Improvements in Serum Bile Acid Levels Are Associated With Improvements in Key Markers of Liver Health After Maralixibat Treatment in Children With Progressive Familial Intrahepatic Cholestasis: Data From the MARCH/MARCH-ON Trials

Poster THU-158

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Introduction

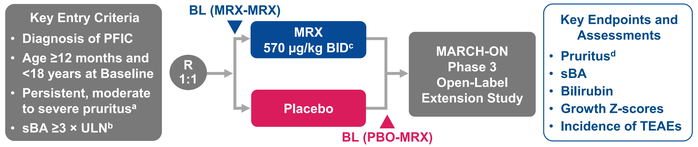
- Progressive familial intrahepatic cholestasis (PFIC) is a group of genetic disorders that result in disrupted bile composition and chronic cholestasis.[1]
  - Key clinical manifestations include debilitating pruritus, impaired growth, reduced quality of life, and progressive liver disease with an eventual need for liver transplantation.[1]
- 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]
- Reductions in sBA and bilirubin are predictors of longer native liver survival in patients with PFIC who have had surgical biliary diversion to interrupt enterohepatic circulation.[3,4]
- 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.[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 sBAs, 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]

Objective

- To report on the impact of maralixibat on liver health using a sub-analysis of the correlations between sBA improvements and key liver parameters, including bilirubin, from the MARCH/MARCH-ON trials.

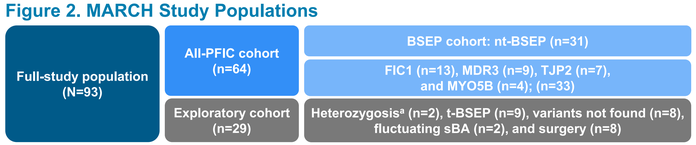
Methods

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.[10] 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.

- Spearman's (r) coefficients were determined to evaluate the relationship between sBA and key liver health parameters (AST, ALT, total bilirubin, and direct bilirubin).

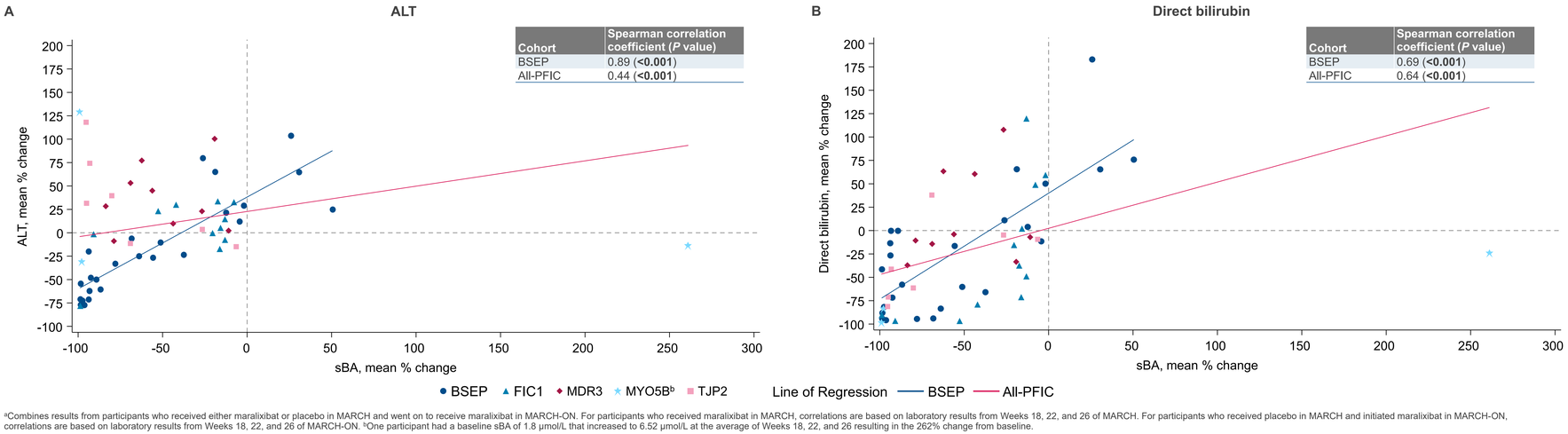
Results

- Sixty-four participants from the All-PFIC cohort were analysed including PFIC types FIC1 (n=13), nt-BSEP (n=31), MDR3 (n=9), TJP2 (n=7), and MYO5B (n=4).
- Mean Baseline age, sBA, pruritus, and liver parameters were well balanced between maralixibat and placebo groups.

Results (cont'd)

Reductions in sBA After Maralixibat Treatment Were Significantly Correlated With Reductions in ALT and Direct Bilirubin

Figure 3. Average Percentage Change From Baseline in sBA and (A) ALT or (B) Direct Bilirubin[a]



[a]Combines results from participants who received either maralixibat or placebo in MARCH and went on to receive maralixibat in MARCH-ON. For participants who received maralixibat in MARCH, correlations are based on laboratory results from Weeks 18, 22, and 26 of MARCH. For participants who received placebo in MARCH and initiated maralixibat in MARCH-ON, correlations are based on laboratory results from Weeks 18, 22, and 26 of MARCH-ON. [b]One participant had a baseline sBA of 1.8 µmol/L that increased to 6.52 µmol/L at the average of Weeks 18, 22, and 26 resulting in the 262% change from baseline.

Significant Correlations Were Observed Between Reductions in sBA and Key Liver Parameters After Treatment With Maralixibat

Table 1. Correlation of sBA with Key Liver Parameters[a]

	Placebo[b]							All MRX[c,d]						
Population	ALT	AST	Total bilirubin	Direct bilirubin	GGT	FGF19	7αC4	ALT	AST	Total bilirubin	Direct bilirubin	GGT	FGF19	7αC4
All-PFIC	0.094 (0.63)	0.25 (0.20)	0.13 (0.51)	0.11 (0.58)	0.027 (0.89)	-0.14 (0.49)	-0.15 (0.46)	0.44 (**<0.001**)	0.62 (**<0.001**)	0.56 (**<0.001**)	0.64 (**<0.001**)	0.13 (0.34)	0.38 (**0.012**)	-0.79 (**<0.001**)
BSEP	-0.032 (0.91)	0.27 (0.33)	0.19 (0.51)	0.16 (0.57)	0.19 (0.49)	0.081 (0.78)	-0.060 (0.84)	0.89 (**<0.001**)	0.83 (**<0.001**)	0.58 (**0.0025**)	0.69 (**<0.001**)	0.60 (**0.0017**)	0.30 (0.21)	-0.88 (**<0.001**)
FIC1, TJP2, MYO5B	0.41 (0.32)	0.45 (0.26)	0.31 (0.46)	0.38 (0.35)	-0.26 (0.53)	-0.41 (0.32)	-0.43 (0.29)	-0.10 (0.65)	0.26 (0.25)	0.64 (**0.0013**)	0.74 (**<0.001**)	-0.31 (0.17)	0.41 (0.11)	-0.72 (**0.0012**)
MDR3	0.20 (0.75)	-0.30 (0.62)	-0.70 (0.19)	-0.70 (0.19)	-0.20 (0.75)	-0.70 (0.19)	NA	0.02 (0.97)	0.00 (1.00)	0.27 (0.49)	0.35 (0.36)	-0.083 (0.83)	0.050 (0.90)	-0.090 (0.85)

[a]All values are Spearman correlation coefficient (*P* value). [b]Results are from MARCH. [c]Combines results from participants who received either maralixibat or placebo in MARCH and went on to receive maralixibat in MARCH-ON. For participants who received maralixibat in MARCH, correlations are based on laboratory results from Weeks 18, 22, and 26 of MARCH. For participants who received placebo in MARCH and initiated maralixibat in MARCH-ON, correlations are based on laboratory results from Weeks 18, 22, and 26 of MARCH-ON. [d]Includes participants from the All-PFIC (n=60), BSEP (n=28), FIC1, TJP2, MYO5B (n=23), and MDR3 (n=9) cohorts.

- In patients who received maralixibat, reductions in sBA were associated with reductions in ALT, AST, total bilirubin, direct bilirubin and FGF19, and with increases in 7αC4. These correlations were largely observed in different PFIC types.
- In participants who received placebo, there was no correlation between changes in sBA and biomarkers of disease.

Conclusions

- Reductions in sBA after maralixibat treatment, as anticipated by the drug's mechanism of action, are correlated with reductions in biomarkers of liver disease which have been associated with long-term clinical outcomes, such as bilirubin, in all PFIC types except for MDR3 disease.
- These results demonstrate the potential for maralixibat to have disease-modifying effects in the treatment of PFIC.

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; FGF19, fibroblast growth factor 19; 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; NA, not applicable; NS, not significant; nt, nontruncated; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; R, randomised; sBA, serum bile acid; t, truncated; TEAE, treatment-emergent adverse event; TJP2, tight junction protein 2; 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. SPH is a hepatic safety adjudication committee member at Albireo and has received a research grant from Mirum Pharmaceuticals, Inc. 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.

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