Maralixibat Can Improve Cholestatic Pruritus in Children With Progressive Familial Intrahepatic Cholestasis Who Previously Underwent a Surgical Biliary Diversion: Data From the MARCH/MARCH-ON Trials

Lorenzo D'Antiga,[1,2] Piotr Czubkowski,[3] Alexander G. Miethke,[4] Adib Moukarzel,[5] Amal A. Aqul,[6] Simon P. Horslen,[7] Wolf-Dietrich Huber,[8] Tiago Nunes,[9] Anamaria Lascau,[9] Douglas B. Mogul,[9] Raul Aguilar,[9] Pamela Vig,[9] Richard J. Thompson[10]

[1]Paediatric Hepatology, Gastroenterology and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy; [2]Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy; [3]Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics, The Children's Memorial Health Institute, Warsaw, Poland; [4]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [5]Hôtel Dieu de France Saint Joseph University Hospital, Beirut, Lebanon; [6]University of Texas Southwestern Medical Center, Dallas, Texas, USA; [7]UPMC Children's Hospital of Pittsburgh, Pediatrics, Pittsburgh, Pennsylvania, USA; [8]Medical University of Vienna, Vienna, Austria; [9]Mirum Pharmaceuticals, Inc., Foster City, California, USA; [10]Institute of Liver Studies, King's College London, London, United Kingdom

Introduction

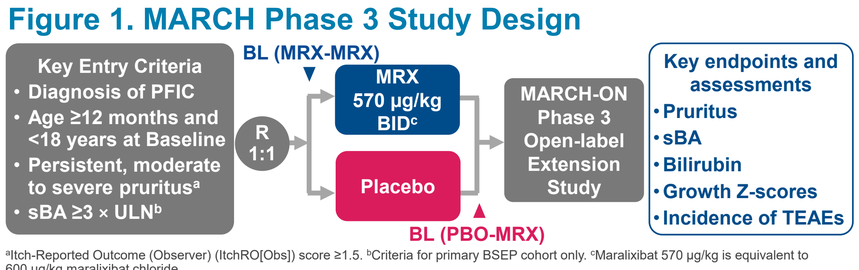
- Progressive familial intrahepatic cholestasis (PFIC) is a group of genetic disorders that result in disrupted bile composition and chronic cholestasis.[1]
  - Key clinical manifestations include debilitating pruritus, impaired growth, reduced quality of life, and progressive liver disease with an eventual need for liver transplantation.[1]
- Surgical biliary diversion (SBD) interrupts enterohepatic circulation and can improve pruritus and native liver survival in patients with PFIC.[1,2]
  - For some patients who undergo SBD, pruritis is not improved or improvements are transient.[2]
- Maralixibat (MRX) is a minimally absorbed ileal bile acid transporter (IBAT) inhibitor that prevents enterohepatic bile acid recirculation and is 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.[3,4]
- 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.[5,6]
  - In MARCH, participants who received maralixibat achieved statistically significant improvements in pruritus, levels of sBAs, bilirubin, and growth.[6]
- MARCH-ON is an open-label, long-term extension study for participants who completed the MARCH study.[7]

Objective

- To report on the use of maralixibat in participants with PFIC with prior SBD in MARCH and MARCH-ON.

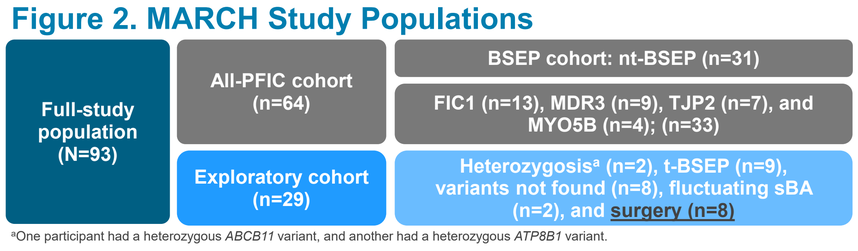
Methods

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.

Figure 2. MARCH Study Populations



[a]One participant had a heterozygous *ABCB11* variant, and another had a heterozygous *ATP8B1* variant.

- Data comparing change from Baseline (CFB) for key efficacy endpoints (pruritus, sBA, and bilirubin) were analysed for participants with prior SBD and 26 weeks of maralixibat treatment.
- Pruritus was measured using the 0-4 Itch-Reported Outcome (Observer) (ItchRO[Obs]) scale (0=no itch, 1=mild, 2=moderate, 3=severe and 4=very severe)[8] in which a ≥1-point reduction is considered clinically meaningful.

Results

Table 1. Key Demographics and Baseline Characteristics

Variable[a]	MRX-MRX (n=5)	PBO-MRX (n=2)
Age, y	3 (1, 6)	7 (4, 10)
Sex, male, %	20	50
Genotype, n (%)		
BSEP	3 (60)	0 (0)
FIC1	2 (40)	2 (100)
Pruritus, ItchRO(Obs)	3.0 (2.6, 3.6)	4.0 (4.0, 4.0)
Total sBA, µmol/L	261 (69, 536)	168 (114, 221)
UDCA usage, %	100	0
Rifampicin usage, %	60	0
ALT, U/L	132 (57, 374)	51 (46, 56)
AST, U/L	135 (65, 216)	82 (69, 96)
7αC4, ng/mL	2.5 (1.3, 11.3)	5.2 (1.3, 9.1)
Platelets, 10^3/µL	218 (152, 461)	381 (241, 520)
Total bilirubin, µmol/L	88.1 (22.7, 212.0)	230.0 (56.4, 403.6)
Direct bilirubin, µmol/L	66.7 (15.9, 159.0)	179.1 (42.8, 315.5)
Height Z-score	-1.7 (-3.2, 0.2)	-2.5 (-3.1, -1.9)
Weight Z-score	-0.9 (-1.4, 1.1)	-3.2 (-3.7, -2.7)

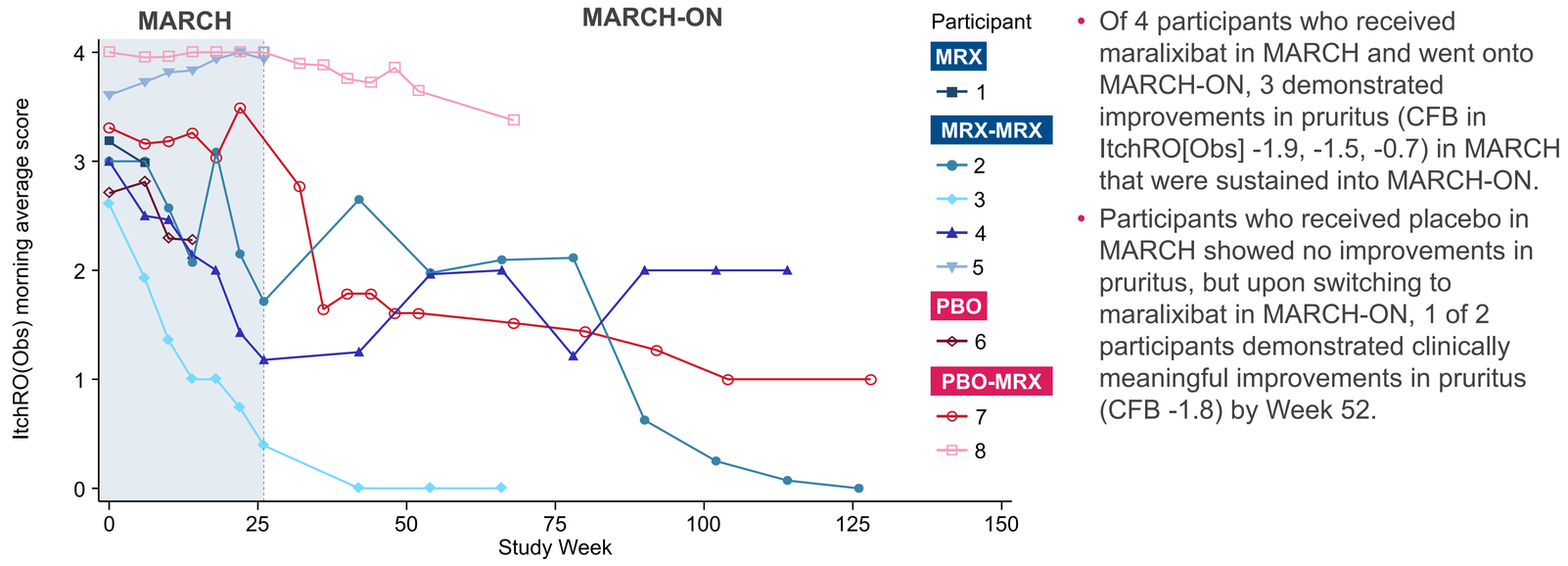
[a]All data are median (min, max) unless otherwise indicated.

Results (cont'd)

- In MARCH, individuals with SBD were randomised to receive maralixibat (n=5) or placebo (n=3).
  - One participant receiving maralixibat underwent early transplant, and 1 participant receiving placebo withdrew consent.
- Four participants with SBD who received maralixibat in MARCH continued to receive maralixibat in MARCH-ON (MRX-MRX).
- Two participants with SBD who received placebo in MARCH initiated maralixibat in MARCH-ON (PBO-MRX).

Most Participants Who Received Maralixibat Showed Improvements in Pruritus

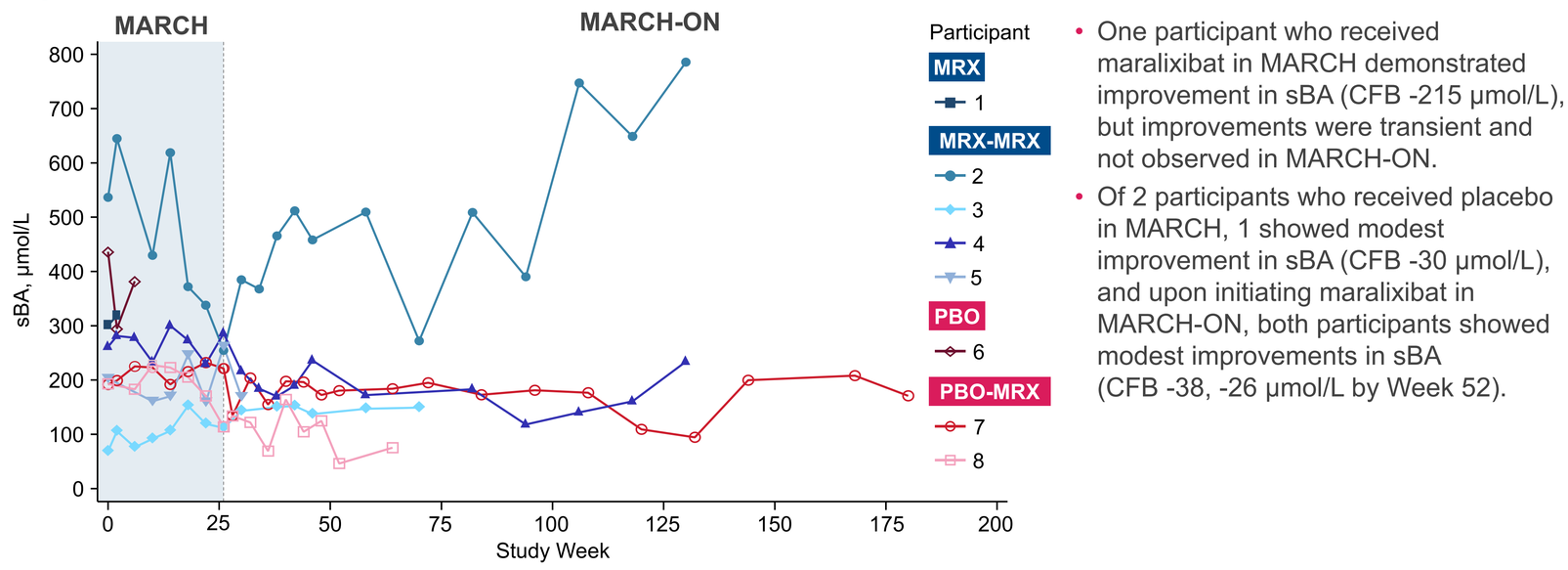
Figure 3. Average Pruritus (ItchRO[Obs]) Scores Over Time



- Of 4 participants who received maralixibat in MARCH and went onto MARCH-ON, 3 demonstrated improvements in pruritus (CFB in ItchRO[Obs] -1.9, -1.5, -0.7) in MARCH that were sustained into MARCH-ON.
- Participants who received placebo in MARCH showed no improvements in pruritus, but upon switching to maralixibat in MARCH-ON, 1 of 2 participants demonstrated clinically meaningful improvements in pruritus (CFB -1.8) by Week 52.

Some Participants Who Received Maralixibat Showed Improvements in sBA

Figure 4. sBA Over Time



- One participant who received maralixibat in MARCH demonstrated improvement in sBA (CFB -215 µmol/L), but improvements were transient and not observed in MARCH-ON.
- Of 2 participants who received placebo in MARCH, 1 showed modest improvement in sBA (CFB -30 µmol/L), and upon initiating maralixibat in MARCH-ON, both participants showed modest improvements in sBA (CFB -38, -26 µmol/L by Week 52).

Table 2. CFB in Pruritus and sBA

Participant	Treatment group	Genotype	CFB in Pruritus ItchRO(Obs) Score[a]		CFB in sBA, µmol/L[b]	
			MARCH	MARCH-ON	MARCH	MARCH-ON
1	MRX	BSEP	-0.2[c]	–	18[c]	–
2	MRX-MRX	BSEP	-0.7	-3.0	-215	249
3	MRX-MRX	BSEP	-1.9	-2.6	59	81
4	MRX-MRX	FIC1	-1.5	-1.0	2	-27
5	MRX-MRX	FIC1	0.4	–	20	-34
6	PBO	TJP2	-0.4[d]	–	-54[d]	–
7	PBO-MRX	FIC1	0.2	-2.3	31	-50
8	PBO-MRX	FIC1	0.0	-0.6	-30	-38

[a]CFB is the average of Weeks 15-26 for MARCH and last assessment in MARCH-ON by participant. [b]CFB is the average of Weeks 18-26 for MARCH and last assessment in MARCH-ON by participant. [c]Values for participant 1 for MARCH are from Week 2. [d]Values for participant 6 for MARCH are from Week 6.

Additional Laboratory Parameters

- One participant who received maralixibat in MARCH demonstrated reduction in total bilirubin (CFB -55.3 µmol/L).
- Participants who received placebo in MARCH showed no improvements in total bilirubin, but upon switching to maralixibat in MARCH-ON, both participants showed modest improvements in total bilirubin (CFB -53.0, -27.6 µmol/L).
- Similar results were observed for direct bilirubin.

No New Safety Signals Were Observed

Table 3. Summary of TEAEs

TEAE, n (%)[a]	MRX-MRX (n=5)	PBO-MRX (n=2)
Any TEAE	5 (100.0)	2 (100.0)
Severe TEAE[b]	2 (40.0)	1 (50.0)
Serious TEAE[c]	2 (40.0)	1 (50.0)
TEAE leading to discontinuation	0	0
TRAE leading to death	0	0
Clinically relevant TEAEs		
Diarrhoea	3 (60.0)	2 (100.0)
Abdominal pain	0	1 (50.0)

[a]Number indicates the number of participants experiencing an event. [b]The severe TEAEs in the MRX-MRX group were adenovirus infection, coronavirus infection and rickets (all in 1 participant) and blood bilirubin increased, pruritus, and haemorrhage (all in 1 participant). The severe TEAEs in the PBO-MRX group were oedema peripheral and stoma site haemorrhage (all in 1 participant). [c]The serious TEAEs in the MRX-MRX group were cholestasis (1 participant) and adenovirus infection, coronavirus infection, and rickets (all in 1 participant). The serious TEAEs in the PBO-MRX group were oedema peripheral and stoma site haemorrhage (both in 1 participant).

Conclusions

- In MARCH, some participants with prior SBD demonstrated improvements in pruritus following treatment with maralixibat that were durable with long-term treatment in MARCH-ON.
  - Reductions in sBA and bilirubin were observed but were less frequent.
- These data support a potential role of maralixibat as a treatment for patients with PFIC with a history of SBD.

Abbreviations

7αC4, 7α-hydroxy-4-cholesten-3-one; ABCB11, adenosine triphosphate binding cassette subfamily B member 11; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATP8B1, ATPase phospholipid transporting 8B1; BID, twice daily; BL, baseline; BSEP, bile salt export pump; CFB, change from Baseline; FIC1, familial intrahepatic cholestasis-associated protein 1; IBAT, ileal bile acid transporter; 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; SBD, surgical biliary diversion; t, truncated; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse evert; TJP2, tight junction protein 2; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Disclosures

LD'A is a consultant and advisor for Mirum Pharmaceuticals, Inc., Albireo, Selecta, Vivet Pharmaceuticals, Tome, Spark, Genespire, and Alexion. AGM is a consultant and has a sponsored research agreement with Mirum Pharmaceuticals, Inc. AAA is a consultant for Mirum Pharmaceuticals, Inc., Albireo, and Sarepta Therapeutics. SPH is a hepatic safety adjudication committee member at Albireo and has received a research grant from Mirum Pharmaceuticals, Inc. TN, AL, DBM, RA, and PV are employees of and shareholders in Mirum Pharmaceuticals, Inc. RJT is a consultant for Mirum Pharmaceuticals, Inc., Albireo, Generation Bio, Rectify Therapeutics, and Alnylam, and is a shareholder in Generation Bio and Rectify Therapeutics. PC, AM, and W-DH have nothing to disclose.

Acknowledgments

The authors would like to thank the clinical trial participants, their families, and 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 PRECISIONscientia in Yardley, Pennsylvania, USA, which was funded by Mirum Pharmaceuticals, Inc.

References

1. Kamath BM, et al. *Liver Int.* 2020;40:1812-1822. **2.** van Wessel DBE, et al. *Hepatology.* 2021;74:892-906. **3.** LIVMARLI® (maralixibat) [prescribing information]. Foster City, CA; Mirum Pharmaceuticals, Inc. Mar 2024. **4.** LIVMARLI® (maralixibat) [summary of product characteristics]. Amsterdam, Netherlands; Mirum Pharmaceuticals International B.V. Jan 2024. **5.** ClinicalTrials.gov identifier: NCT03905330. Updated December 11, 2023. Accessed March 18, 2024. https://clinicaltrials.gov/ct2/show/NCT03905330. **6.** Thompson RJ, et al. Presented at AASLD 2022. **7.** ClinicalTrials.gov identifier: NCT04185363. Updated October 5, 2023. Accessed March 13, 2024. https://www.clinicaltrials.gov/study/NCT04185363 **8.** Kamath BM, et al. *Hepatol Commun*. 2020;4:1012-1018.

Presented at the 56th Annual Meeting of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN); May 15-18, 2024; Milan, Italy