Maralixibat Leads to Significant Improvement in Cholestatic Pruritus for Children With Progressive Familial Intrahepatic Cholestasis Due to TJP2 or MYO5B Deficiency: Data From MARCH-PFIC Trial

Poster 4604-C

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Introduction

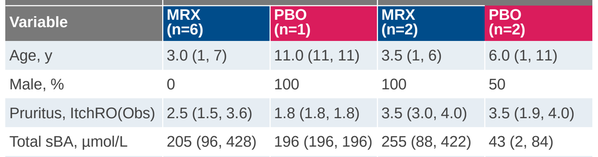
- Progressive familial intrahepatic cholestasis (PFIC) is a group of genetic disorders that result in disrupted bile composition and chronic cholestasis.[1]
  - Key clinical manifestations include debilitating pruritus, impaired growth, reduced quality of life, and progressive liver disease with an eventual need for liver transplantation.[1]
- The most common causes of PFIC are deficiencies in BSEP, FIC1, MDR3, TJP2, and MYO5B.[2]
  - Patients with TJP2 deficiency have a predisposition to developing hepatocellular carcinoma.[2]
  - Clinical presentation in patients with MYO5B deficiency varies from isolated cholestasis to microvillous inclusion disease or both.[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) was conducted to evaluate the efficacy and safety of maralixibat for the treatment of participants with PFIC.[5]
  - MARCH is the largest and most genetically inclusive clinical trial of PFIC to date and to our knowledge, the first trial of IBAT inhibition in participants with TJP2 or MYO5B deficiency.[6]
  - The trial achieved its primary endpoint of reduction in cholestatic pruritus, secondary endpoint of reduction in sBA, and exploratory endpoints of improved bilirubin and growth.[6]

Objective

- To analyze the efficacy and safety of maralixibat for participants with TJP2 or MYO5B deficiencies enrolled in the MARCH trial.

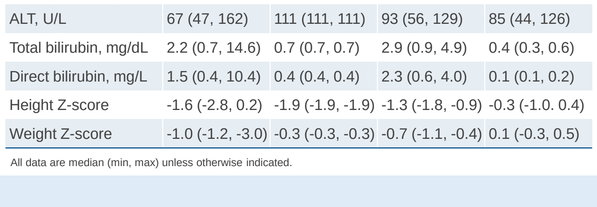
Methods

Figure 1. MARCH Phase 3 Study Design



[a]Key entry criteria sBA ≥3 x ULN 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.

- Data comparing change from Baseline (CFB) to Weeks 15-26 for key efficacy endpoints (pruritus, sBA, and bilirubin) were analyzed for participants with TJP2 or MYO5B deficiency.
- Pruritus was measured using the 0-4 Itch-Reported Outcome (Observer) (ItchRO[Obs]) scale (0=no itch, 1=mild, 2=moderate, 3=severe and 4=very severe)[7] in which a ≥1-point reduction is considered clinically meaningful.

Results

Table 1. Key Demographics and Baseline Characteristics

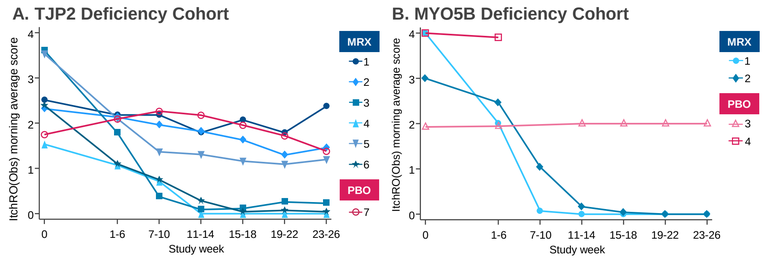
	TJP2 (N=7)		MYO5B (N=4)	
Variable	MRX (n=6)	PBO (n=1)	MRX (n=2)	PBO (n=2)
Age, y	3.0 (1, 7)	11.0 (11, 11)	3.5 (1, 6)	6.0 (1, 11)
Male, %	0	100	100	50
Pruritus, ItchRO(Obs)	2.5 (1.5, 3.6)	1.8 (1.8, 1.8)	3.5 (3.0, 4.0)	3.5 (1.9, 4.0)
Total sBA, µmol/L	205 (96, 428)	196 (196, 196)	255 (88, 422)	43 (2, 84)
UDCA usage, %	83.3	100	50	100
Rifampicin usage, %	50	0	50	0
ALT, U/L	67 (47, 162)	111 (111, 111)	93 (56, 129)	85 (44, 126)
Total bilirubin, mg/dL	2.2 (0.7, 14.6)	0.7 (0.7, 0.7)	2.9 (0.9, 4.9)	0.4 (0.3, 0.6)
Direct bilirubin, mg/L	1.5 (0.4, 10.4)	0.4 (0.4, 0.4)	2.3 (0.6, 4.0)	0.1 (0.1, 0.2)
Height Z-score	-1.6 (-2.8, 0.2)	-1.9 (-1.9, -1.9)	-1.3 (-1.8, -0.9)	-0.3 (-1.0. 0.4)
Weight Z-score	-1.0 (-1.2, -3.0)	-0.3 (-0.3, -0.3)	-0.7 (-1.1, -0.4)	0.1 (-0.3, 0.5)

All data are median (min, max) unless otherwise indicated.

Results

Most Participants Who Received Maralixibat Showed Improvements in Pruritus

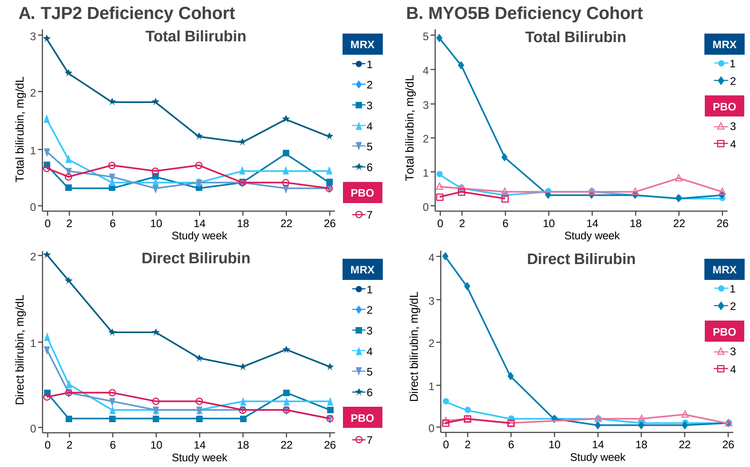
Figure 3. Average Pruritus (ItchRO[Obs]) Scores Over Time



- **TJP2 deficiency:** The median (min, max) CFB in ItchRO(Obs) was -1.9 (-0.4, -3.4) in the maralixibat group, with no change for the participant who received placebo.
- **MYO5B deficiency:** Both participants who received maralixibat experienced complete resolution of pruritus, with Baseline ItchRO(Obs) scores of 4 and 3 decreasing to 0. One participant who received placebo experienced no change; the other stopped at Week 6 due to no perceived benefit.

Bilirubin Was Normalized Upon Maralixibat Treatment in the Participant With Abnormal Bilirubin at Baseline

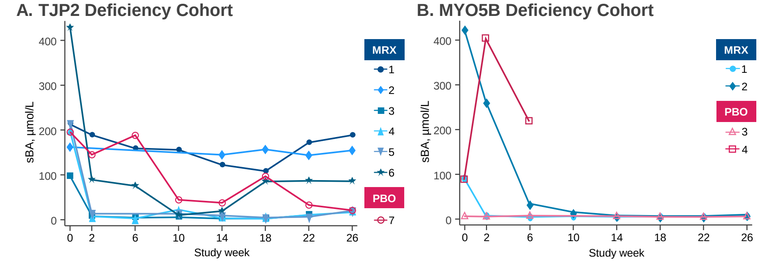
Figure 4. Total and Direct Bilirubin Levels Over Time



- **TJP2 deficiency:** Neither group experienced meaningful changes in total or direct bilirubin levels.
- **MYO5B deficiency:** One participant who received maralixibat had elevated Baseline bilirubin levels (4.9 mg/dL total; 4.0 mg/dL direct) that normalized (0.3 mg/dL total; 0.1 mg/dL direct) on treatment. Both participants who received placebo had normal Baseline bilirubin levels.

Most Participants Who Received Maralixibat Showed Reductions in sBA Levels

Figure 5. sBA Levels Over Time



- **TJP2 deficiency:** The median (min, max) CFB in sBA was -138 (-10, -342) µmol/L in the maralixibat group. The 1 participant who received placebo experienced a CFB of -146 µmol/L.
- **MYO5B deficiency:** Both participants who received maralixibat experienced complete normalization of sBA (from Baseline 88 and 422 µmol/L to 4 and 2 µmol/L, respectively). One participant who received placebo maintained normal levels through Week 26; the other had elevated levels to Week 6.
- There were no meaningful changes in ALT levels for participants who received maralixibat or placebo in either the TJP2 or MYO5B cohort.

No New Safety Signals Were Observed, Consistent With Other PFIC Types

Table 2. Summary of TEAEs

	TJP2 (N=7)		MYO5B (N=4)	
TEAE, n (%)	MRX (n=6)	PBO (n=1)	MRX (n=2)	PBO (n=2)
Any TEAE	6 (100.0)	1 (100.0)	2 (100.0)	2 (100)
Severe TEAE	0	0	0	0
Serious TEAE	0	0	0	0
TEAE leading to discontinuation	0	0	0	0
TEAE leading to death	0	0	0	0
Clinically relevant TEAEs				
Diarrhea	3 (50.0)	0	2 (100.0)	0
Abdominal pain	3 (50.0)	0	1 (50.0)	0

Conclusions

- MARCH is the first trial showing the benefit of IBAT inhibition for TJP2 and MYO5B deficiencies.
- All participants who received maralixibat showed substantial improvements in pruritus and reductions in sBA while participants who received placebo experienced little benefit.
- Bilirubin levels were normalized in one participant with MYO5B deficiency who received maralixibat.
- These data support the use of maralixibat in patients with identified TJP2 or MYO5B deficiencies.

Abbreviations

ABCB11, adenosine triphosphate binding cassette subfamily B member 11; ALT, alanine aminotransferase; *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; 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.

Disclosures

AGM is a consultant and has a sponsored research agreement with 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. DBM, TN, RA, and PV are employees of and shareholders in Mirum Pharmaceuticals, Inc. GP, AM, CHL, DD'A, and FKC have nothing to disclose.

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References

1. Kamath BM, et al. *Liver Int*. 2020;40(8):1812-1822. **2.** Vinayagamoorthy V, et al. *World J Hepatol*. 2021;13(12):2024-2038. **3.** LIVMARLI. Prescribing information. Mirum Pharmaceuticals Inc.; 2023. **4.** LIVMARLI. Summary of product characteristics. Mirum Pharmaceuticals, Inc.; 2022. **5.** ClinicalTrials.gov identifier: NCT03905330. Updated July 6, 2023. Accessed August 25, 2023. https://clinicaltrials.gov/ct2/show/NCT03905330. **6.** Thompson RJ, et al. Oral presentation at: American Association for the Study of Liver Diseases; November 4-8, 2022; Washington, DC. **7.** Kamath BM, et al. *Hepatol Commun*. 2020;4(7):1012-1018.

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