Improvements in Pruritus With Maralixibat Are Associated With Improved Quality of Life for Patients With Progressive Familial Intrahepatic Cholestasis: Data From the March-PFIC Trial

Poster 4602-C

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Introduction

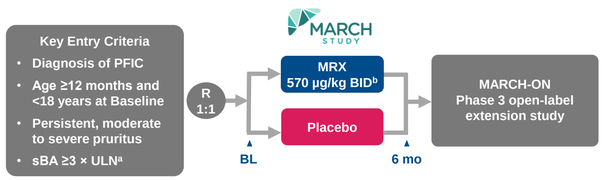
- Progressive familial intrahepatic cholestasis (PFIC) is a group of genetic disorders that result in disrupted bile composition and chronic cholestasis.[1]
  - Key clinical manifestations include impaired growth, reduced quality of life (QoL), progressive liver disease, and debilitating pruritus.[1]
- Pruritus is one of the most burdensome symptoms of PFIC, occurring in the majority of patients and leading to sleep disturbances, self-mutilation, and decreased school performance, further contributing to impaired QoL.[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]
- MARCH was a 26-week, randomized, placebo-controlled phase 3 clinical trial with maralixibat in children with PFIC that achieved its primary endpoint of improvements in pruritus as well as its key secondary endpoint of reduction in sBAs.[5,6]

Objective

- To analyze whether improvements in pruritus are associated with an improvement in QoL for patients with PFIC based on data from the MARCH clinical trial.

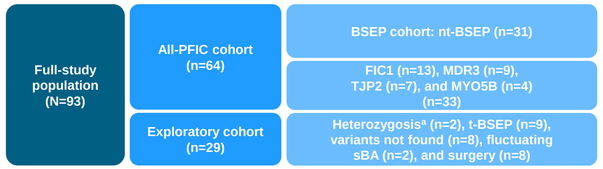
Methods

Figure 1. MARCH Phase 3 Study Design



[a]Criteria for 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.

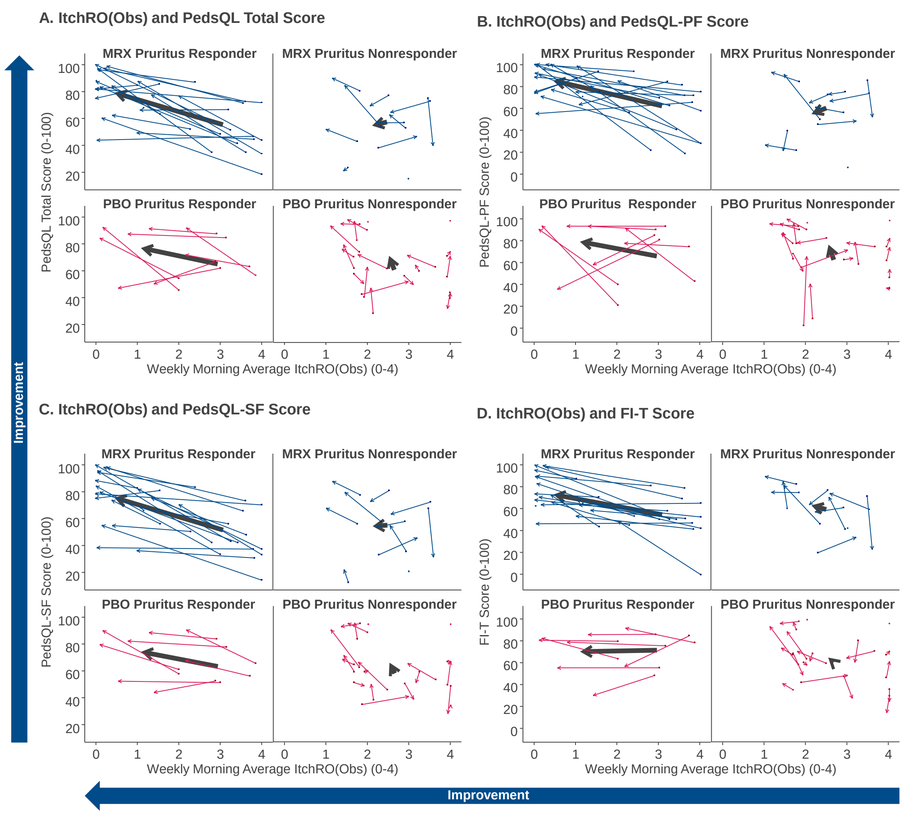
- Change in QoL from Baseline to Week 18-26 was assessed using the PedsQL, Peds-QL Social Functioning (PedsQL-SF), Peds-QL Physical Functioning (PedsQL-PF), and the Family Impact Total Scale (FI-T).
  - The minimal clinically important difference (MCID) of these assessments is 4-5 points, depending on the scale.[7]
  - All assessments use a 0-100 scale, with higher scores indicating better QoL.[7]
- Itch-Reported (Observer) (ItchRO[Obs]) is a 0-4 scale, where 0 = no itch, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe.[8] A ≥1-point reduction in ItchRO(Obs) is considered clinically meaningful.
- QoL scores were compared between maralixibat treatment responders, defined as those with ≥1 point reduction in ItchRO(Obs), and nonresponders.

Results

- A total of 64 participants (BSEP, n=31; FIC1, n=13; MDR3, n=9; TJP2, n=7; MYO5B, n=4) were randomized into maralixibat (n=33) and placebo groups (n=31).
- Baseline disease characteristics were well balanced between maralixibat and placebo groups, and participants had similar Baseline QoL scores.

Improvements in Pruritus Were Associated With Improvements in QoL Across Multiple Domains

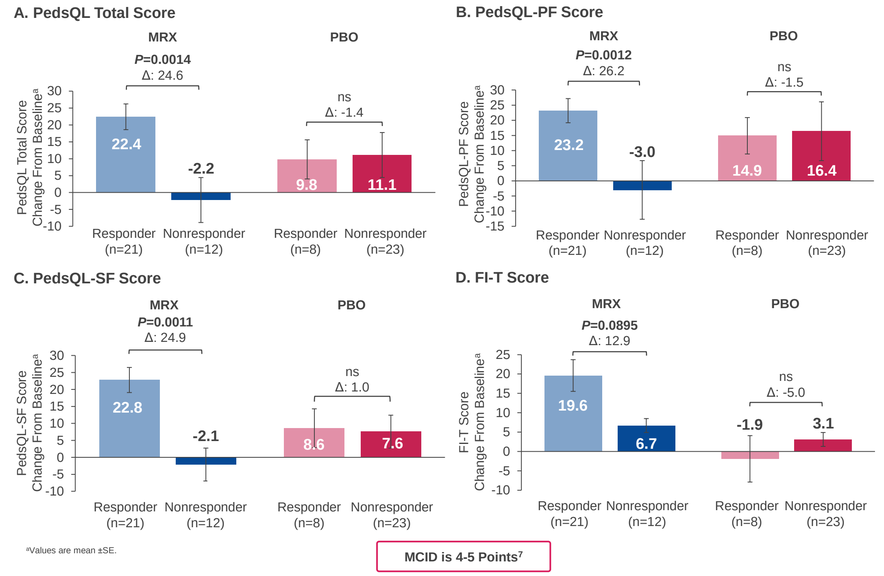
Figure 3. Baseline and Averaged Values for Weekly Morning Average ItchRO(Obs) and (A) PedsQL Total Score, (B) PedsQL-PF Score, (C) PedsQL-SF Score, and (D) FI-T Score



Arrows denote the change from BL to average of Week 18, 22, and 26. Thick arrows denote the group average.

Pruritus Responders in the Maralixibat Group Demonstrated Clinically Meaningful Improvements Across Multiple QoL Assessments Compared With Nonresponders

Figure 4. Change From Baseline in (A) PedsQL Total Score, (B) PedsQL-PF Score, (C) PedsQL-SF Score, and (D) FI-T Score



[a]Values are mean ±SE.

MCID is 4-5 Points[7]

- The maralixibat group demonstrated significant differences between pruritus responders and nonresponders for PedsQL (*P*=0.0014), PedsQL-SF (*P*=0.0011), PedsQL-PF (*P*=0.0012), and a trend toward significance with FI-T (*P*=0.0895).
- Clinically meaningful improvements (MCID >4-5 points) across all HRQoL scales were experienced by responders to maralixibat treatment.
- The placebo group showed no significant differences between pruritus responders and nonresponders in any of the assessments.

Conclusions

- In the MARCH trial, clinically significant reductions in pruritus were associated with meaningful improvements in QoL, across several domains.
- Reductions in pruritus were greater in the maralixibat group compared with placebo.
- These data suggest that benefits of maralixibat may extend beyond pruritus and yield meaningful improvements in QoL as well.

Abbreviations

BID, twice daily; BL, baseline; BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis-associated protein 1; FI-T, Family Impact Total Scale; HRQoL, health-related quality of life; IBAT, ileal bile acid transporter; ItchRO(Obs), Itch-Reported Outcome (Observer); MCID, minimal clinically important difference; MDR3, multidrug resistance protein 3; MRX, maralixibat; MYO5B, myosin Vb; ns, not significant; nt, nontruncated; PBO, placebo; PedsQL-PF, Peds-QL Physical Functioning; PedsQL-SF, Peds-QL Social Functioning; PFIC, progressive familial intrahepatic cholestasis; QoL, quality of life; R, randomized; sBA, serum bile acid; t, truncated; TJP2, tight junction protein 2; ULN, upper limit of normal.

Disclosures

AAA is a consultant for Mirum Pharmaceuticals, Inc., Albireo, and Sarepta Therapeutics. AGM is a consultant and has a sponsored research agreement for Mirum Pharmaceuticals, Inc. EMS is the founder and chairman of Cellaion; an investigator for Mirum Pharmaceuticals, Inc., Albireo, and Intercept; and an advisor for Albireo. UB is a consultant for Mirum Pharmaceuticals, Inc., Albireo, and Vivet Pharmaceuticals. RJT is a consultant for Mirum Pharmaceuticals, Inc., Albireo, Generation Bio, Rectify Therapeutics, and Alnylam and a shareholder in Generation Bio and Rectify Therapeutics. DBM, TN, MB, and PV are employees of and shareholders in Mirum Pharmaceuticals, Inc. C-HL and GP have nothing to disclose.

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