Maralixibat Improves Growth in Patients With Progressive Familial Intrahepatic Cholestasis: Data From the MARCH/MARCH-ON Trials

Poster THU-129

Regino P. Gonzalez-Peralta,[1] Alexander G. Miethke,[2] Amal A. Aqul,[3] Douglas B. Mogul,[4] Tiago Nunes,[4] Will Garner,[4] Pamela Vig,[4] Richard J. Thompson[5]

[1]Pediatric Gastroenterology, Hepatology, and Liver Transplant, AdventHealth for Children and AdventHealth Transplant Institute, Orlando, Florida, USA; [2]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [3]University of Texas Southwestern Medical Center, Dallas, Texas, USA; [4]Mirum Pharmaceuticals, Inc., Foster City, California, USA; [5]Institute of Liver Studies, King's College London, London, United Kingdom

Introduction

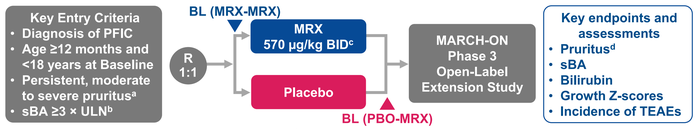
- Progressive familial intrahepatic cholestasis (PFIC) is a group of genetic disorders that result in disrupted bile composition and chronic cholestasis.[1]
  - Key clinical manifestations include debilitating pruritus, impaired growth, reduced quality of life, and progressive liver disease with an eventual need for liver transplantation.[1]
- 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.[2]
- In a phase 2 study of maralixibat in participants with PFIC (INDIGO), those with bile salt export pump (BSEP) deficiency who were sBA responders showed significant improvements in growth with >5 years of maralixibat treatment compared with non-responders.[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 and with a higher dose than with INDIGO.[3,5-6]
  - In MARCH, participants who received maralixibat achieved statistically significant improvements in pruritus, levels of sBAs, bilirubin, and growth.[6]
- 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.[7,8]

Objective

- To report on the long-term impact of maralixibat on improvements in growth across a variety of PFIC types from the MARCH/MARCH-ON trials.

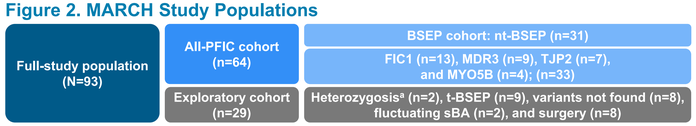
Methods

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 0-4 scale, where 0 = no itch, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.[9] A ≥1-point reduction in ItchRO(Obs) is considered clinically meaningful.

Figure 2. MARCH Study Populations



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

- Height and weight Z-scores based on a participant's sex and age at each scheduled trial visit were analysed.
- Data for MARCH and MARCH-ON are presented. For MARCH-ON, data were combined for participants who received maralixibat during MARCH and continued into MARCH-ON (MRX-MRX) and participants who received placebo (PBO) in MARCH and initiated maralixibat in MARCH-ON (PBO-MRX).
- Baseline was defined as last assessment before the start of maralixibat treatment for each group.

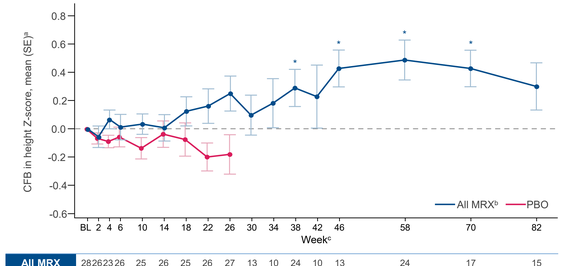
Results

- Sixty participants from the All-PFIC cohort in MARCH-ON were analysed including PFIC types FIC1 (n=13), nt-BSEP (n=28), MDR3 (n=9), TJP2 (n=7), and MYO5B (n=3).
- Baseline characteristics (eg, age, sBA, pruritus, and liver biochemistries) were well-balanced between groups.
- Growth (mean [SE]) for the overall PFIC study population was stunted at Baseline (height Z-score -2.11 [0.17]; weight Z-score -1.50 [0.17]).

Results (cont'd)

Significant Improvements in Height Z-Score Were Maintained for >2 Years of Continuous Treatment With Maralixibat

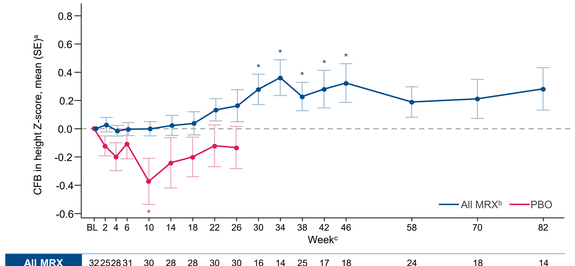
Figure 3. Mean Change in Height Z-Score Over Time in the BSEP Cohort



	BL	2	4	6	10	14	18	22	26	30	34	38	42	46	58	70	82
All MRX	28	26	23	26	25	26	25	26	27	13	10	24	10	13	24	17	15
PBO[d]	17	17	17	16	16	15	13	14	15								

[a]Two-tailed *P* value for Student's t test: * ≤0.05. [b]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively. [c]Results up to Week 82 are shown. [d]Baseline is from MARCH.

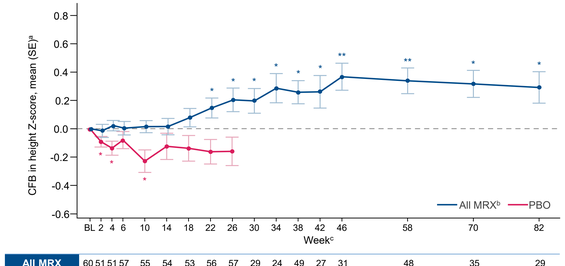
Figure 4. Mean Change in Height Z-Score Over Time in the FIC1, MDR3, TJP2, MYO5B Cohort



	BL	2	4	6	10	14	18	22	26	30	34	38	42	46	58	70	82
All MRX	32	25	28	31	30	28	28	30	30	16	14	25	17	18	24	18	14
PBO[d]	14	13	13	13	10	11	13	13	13								

[a]Two-tailed *P* value for Student's t test: * ≤0.05. [b]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively. [c]Results up to Week 82 are shown. [d]Baseline is from MARCH.

Figure 5. Mean Change in Height Z-Score Over Time in the All-PFIC Cohort



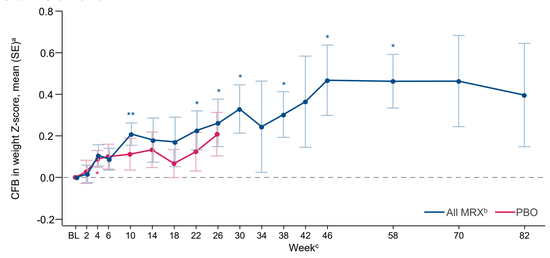
	BL	2	4	6	10	14	18	22	26	30	34	38	42	46	58	70	82
All MRX	60	51	51	57	55	54	53	56	57	29	24	49	27	31	48	35	29
PBO[d]	31	30	30	29	26	26	26	27	28								

[a]Two-tailed *P* value for Student's t test: * ≤0.05, ** ≤0.001. [b]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively. [c]Results up to Week 82 are shown. [d]Baseline is from MARCH.

- For participants who received maralixibat, improvements in height Z-score were observed at 26 weeks of therapy in BSEP (mean CFB [SE] +0.25 [0.12]; *P*=0.054), FIC1, MDR3, TJP2, MYO5B (+0.16 [0.11]; *P*=0.16), and All-PFIC (+0.21 [0.08]; *P*=0.017) participants, which continued through 82 weeks; there were no changes in height for participants who received placebo.
- In participants who received placebo in MARCH and received maralixibat in MARCH-ON for up to 1 year, comparable significant improvements were observed in height Z-score (+0.37 [0.13]; *P*=0.012).

Significant Improvements in Weight Z-Score Were Maintained for >2 Years of Continuous Treatment With Maralixibat

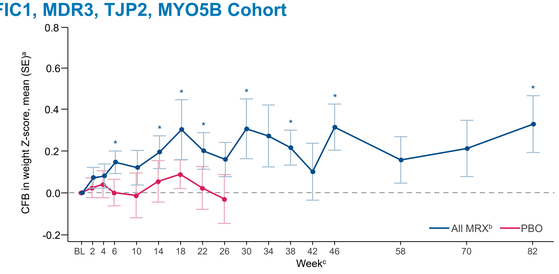
Figure 6. Mean Change in Weight Z-Score Over Time in the BSEP Cohort



	BL	2	4	6	10	14	18	22	26	30	34	38	42	46	58	70	82
All MRX	28	26	23	26	25	26	25	26	27	13	10	24	10	13	24	17	15
PBO[d]	17	17	17	16	16	15	13	14	15								

[a]Two-tailed *P* value for Student's t test: * ≤0.05, ** ≤0.001. [b]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively. [c]Results up to Week 82 are shown. [d]Baseline is from MARCH.

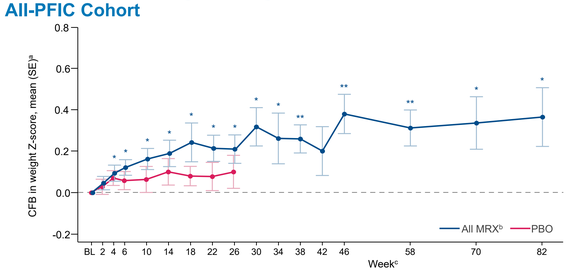
Figure 7. Mean Change in Weight Z-Score Over Time in the FIC1, MDR3, TJP2, MYO5B Cohort



	BL	2	4	6	10	14	18	22	26	30	34	38	42	46	58	70	82
All MRX	32	25	28	31	30	31	29	31	30	16	14	26	17	18	24	18	14
PBO[d]	14	14	13	13	11	12	13	13	13								

[a]Two-tailed *P* value for Student's t test: * ≤0.05. [b]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively. [c]Results up to Week 82 are shown. [d]Baseline is from MARCH.

Figure 8. Mean Change in Weight Z-Score Over Time in the All-PFIC Cohort



	BL	2	4	6	10	14	18	22	26	30	34	38	42	46	58	70	82
All MRX	60	51	51	57	55	57	54	53	56	57	29	24	50	27	31	48	35	29
PBO[d]	31	31	30	29	27	27	26	27	28									

[a]Two-tailed *P* value for Student's t test: * ≤0.05, ** ≤0.001. [b]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively. [c]Results up to Week 82 are shown. [d]Baseline is from MARCH.

- For participants who received maralixibat, the improvements in weight Z-scores that have been previously reported at 26 weeks for BSEP (+0.26 [0.11]; *P*=0.03), FIC1, MDR3, TJP2, MYO5B (+0.16 [0.08]; *P*=0.06), and All-PFIC (+0.21 [0.07]; *P*=0.0038) continued to 82 weeks for the participants.
- In participants who received placebo in MARCH and received maralixibat in MARCH-ON for up to 1 year, comparable significant improvements were observed in weight Z-score (+0.32 [0.13]; *P*=0.03).

Conclusions

- Participants treated with maralixibat had statistically significant increase in height Z-scores following 26 weeks of therapy with improvements observed out to 82 weeks.
- Previous reported increase in weight Z-scores following 26 weeks of treatment with maralixibat persisted through 82 weeks.
- Improvements in growth were seen across all types of PFIC.
- These consistent trends in growth for participants who received maralixibat indicate a potential disease-modifying effect of maralixibat treatment in PFIC.

Abbreviations

ABCB11, adenosine triphosphate binding cassette subfamily B member 11; 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; 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; SE, standard error; t, truncated; TEAE, treatment-emergent adverse event; TJP2, tight junction protein 2; ULN, upper limit of normal.

Disclosures

RPG-P has received a research grant from Mirum Pharmaceuticals, Inc., and is an advisor, teacher, and educator for Mirum Pharmaceuticals, Inc., and Albireo. 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. DBM, TN, WG, 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.

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 Precision AQ in Yardley, Pennsylvania, USA, which was funded by Mirum Pharmaceuticals, Inc.

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Presented at European Association for the Study of the Liver (EASL) Congress; 5-8 June 2024; Milan, Italy