Maralixibat Leads to Significant Improvements in Cholestatic Pruritus for Children With Progressive Familial Intrahepatic Cholestasis Without a Genetic Diagnosis: Data From the MARCH-PFIC Trial

Poster 4605-C

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Introduction

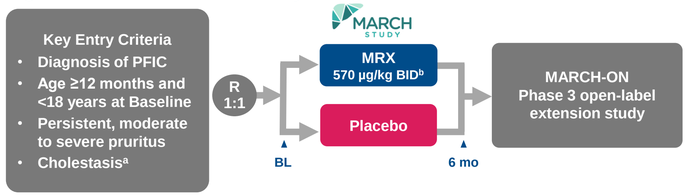
- Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of genetic disorders that result in disrupted bile composition and chronic cholestasis.[1,2]
  - Key clinical manifestations include debilitating cholestatic pruritus, impaired growth, and progressive liver disease and failure.[1,2]
- PFIC types include deficiencies of bile salt export pump (BSEP), familial intrahepatic cholestasis-associated protein 1 (FIC1), multidrug resistance protein 3 (MDR3), tight junction protein 2 (TJP2), and myosin Vb (MYO5B), as well as new genetic variants continue to be discovered. However, some individuals with the PFIC phenotype lack an identifiable genetic cause.[1,2]
- 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 ≥3 months of age in the US and ≥2 months of age in the EU.[3,4]
- A 26-week, randomized, phase 3 clinical trial (MARCH) evaluated the efficacy and safety of maralixibat for the treatment of participants with PFIC.[5]
  - MARCH is the largest and most genetically diverse trial of PFIC to date, enrolling participants with deficiencies in BSEP, FIC1, MDR3, TJP2, and MYO5B, as well as those with PFIC without a genetic diagnosis.[6,7]
  - The trial achieved its primary endpoint of reduced cholestatic pruritus, secondary endpoint of reduced sBA, as well as exploratory endpoint of improved bilirubin in participants with BSEP deficiency and a genetic diagnosis of PFIC (All-PFIC cohort).[6]

Objective

- To report MARCH efficacy and safety data for participants without an identified genetic cause of PFIC.

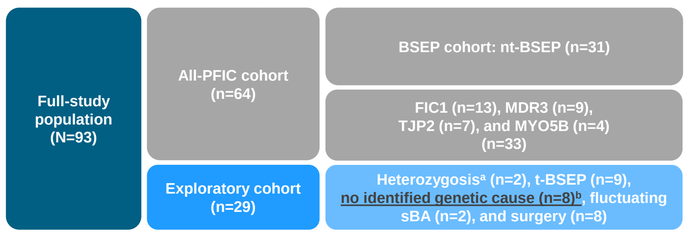
Methods

Figure 1. MARCH Phase 3 Study Design



[a]sBA ≥3 × ULN was criteria for the primary BSEP cohort only. [b]Maralixibat 570 µg/kg is equivalent to 600 µg/kg maralixibat chloride.

Figure 2. MARCH Study Populations



[a]One subject had a heterozygous *ABCB11* variant, and another had a heterozygous *ATP8B1* variant.
[b]Participants underwent standard genotype testing for PFIC variants prior to randomization. Participants were included in this cohort if no identified genetic cause was determined but they had a documented clinical diagnosis of PFIC.

- A mixed effects model of repeated measurements was used to analyze key efficacy endpoints (pruritus, sBA, and bilirubin) for participants with no identified genetic cause.

Results

Table 1. Key Demographics and Baseline Characteristics (N=8)

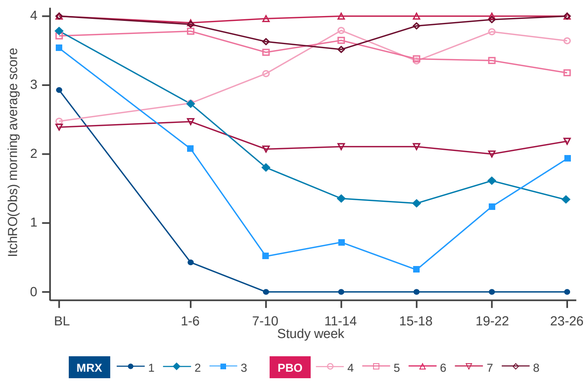
Variable	MRX (n=3)	PBO (n=5)
Age, y	5.3	4.2
Sex, male, %	33.3	40.0
Pruritus, ItchRO(Obs)	3.4	3.3
Total sBA, µmol/L	140	129
UDCA usage, %	33.3	60.0
Rifampicin usage, %	33.3	60.0
ALT, U/L	72	89
Total bilirubin, mg/dL	2.8	1.6
Direct bilirubin, mg/dL	2.1	1.1
Height Z-score	-1.1	-1.6
Weight Z-score	-1.2	-1.0

All data are mean unless otherwise indicated.

- 8 participants with PFIC but with no identified genetic cause were randomized to receive maralixibat (n=3) or placebo (n=5).
- Participants in the maralixibat and placebo groups were well balanced with respect to Baseline pruritus score (3.4 vs 3.3 on 0-4 ItchRO[Obs] score) and sBA (140 vs 129 µmol/L).

Significant Improvements in Pruritus Were Observed in the Maralixibat Group

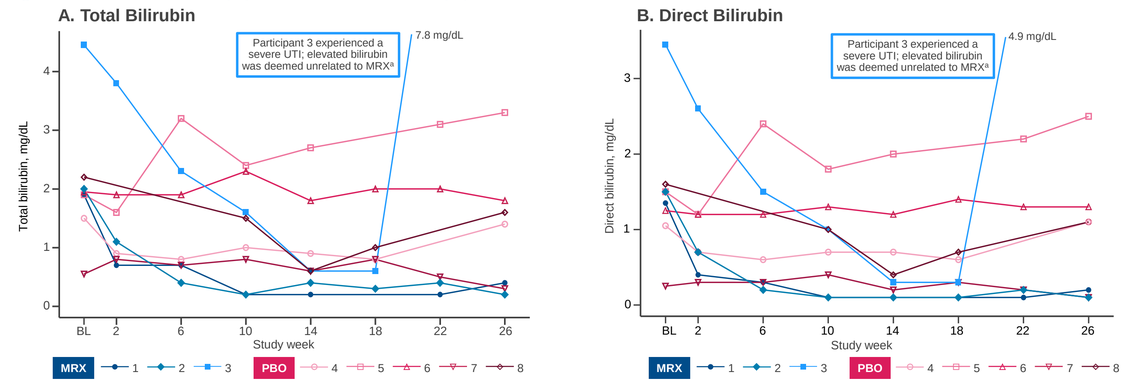
Figure 3. Weekly Average Pruritus Score (ItchRO[Obs]) Over Time



- The mean percentage of assessments with severity scores of 0 (none) or 1 (mild) was greater in the maralixibat group (66.8%) versus the placebo group (0.4%; *P*=0.0007).

Decreases in Total and Direct Bilirubin Were Observed in the Maralixibat Group

Figure 4. Total Bilirubin (A) and Direct Bilirubin (B) Levels Over Time



[a]Participant 3 continued on maralixibat through MARCH-ON; at Week 46, their total and direct bilirubin were 1.3 mg/dL and 0.9 mg/dL, respectively.

Reductions in sBA Were Consistently Observed in the Maralixibat Group

Figure 5. Mean sBA Over Time

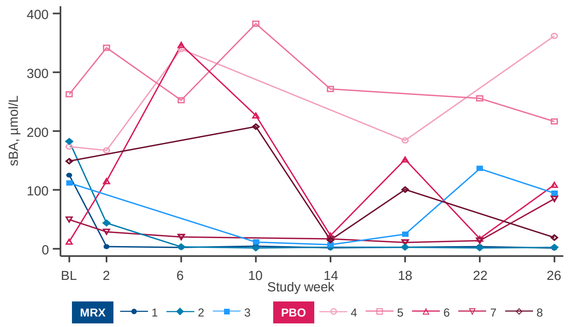


Table 2. Summary of TEAEs

TEAE, n (%)	MRX (n=3)	PBO (n=5)
Any TEAE	3 (100.0)	5 (100.0)
Severe TEAE	1 (33.3)	0
Serious TEAE	1 (33.3)[a]	0
TEAE leading to discontinuation	0	0
TEAE leading to death	0	0
Clinically relevant TEAEs		
Diarrhea	2 (66.7)[b]	2 (40.0)
ALT increased	1 (33.3)	0

[a]One serious TEAE (UTI, unrelated) was reported in the maralixibat group.
[b]All cases of diarrhea were mild in severity.

- Diarrhea was mild in severity and transient in nature with a median duration of 5 days, similar to the BSEP cohort.
- There were no clinically meaningful changes in ALT levels for participants who received maralixibat or placebo.

Conclusions

- We provide the first evidence, to our knowledge, of efficacy and safety with IBAT inhibition in patients with PFIC without an identified genetic cause.
- Maralixibat was associated with improvements in pruritus, sBA levels, total bilirubin, and direct bilirubin levels compared with placebo.
- Maralixibat was well tolerated, with the most common TEAE being diarrhea that was mild in severity.

Abbreviations

ALT, alanine aminotransferase; BID, twice daily; BL, baseline; BSEP, bile salt export pump; 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, randomized; sBA, serum bile acid; t, truncated; TEAE, treatment-emergent adverse event; TJP2, tight junction protein 2; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; UTI, urinary tract infection.

Disclosures

SPH is a Hepatic Safety Adjudication Committee (HSAC) member at Albireo and has received a research grant from Mirum Pharmaceuticals, Inc. AGM is a consultant and has a sponsored research agreement for Mirum Pharmaceuticals, Inc. NM is an investigator for Mirum Pharmaceuticals, Inc. UE is a steering committee member for Mirum Pharmaceuticals, Inc. NK is a consultant for Mirum Pharmaceuticals, Inc. DBM, TN, 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 a shareholder in Generation Bio and Rectify Therapeutics. AM and SMG have nothing to disclose.

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