Maralixibat Leads to Improvements in Cholestatic Pruritus for Children With Progressive Familial Intrahepatic Cholestasis due to MDR3 Deficiency: Data From the MARCH/MARCH-ON Trials

Etienne Sokal,[1] Alexander G. Miethke,[2] Adib Moukarzel,[3] Gilda Porta,[4] Felipe Ordonez,[5] Antonella Mosca,[6] Ulrich Baumann,[7] Cigdem Arikan,[8] Chuan-Hao Lin,[9] Tiago Nunes,[10] Anamaria Lascau,[10] Douglas B. Mogul,[10] Raul Aguilar,[10] Pamela Vig,[10] Richard J. Thompson[11]

[1]UCLouvain, Cliniques Universitaires St Luc, Pediatric Hepatology, Brussels, Belgium; [2]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [3]Hôtel Dieu de France Saint Joseph University Hospital, Beirut, Lebanon; [4]Hospital Sírio-Libanês, São Paulo, Brazil; [5]Cardioinfantil Foundation-La Cardio, Bogotá, Colombia; [6]Ospedale Pediatrico Bambino Gesù Irccs, Lazio, Italy; [7]Hannover Medical School, Pediatric Gastroenterology and Hepatology, Hannover, Germany; [8]Koc University School of Medicine, Istanbul, Turkey; [9]Children's Hospital Los Angeles, Los Angeles, California, USA; [10]Mirum Pharmaceuticals, Inc., Foster City, California, USA; [11]Institute of Liver Studies, King's College London, London, United Kingdom

Introduction

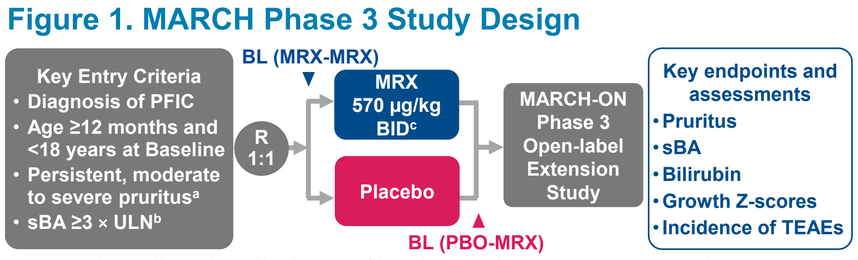
- Progressive familial intrahepatic cholestasis (PFIC) is a group of genetic disorders that result in disrupted bile composition and chronic cholestasis.[1]
  - Key clinical manifestations include debilitating pruritus, impaired growth, reduced quality of life, and progressive liver disease with an eventual need for liver transplantation.[1]
- The most common causes of PFIC are deficiencies in BSEP, FIC1, MDR3, TJP2, and MYO5B.[2]
- Unlike other PFIC types, MDR3 deficiency is characterised as a cholangiopathy in which affected patients have elevated GGT in addition to pruritus and elevated sBA.[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 cholestatic pruritus in patients with Alagille syndrome ≥2 months of age in the EU and ≥3 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, sBA levels, bilirubin, and growth.[7]
- MARCH-ON is an open-label, long-term extension study for participants who completed the MARCH study.[8]

Objective

- To report on the response to maralixibat in participants with PFIC with MDR3 deficiency in MARCH and MARCH-ON.

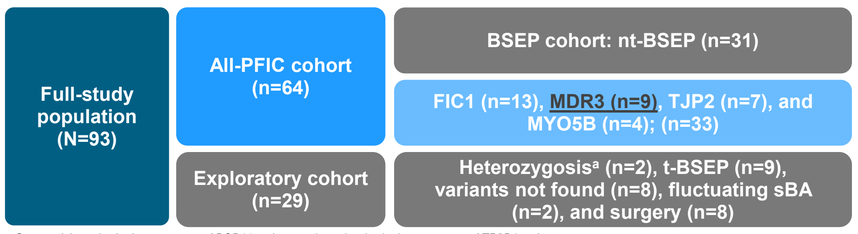
Methods

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) with up to 2 years of maralixibat treatment for key efficacy endpoints (pruritus, sBA, bilirubin, and GGT) were analysed for participants with MDR3 deficiency.
- 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)[9] in which a ≥1-point reduction is considered clinically meaningful.

Results

Table 1. Key Demographics and Baseline Characteristics

Variable[a]	MRX-MRX (n=4)	PBO-MRX (n=5)[b]
Age, y	6.0 (2, 10)	7.0 (4, 10)
Sex, male, %	50	40
Pruritus, ItchRO(Obs)	1.9 (1.0, 3.8)	2.0 (0.0, 3.8)
Total sBA, µmol/L	231 (74, 340)	260 (127, 354)
UDCA usage, %	75	100
Rifampicin usage, %	75	40
ALT, U/L	107 (83, 129)	99 (92, 147)
AST, U/L	124 (109, 192)	123 (109, 167)
7αC4, ng/mL	5.0 (1.3, 8.3)	BLQ <2.5
Platelets, 10^3/µL	264 (128, 268)	90 (65, 105)
GGT, U/L	341 (112, 708)	307 (274, 434)
Total bilirubin, µmol/L	50.9 (25.7, 157.3)	53.9 (37.6, 202.6)
Direct bilirubin, µmol/L	39.3 (17.1, 127.4)	35.9 (27.4, 153.0)
Height Z-score	-1.9 (-4.0, -1.7)	-1.5 (-2.8, 0.2)
Weight Z-score	-2.5 (-3.1, -2.1)	-1.1 (-2.7, 0.1)

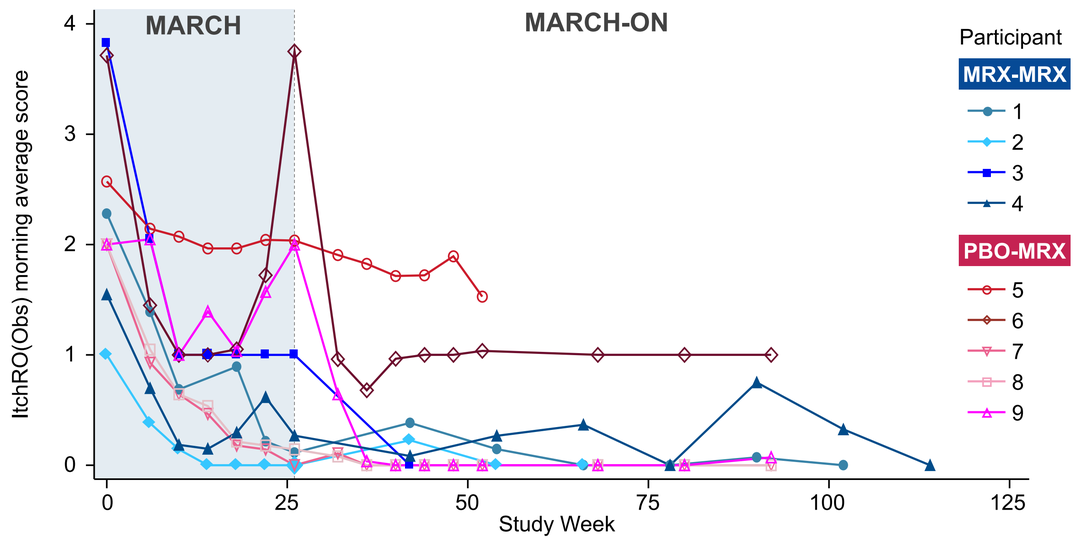
[a]All data are median (min, max) unless otherwise indicated. [b]PBO-MRX participants were rebaselined prior to starting MARCH-ON.

Results (cont'd)

- Four participants with MDR3 deficiency who received maralixibat in MARCH continued to receive maralixibat in MARCH-ON (MRX-MRX).
- Five participants with MDR3 deficiency who received placebo in MARCH initiated maralixibat in MARCH-ON (PBO-MRX).

All Participants Who Received Maralixibat Showed Improvements in Pruritus

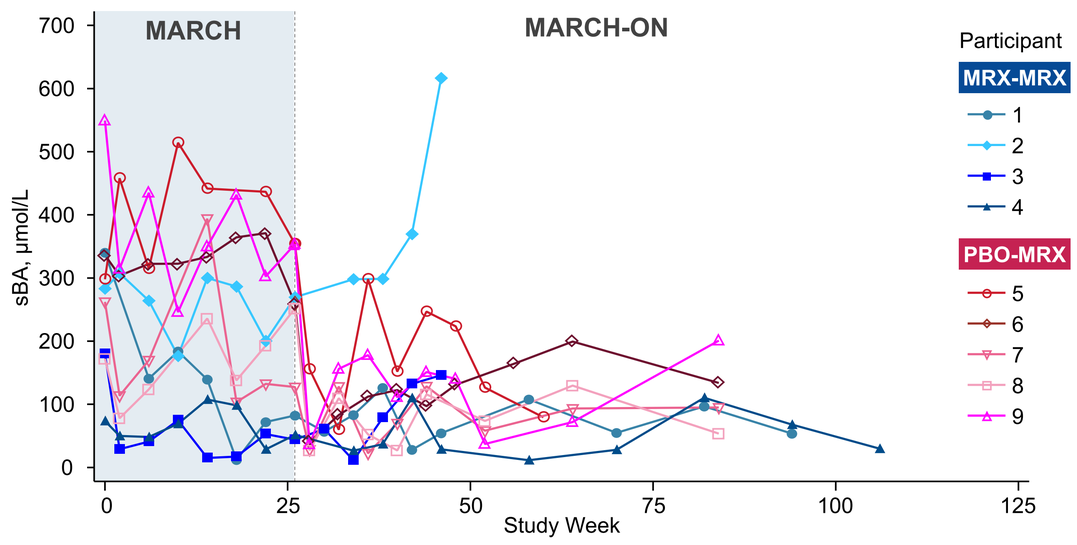
Figure 3. Average Pruritus (ItchRO[Obs]) Scores Over Time



- All participants who received maralixibat in MARCH had clinically meaningful reductions in pruritus (CFB median [min, max], -1.7 [-2.8, -1.0]) that were sustained to 102 weeks in MARCH-ON.
- Among participants who received placebo in MARCH, 3 had large reductions in pruritus, and 2 had modest reductions in pruritus. After receiving maralixibat in MARCH-ON, reductions in pruritus were either sustained or improved further.

Most Participants Who Received Maralixibat Showed Improvements in sBA

Figure 4. sBA Over Time



- Participants who received maralixibat in MARCH had clinically meaningful reductions in sBA (CFB median [min, max], -118 [-285, -14] µmol/L) that were sustained to 102 weeks in MARCH-ON.
- Participants who received placebo in MARCH had variable sBA response, but upon receiving maralixibat in MARCH-ON demonstrated clinically meaningful reductions in sBA (CFB median [min, max], -147 [-244, -34] µmol/L) out to 52 weeks.

Table 2. CFB in Pruritus and sBA

Participant	Treatment group	CFB in pruritus ItchRO(Obs) score[a]		CFB in sBA, µmol/L[b]	
		MARCH	MARCH-ON	MARCH	MARCH-ON
1	MRX-MRX	-1.9	-2.3	-285	-286
2	MRX-MRX	-1.0	-1.0	-31	333
3	MRX-MRX	-2.8	-3.8	-142	-34
4	MRX-MRX	-1.2	-1.6	-14	-44
5	PBO-MRX	-0.6	-0.5	97	-275
6	PBO-MRX	-1.5	-2.8	-5	-126
7	PBO-MRX	-1.9	0.0	-141	-32
8	PBO-MRX	-1.8	0.0	22	-198
9	PBO-MRX	-0.5	-1.9	-187	-153

[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.

Additional Laboratory Parameters

- Participants who received maralixibat in MARCH had reductions in total bilirubin (CFB median [min, max], -12.0 [-17.1, -4.3]) that were sustained out to 102 weeks in MARCH-ON.
- No consistent reductions in total and direct bilirubin were observed in participants who received placebo in MARCH or upon initiation of maralixibat in MARCH-ON.
- No consistent reductions in GGT were observed in either the MRX-MRX group or the PBO-MRX group.

Safety Signals Were Consistent With Other PFIC Types

Table 3. Summary of TEAEs

TEAE, n (%)[a]	MRX-MRX (n=4)	PBO-MRX (n=5)
Any TEAE	4 (100.0)	5 (100.0)
Severe TEAE[b]	0	1 (20.0)
Serious TEAE[c]	0	1 (20.0)
TEAE leading to discontinuation[d]	1 (25.0)	0
TRAE leading to death	0	0
Clinically relevant TEAEs		
Diarrhoea	2 (50.0)	0
Abdominal pain	3 (75.0)	1 (20.0)

[a]Number indicates the number of participants experiencing an event. [b]The severe TEAE was blood bilirubin increased (1 participant). [c]The serious TEAE was esophageal varices haemorrhage and haematoma (both in 1 participant). [d]The TEAE leading to discontinuation was alanine aminotransferase increased and blood bilirubin increased (both in 1 participant)

Conclusions

- In MARCH/MARCH-ON, treatment with maralixibat in participants with MDR3 deficiency resulted in improvements in pruritus and sBA that were sustained for up to 2 years.
- These data support the efficacy and tolerability of maralixibat across a broad range of PFIC types.

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; BLQ, below the limit of quantification; BSEP, bile salt export pump; CFB, change from Baseline; FIC1, familial intrahepatic cholestasis-associated protein 1; GGT, gamma-glutamyl transferase; 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; t, truncated; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; TJP2, tight junction protein 2; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Disclosures

ES is the founder and chairman of Cellaïon; an investigator for Mirum Pharmaceuticals, Inc., Albireo, and Intercept; and an advisor for Mirum Pharmaceuticals, Inc., and Albireo. AGM is a consultant and has a sponsored research agreement with Mirum Pharmaceuticals, Inc. FO is a speaker for Alexion Pharmaceuticals and Valentech Pharma. UB is a consultant for Mirum Pharmaceuticals, Inc., Albireo, and Vivet Pharmaceuticals. 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. A Moukarzel, GP, A Mosca, CA, and C-HL have nothing to disclose.

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