Maralixibat Leads to Significant Reductions in Pruritus and Improvements in Sleep for Children With Progressive Familial Intrahepatic Cholestasis: Data From MARCH-PFIC

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Introduction

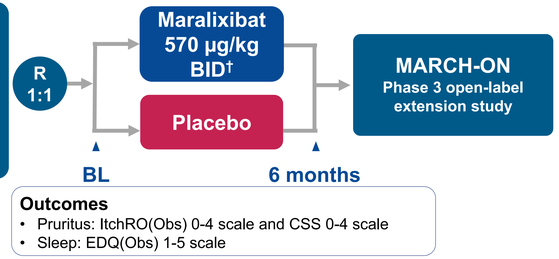
- Progressive familial intrahepatic cholestasis (PFIC) is a collection of disorders in bile formation that can lead to intrahepatic cholestasis, chronic liver disease and severe pruritus, with markedly reduced quality of life in several domains, including sleep.[1]
- Maralixibat is an ileal bile acid transporter inhibitor (IBATi) approved for the treatment of cholestatic pruritus in patients with Alagille syndrome ≥ 2 months of age in the EU and ≥ 3 months of age in the US.[2,3]
- MARCH-PFIC (MARCH), a Phase 3, 26-week, randomised, placebo-controlled trial of maralixibat, achieved its primary and key secondary endpoints of improvements in pruritus and serum bile acid (sBA) in children with PFIC.[4]

Aim

- To further characterise the pruritus response for participants in the MARCH trial with respect to: (1) proportion of participants with itch score ≤ 1 during treatment; (2) measurement of pruritus at different times throughout the day; (3) physician's assessment of pruritus; and (4) the relationship between pruritus and sleep.

Methods

Key entry criteria
- Diagnosis of PFIC
- Age ≥ 12 months and < 18 years at BL
- Persistent, moderate-to-severe pruritus*
- sBA ≥ 3 × ULN



Outcomes
- Pruritus: ItchRO(Obs) 0-4 scale and CSS 0-4 scale
- Sleep: EDQ(Obs) 1-5 scale

*ItchRO(Obs) score ≥ 1.5; †Maralixibat 570 µg/kg is equivalent to 600 µg/kg maralixibat chloride.
BL, Baseline; CSS, Clinician Scratch Scale; EDQ(Obs), Exploratory Diary Questionnaire (Observer); ItchRO(Obs), Itch-Reported Outcome (Observer); R, randomised.

- Sixty-four patients: non-truncated BSEP (n = 31), FIC1 (n = 13), MDR3 (n = 9), TJP2 (n = 7) and MYO5B (n = 4) were randomised to maralixibat (n = 33) or placebo (n = 31).
- Itch-Reported-Outcome (Observer) (ItchRO[Obs]) is a 0-4 scale, where 0 = no itch, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe.[5] A ≥ 1-point reduction in ItchRO(Obs) is considered clinically meaningful.[6]
- Clinician Scratch Scale (CSS) is scored on a 0-4 scale, where 0 = none and 4 = cutaneous mutilations, haemorrhage and scarring (worst scratching).[7]
- Exploratory Diary Questionnaire (Observer) (EDQ[Obs]) is a 1-5 scale (1 = never/no itch to 5 = almost always/very severe) that includes questions focused on sleep disturbances related to pruritus.

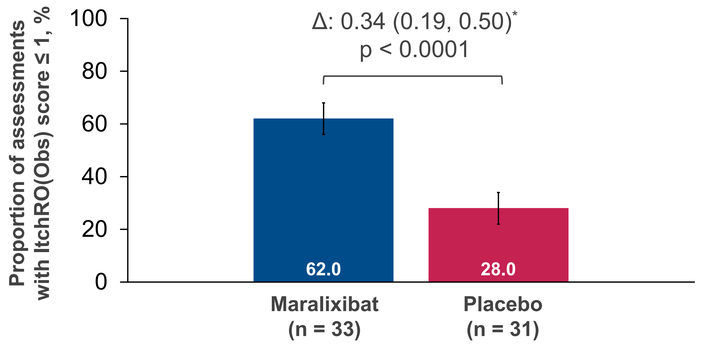
Baseline characteristics were well balanced between treatment arms

Variable	Maralixibat (n = 33)	Placebo (n = 31)
Age, years	4.9	4.4
Male, %	52	42
Pruritus, ItchRO(Obs) score	2.85	2.73
Baseline CSS score	2.8	2.6
Baseline EDQ(Obs) sleep disturbance	3.70	3.66
Total sBA, µmol/L	254	272
UDCA usage, %	82	97
Rifampicin usage, %	55	48
Alanine aminotransferase, U/L	88	127
Total bilirubin, mg/dL	4.12	4.04
Direct bilirubin, mg/dL	2.98	2.93
Height Z-score	-2.08	-2.06
Weight Z-score	-1.75	-1.28

All data are mean unless otherwise indicated. Percentages are 100 × n/N.
UDCA, ursodeoxycholic acid.

Results

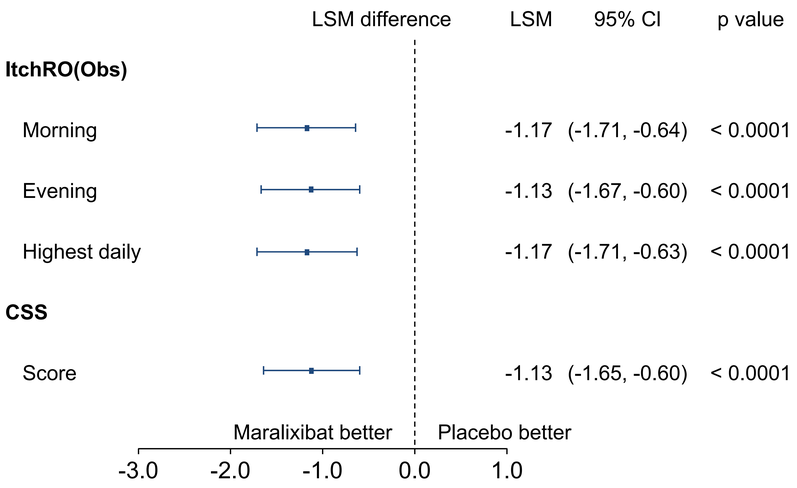
Patients on maralixibat had significantly more days with minimal to no itch than patients on placebo



Error bars represent SE. Percentage values represent the proportion of assessments from Baseline to Week 26.
*Delta with 95% CI. CI, confidence interval; SE, standard error.

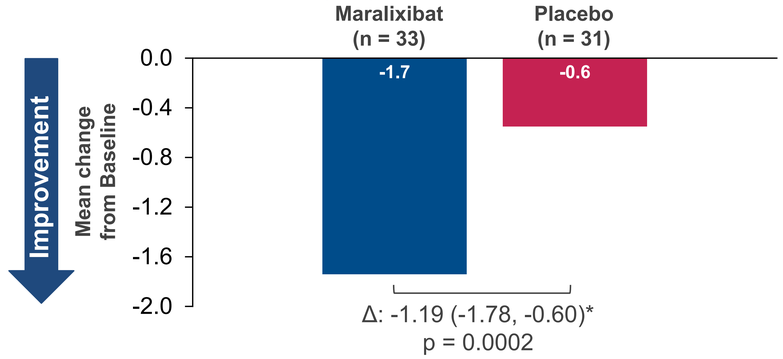
- From Weeks 15 to 26, the median proportion of reported days with an ItchRO(Obs) score of 0-1 was 95% for maralixibat and 9% for placebo (p = 0.0005).

Patients on maralixibat had significant reductions in pruritus compared with placebo irrespective of when or how it was measured



Data are averaged treatment effect over the last 12 weeks of the study. LSM, least squares mean.

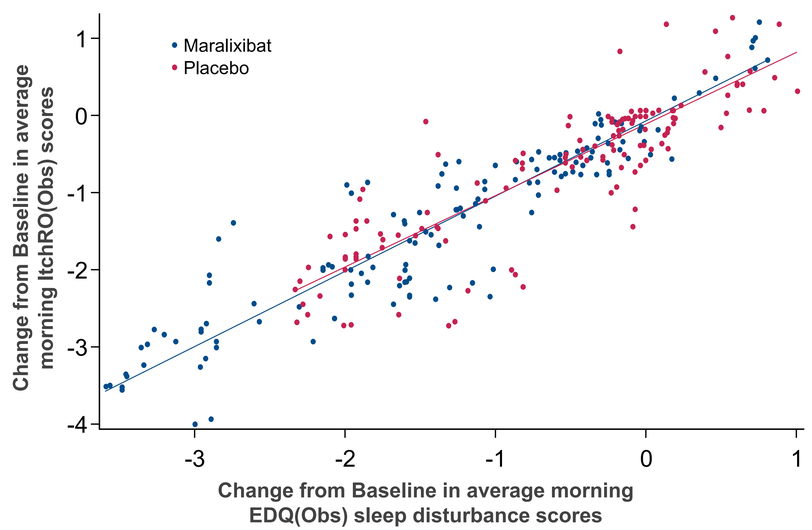
Significant improvement in change from Baseline sleep with maralixibat vs placebo, measured via the EDQ(Obs)



*Delta with 95% CI.

Change in pruritus was strongly correlated with change in sleep

- There was a strong correlation between absolute values in pruritus and sleep scores (Spearman's r = 0.93; p < 0.0001).
- There was also a strong correlation between change from Baseline for pruritus and sleep (Spearman's r = 0.93; p < 0.0001).



Conclusions

- **Maralixibat was associated with complete or near-complete resolution of pruritus in the majority of patients with PFIC.**
- **The effect of maralixibat on pruritus was independent of when or how it was measured, or who made the assessments.**
- **Changes in pruritus were strongly correlated with improvements in sleep, suggesting that the use of maralixibat may yield meaningful improvements in this domain of quality of life.**

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References
1. Loomes KM, et al. *Hepatol Commun*. 2022;6:2379-2390.
2. LIVMARLI® (maralixibat) [prescribing information]. Foster City, CA: Mirum Pharmaceuticals, Inc. Mar 2023.
3. LIVMARLI® (maralixibat) [summary of product characteristics]. Amsterdam, Netherlands: Mirum Pharmaceuticals, Inc. Dec 2022.
4. ClinicalTrials.gov ID: NCT03905330. Retrieved from website https://www.clinicaltrials.gov/ct2/show/NCT03905330 Accessed 23 May 2023.
5. Kamath BM, et al. *Hepatol Commun*. 2020;4:1012-1018.
6. Kamath BM, et al. *Patient*. 2018;11:69-82.
7. Whitington PF, Whitington GL. *Gastroenterology*. 1988;95:130-136.

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