Abstract 1102

Greater Improvements in Bilirubin Were Observed in Pruritus Responders After Maralixibat Treatment in Patients With PFIC: Data From the MARCH/MARCH-ON Trials

Richard J. Thompson,[1] Lorenzo D'Antiga,[2,3] Nadia Ovchinsky,[4] Chuan-Hao Lin,[5] Douglas B. Mogul,[6] Tiago Nunes,[6] Shannon Vandriel,[6] Cheng Chen,[6] Joanne Quan,[6] Pamela Vig,[6] Alexander G. Miethke[7]

[1]Institute of Liver Studies, King's College London, London, United Kingdom; [2]Pediatric Hepatology, Gastroenterology and Transplantation, ASST Papa Giovanni XXIII, Bergamo, Italy; [3]Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy; [4]New York University Grossman School of Medicine, New York, New York, USA; [5]Children's Hospital Los Angeles, Los Angeles, California, USA; [6]Mirum Pharmaceuticals, Inc., Foster City, California, USA; [7]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

Introduction

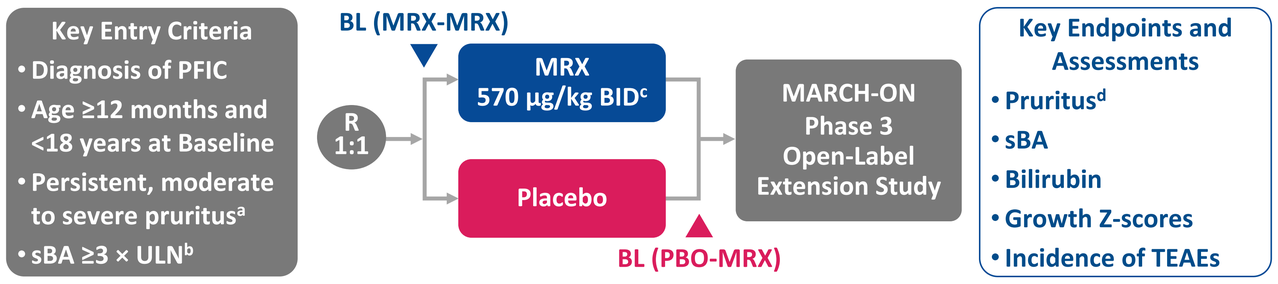
- Progressive familial intrahepatic cholestasis (PFIC) is a group of genetic disorders that result in disrupted bile composition and chronic cholestasis.[1]
  - Key clinical manifestations include debilitating pruritus, impaired growth, reduced quality of life and progressive liver disease with an eventual need for liver transplantation.
- Most patients with PFIC develop end-stage liver disease before adulthood and become candidates for liver transplantation, highlighting the importance of liver health in this population.[2]
- Reduction in bilirubin level is a predictor of longer native liver survival in patients with PFIC who have had surgical biliary diversion to interrupt enterohepatic circulation.[3]
- Maralixibat (MRX) is a minimally absorbed ileal bile acid transporter inhibitor that prevents enterohepatic bile acid recirculation and is approved for the treatment of PFIC in patients ≥3 months of age in the EU and for the treatment of cholestatic pruritus in patients with PFIC ≥12 months of age in the US.[4,5]
- MARCH was a phase 3, randomised, double-blind, placebo-controlled, 26-week trial investigating the efficacy and safety of maralixibat in participants with PFIC across the broadest range of PFIC types studied to date.[6,7]
  - In MARCH, participants who received maralixibat achieved statistically significant improvements in pruritus, levels of sBA and bilirubin and growth.[7]
  - Long-term maintenance of effect was observed for up to 2 years in MARCH-ON, an open-label extension study for participants who completed the MARCH study.[8,9]
- Among participants who received maralixibat in MARCH, statistically significant decreases were observed in total and direct bilirubin levels, and almost half of participants with abnormal total bilirubin levels at Baseline experienced normalisation of total bilirubin levels.[10]

Objective

- To present the results of an exploratory analysis that evaluated the relationship between pruritus response and changes in total bilirubin level in participants who received maralixibat in MARCH/MARCH-ON.

Methods

Figure 1. MARCH Phase 3 Study Design



[a]Itch-Reported Outcome (Observer) (ItchRO[Obs]) score ≥1.5. [b]Criteria for primary BSEP cohort only. [c]Maralixibat 570 µg/kg is equivalent to 600 µg/kg maralixibat chloride. [d]ItchRO(Obs) is a 0 to 4 scale, where 0 = no itch, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.[11] A ≥1-point reduction in ItchRO(Obs) score is considered clinically meaningful.

- Data were analysed for participants who received maralixibat in MARCH/MARCH-ON in the MRX-MRX and PBO-MRX treatment groups.
  - Baseline for MRX-MRX is from MARCH, and for PBO-MRX, from MARCH-ON.
- Changes in total bilirubin level were evaluated during the first 26 weeks of maralixibat treatment by using the average of Weeks 18, 22 and 26.
- Pruritus was assessed using average morning ItchRO(Obs) score from three 4-week periods (Weeks 15-18, 19-22 and 23-26).
  - Pruritus response was defined as ≥1-point reduction in ItchRO(Obs) score from Baseline or a score of ≤1.0.[a]
- The difference between pruritus responders and nonresponders was analysed using the Wilcoxon signed-rank test and Fisher exact test.

[a]A participant is defined as an ItchRO nonresponder if the 4-week average Baseline score is missing or all 3 post-Baseline scores are missing.

Results

Pruritus Responders Had Lower Bilirubin Levels at Baseline Compared With Nonresponders

Table 1. Baseline Demographics and Characteristics

Parameter[a]	Pruritus responders (n=37)	Pruritus nonresponders (n=22)	*P* value[c]	Total (N=59)
Age, y	6.0 (3.9)	3.6 (3.6)	0.011	5.1 (4.0)
Sex, male, %	41	55	-	46
Pruritus, ItchRO(Obs) score[b]	2.5 (1.3)	2.5 (0.8)	0.86	2.5 (1.1)
ALT, U/L	92 (50)	99 (72)	0.86	94 (58)
AST, U/L	106 (72)	108 (64)	0.94	107 (68)
Total bilirubin, µmol/L	52 (52)	107 (84)	0.006	73 (70)
Direct bilirubin, µmol/L	37 (40)	80 (60)	0.004	53 (52)
Height Z-score	-1.8 (1.3)	-2.7 (1.2)	0.011	-2.1 (1.3)
Weight Z-score	-1.3 (1.0)	-1.8 (1.6)	0.26	-1.4 (1.3)

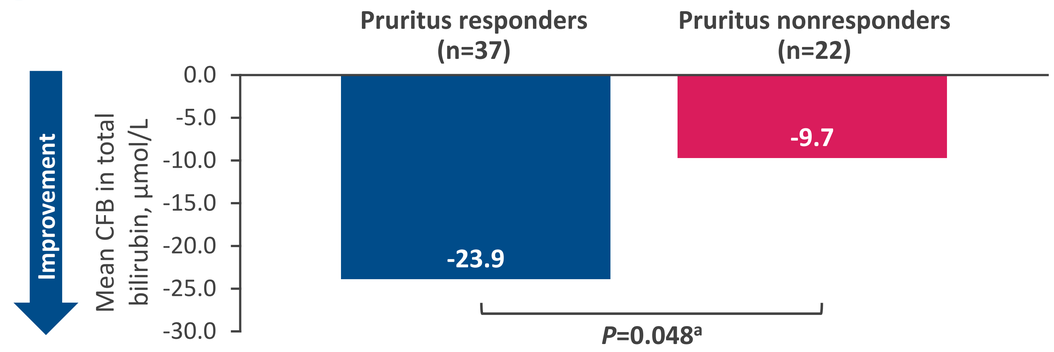
[a]All data are mean (SD) except where otherwise indicated. [b]Baseline ItchRO(Obs) score is the 4-week morning average severity score. [c]Wilcoxon signed-rank test.

- Fifty-nine participants received maralixibat, including participants with PFIC types FIC1 (n=12; 20%), nt-BSEP (n=28; 47%), MDR3 (n=9; 15%), TJP2 (n=7; 12%), and MYO5B (n=3; 5%).

Results (cont.)

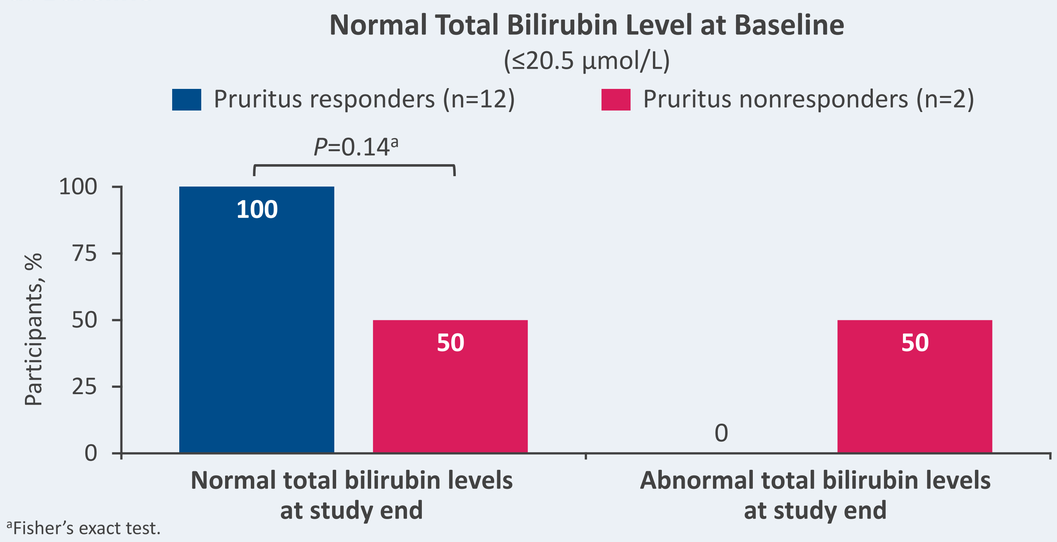
Pruritus Responders Had Significantly Greater Reductions in Total Bilirubin Levels Than Nonresponders

Figure 2. CFB in Total Bilirubin Level



[a]Fisher's exact test.

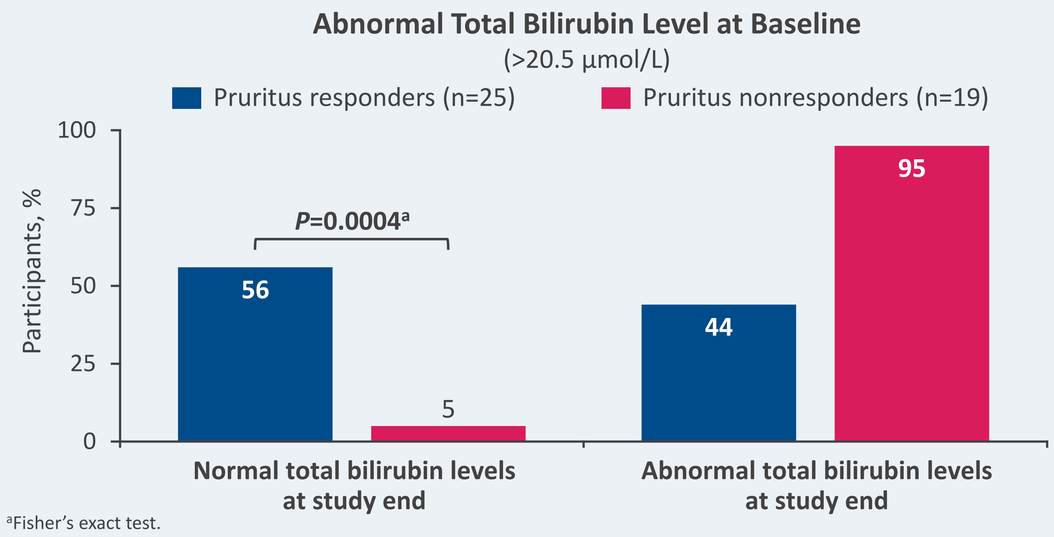
Figure 3. Maintenance of Total Bilirubin Levels in Participants With Normal Levels at Baseline



[a]Fisher's exact test.

- **All pruritus responders with normal total bilirubin levels at Baseline had normal levels at study end.**
- **Of the 2 nonresponders with normal total bilirubin levels at Baseline, 1 became abnormal.**

Figure 4. Normalisation of Total Bilirubin Levels in Participants With Abnormal Levels at Baseline



[a]Fisher's exact test.

- **Over half of pruritus responders with abnormal total bilirubin levels at Baseline had normal levels at study end.**
- **Nearly all pruritus nonresponders with abnormal total bilirubin levels at Baseline had abnormal levels at study end.**

- Overall, 70% of pruritus responders and 10% of pruritus nonresponders had normal total bilirubin levels at study end.

Conclusions

- This analysis shows that changes in total bilirubin level and pruritus are linked in participants who received maralixibat, with greater reductions in bilirubin level, an important marker of liver health, observed in pruritus responders than in pruritus nonresponders.
- Individuals who have lower bilirubin levels at Baseline may have greater likelihood of improvement in pruritus following treatment with maralixibat.

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; BL, Baseline; BSEP, bile salt export pump; CFB, change from Baseline; FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer); MDR3, multidrug resistance protein 3; MRX, maralixibat; MYO5B, myosin Vb; nt, nontruncated; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; R, randomised; sBA, serum bile acid; TEAE, treatment-emergent adverse event; TJP2, tight junction protein 2; ULN, upper limit of normal.

Disclosures

RJT is a consultant for Mirum Pharmaceuticals, Inc., Albireo/Ipsen, Generation Bio, Rectify Therapeutics and Alnylam and a shareholder in Generation Bio and Rectify Therapeutics. LDA is a consultant and advisor for Mirum Pharmaceuticals, Inc., Albireo, Selecta, Vivet Pharmaceuticals, Tome, Spark, Genespire and Alexion. NO is a consultant for Albireo and received research support to her institution from Mirum Pharmaceuticals, Inc., Albireo and Travere. CHL has nothing to disclose. DBM, TN, SV, CC, JQ and PV are employees of and shareholders in Mirum Pharmaceuticals, Inc. AGM is a consultant and has a sponsored research agreement for Mirum Pharmaceuticals, Inc.

Acknowledgments

The authors would like to thank the clinical trial participants, their families, and the investigators for their participation in this study. Maralixibat is owned by Mirum Pharmaceuticals, Inc. This analysis was funded by Mirum Pharmaceuticals, Inc. Medical writing and editorial support for the development of this poster was provided by Precision AQ in Bethesda, Maryland, which was funded by Mirum Pharmaceuticals, Inc.

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Presented at the 57th Annual Meeting of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN); 14-17 May 2025; Helsinki, Finland