The Relationship Between Serum Bile Acids and Event-Free Survival Following the Use of Maralixibat for Progressive Familial Intrahepatic Cholestasis: Data From MARCH/MARCH-ON

Poster 4432

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Introduction

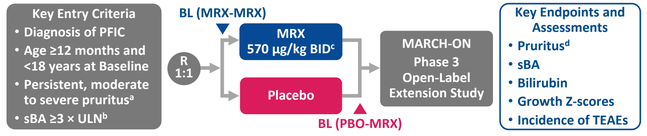
- Progressive familial intrahepatic cholestasis (PFIC) is a group of genetic disorders that result in disrupted bile composition and chronic cholestasis.[1]
  - Key clinical manifestations include debilitating pruritus, impaired growth, reduced quality of life, and progressive liver disease with an eventual need for liver transplantation.[1]
- 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 PFIC ≥12 months of age in the US and for the treatment of PFIC in patients ≥3 months of age in the EU.[2,3]
- Improved event-free survival (EFS) has been previously demonstrated following treatment with maralixibat in patients with Alagille syndrome.[4]
  - Improvement in EFS was associated with reductions in sBA levels.[5]
- MARCH (NCT03905330) was a phase 3, randomized, 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 and bilirubin, and growth.[6]
  - Significant and sustained responses were observed with up to 2 years of maralixibat treatment in MARCH-ON (NCT04185363), an open-label extension study for participants who completed the MARCH study.[8,9]

Objective

- To report on the impact of sBA reduction on EFS in participants with PFIC 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.[10] A ≥1-point reduction in ItchRO(Obs) is considered clinically meaningful.

EFS was defined as the absence of manifestations of first events. First events were defined as liver transplant, decompensation, surgical biliary diversion (SBD), or death.[4]

- First events were identified for participants with different PFIC types who received maralixibat in MARCH or MARCH-ON.
- Two-year EFS was calculated for the overall cohort and further stratified by sBA response at Week 26 (averaged over last 12 weeks) for BSEP and FIC1 cohorts, using thresholds developed by the NAPPED Consortium (BSEP: >75% reduction from Baseline or concentrations <102 µmol/L; FIC1: concentrations <65 µmol/L).[11,12]
- Data were administratively censored in June 2023.

Results

Table 1. Key Demographics and Baseline Characteristics

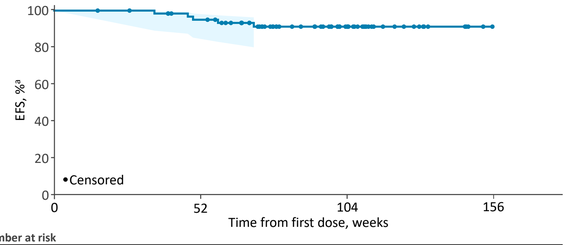
Parameter[a]	BSEP cohort[b]		BSEP+FIC1 cohort[b]		All-PFIC+No Variants cohort[c] (N=72)
	sBA responder (n=12)	sBA nonresponder (n=17)	sBA responder (n=16)	sBA nonresponder (n=26)	
Age, y	6 (3, 11)	3 (3, 7)	7 (3, 11)	3 (1, 4)	4 (2, 8)
Sex, male, %	33	41	38	54	44
Pruritus, ItchRO(Obs) score	2.7 (1.5, 3.9)	2.9 (1.8, 3.6)	2.8 (1.8, 3.9)	2.9 (1.9, 3.6)	2.9 (1.9, 3.6)
CSS score	3 (2, 3)	2 (2, 3)	3 (2, 3)	2 (2, 3)	3 (2, 3)
sBA, µmol/L	247 (53, 386)	376 (244, 455)	175 (39, 359)	286 (202, 413)	217 (112, 354)
Total bilirubin, mg/dL	1.5 (0.5, 3.8)	2.6 (0.9, 3.5)	1.8 (0.5, 4.2)	3.4 (1.9, 9.0)	2.6 (1.1, 5.0)
Direct bilirubin, mg/dL	1.0 (0.2, 2.4)	2.0 (0.5, 2.4)	1.2 (0.2, 2.8)	2.5 (1.3, 6.7)	2.0 (0.7, 3.6)
Height Z-score	-1.0 (-1.6, 0.0)	-1.2 (-1.8, -0.8)	-1.0 (-1.7, 0.0)	-1.4 (-2.5, -0.9)	-1.2 (-2.0, -0.6)
Weight Z-score	-1.9 (-3.0, -1.3)	-1.9 (-2.5, -1.2)	-1.7 (-3.0, -1.0)	-2.4 (-3.6, -1.5)	-1.9 (-2.9, -1.2)

[a]All data are median (Q1, Q3) unless otherwise indicated. [b]Two BSEP participants and 1 FIC1 participant had missing baseline sBA data and thus could not be classified. [c]All-PFIC included BSEP, FIC1, MDR3, MYO5B, and TJP2. Did not include heterozygous, surgery, or t-BSEP participants.

- The median (Q1, Q3) follow-up time was 94 (68, 110) weeks.

92% EFS for Maralixibat-treated Participants in the All-PFIC+No Variants Cohort

Figure 2. Kaplan-Meier Estimates of EFS in the All-PFIC+No Variants Cohort (N=72)



Number at risk

All-PFIC+ No Variants	72	64	25	0

sBA Responders Had an EFS of 100% and sBA Nonresponders Had an EFS of 81% in the Combined BSEP+FIC1 Cohort

Table 2. EFS and Events Observed in the BSEP and FIC1 Cohorts by sBA Response[a]

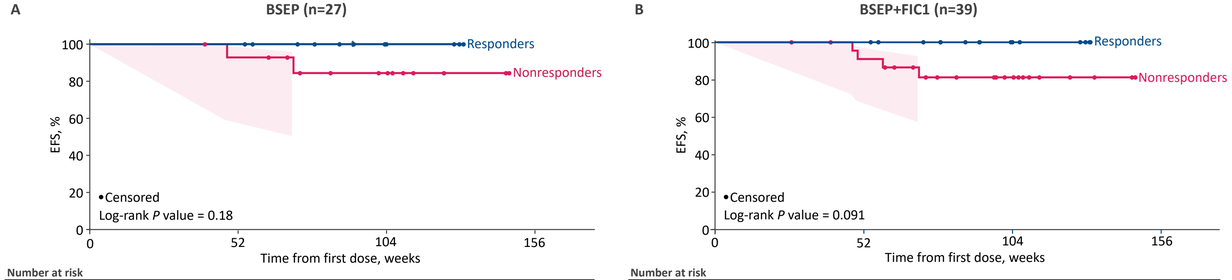
Parameter	BSEP (n=27)		FIC1 (n=12)	
	sBA responder (n=12; 44%)	sBA nonresponder (n=15; 56%)[b]	sBA responder (n=3; 25%)	sBA nonresponder (n=9; 75%)[c]
EFS, %	100	84	100	78
Any event	0	2	0	2
Transplant	0	1	0	0
Decompensation	0	1	0	0
SBD	0	0	0	1
Death	0	0	0	1

[a]sBA response was defined as >75% reduction from baseline or concentrations <102 µmol/L in the BSEP cohort and concentrations <65 µmol/L in the FIC1 cohort.[11,12] [b]The 2 participants who had events had sBA reductions of 19% and 26%, respectively. [c]The 2 participants who had events had sBA reductions of 18% and 16%, respectively.

- One participant in the MDR3 cohort with sBA reduction of 44% required a transplant.

Higher EFS Was Observed Among sBA Responders Compared With Nonresponders

Figure 3. Kaplan-Meier Estimates of EFS in the (A) BSEP Cohort and (B) BSEP+FIC1 Cohort by sBA Response[a,b]



Number at risk

Responders	12	12	3	0
Nonresponders	15	13	7	0

Number at risk

Responders	15	15	5	0
Nonresponders	24	20	9	0

[a]sBA response was defined as >75% reduction from baseline or concentrations <102 µmol/L in the BSEP cohort and concentrations <65 µmol/L in the FIC1 cohort.[11,12] [b]Dashed vertical line denotes administratively censored date.

Conclusions

- Results from this analysis demonstrate a high overall EFS in participants with PFIC who received maralixibat in MARCH/MARCH-ON clinical trials.
- Consistent with NAPPED sBA response thresholds associated with EFS, participants who achieved reduction in sBA levels below the threshold (responders) did not have clinically meaningful events, whereas some individuals who had lower reductions in sBA (nonresponders) experienced events.
- These data support the importance of sBA reduction in PFIC and the potential of maralixibat to facilitate this biochemical change and improve EFS in patients with PFIC.
- While these results are promising, additional time is needed to assess longer-term outcomes.

Abbreviations

BID, twice daily; BL, Baseline; BSEP, bile salt export pump; CSS, clinical scratch scale; EFS, event-free survival; FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer); MDR3, multidrug resistance protein 3; MRX, maralixibat; MYO5B, myosin Vb; NAPPED, NAtural course and Prognosis of PFIC and Effect of biliary Diversion; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; R, randomized; sBA, serum bile acid; SBD, surgical biliary diversion; t, truncated; 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, 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. SPH is a hepatic safety adjudication committee (HSAC) 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. AGM is a consultant and has a sponsored research agreement for Mirum Pharmaceuticals, Inc.

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