholestasis: data from the MARCH-ON trial. Presented at: American Association for the Study of Liver Diseases (AASLD) The Liver Meeting: November 15-19, 2024; San Diego, CA. 5. Nicholas MN, Keown-Stoneman CDG, Maguire JL, Drucker AM. Association between atopic dermatitis and height, body mass index, and weight in children. *JAMA Dermatol.* 2022;158(1):26-32. doi:10.1001/jamadermatol.2021.4529 6. Gerard G, Ng WWV, Koh JKJ, et al. The association between atopic dermatitis and linear growth in children- a systematic review. *Eur J Pediatr.* 2024;183(12):5113-5128. <https://doi.org/10.1007/s00431-024-05804-z> 7. Zhang M, He M, Tang T. The effect of atopic dermatitis in pediatric patients on height: reflections triggered by a real-life case report. *Medicine (Baltimore).* 2023;102(47):e36150. doi:10.1097/MD.00000000000036150 8. Melter M, Rodeck B, Kardorff R, et al. Progressive familial intrahepatic cholestasis: partial biliary diversion normalizes serum lipids and improves growth in noncirrhotic patients. *Am J Gastroenterol.* 2000;95(12):3522-3528. doi:10.1111/j.1572-0241.2000.03370 9. 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.

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