Long-Term Maintenance of Response and Improved Liver Health With Maralixibat in Patients With Progressive Familial Intrahepatic Cholestasis (PFIC): 2-Year Data From the MARCH-ON Study

Poster 5048-C

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Introduction

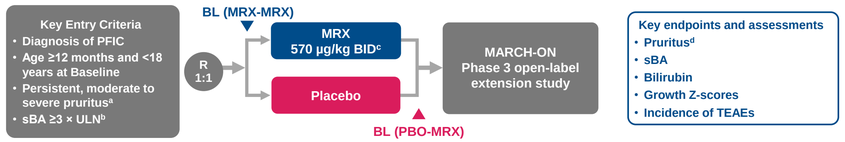
- Progressive familial intrahepatic cholestasis (PFIC) is a collection of disorders in bile formation that can lead to intrahepatic cholestasis, chronic liver disease, and severe pruritus.[1]
- Maralixibat (MRX) is a minimally absorbed ileal bile acid transporter (IBAT) inhibitor that prevents enterohepatic 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.[2,3]
- MARCH was a phase 3, randomized, double-blind, placebo-controlled, 26-week trial, investigating the efficacy and safety of maralixibat in patients with PFIC.[4]
  - Maralixibat achieved significant improvements in pruritus, levels of sBAs, bilirubin, and growth in patients across the broadest range of PFIC types studied to date.[5]
- MARCH-ON is an open-label, long-term extension study for patients who completed the MARCH study.[6]

Objective

- To assess the long-term maintenance of response of up to 2 years of treatment in participants who were randomized to receive maralixibat (MRX-MRX) or placebo (PBO-MRX) in MARCH and continued treatment with maralixibat in 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 0-4 scale, where 0 = no itch, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe.[7] A ≥1-point reduction in ItchRO(Obs) is considered clinically meaningful.

- Long-term maintenance of response to maralixibat treatment was assessed for pruritus, sBA, total bilirubin, height and weight Z-scores, and incidence of treatment-emergent adverse events (TEAEs).
- Baseline was defined as last assessment before the start of maralixibat treatment for each group.

Results

Baseline Characteristics Were Well Balanced Between Treatment Arms

Table 1. Key Demographics and Baseline Characteristics

Variable	MRX-MRX (n=47)	PBO-MRX (n=41)
Age, y	4.8	5.2
Sex, male, %	43	44
Pruritus, ItchRO(Obs) score	2.8	2.5
Total sBA, µmol/L	263	246
UDCA usage, %	83	83
Rifampicin usage, %	55	54
ALT, U/L	108	102
Total bilirubin, mg/dL	4.1	4.3
Direct bilirubin, mg/dL	3.0	3.2
Height Z-score	-2.0	-1.9
Weight Z-score	-1.6	-1.1

All data are mean unless otherwise indicated.

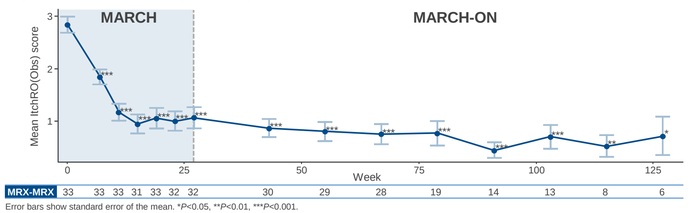
- Of the 88 patients dosed with maralixibat in either MARCH or MARCH-ON as of June 10, 2023, 47 received maralixibat in MARCH and could continue to receive maralixibat in MARCH-ON (MRX-MRX).[a]
- Forty-one participants who received placebo in MARCH initiated maralixibat in MARCH-ON (PBO-MRX).[a]
- PFIC subtypes of patients included in the study were: nt-BSEP (n=28), FIC1 (n=13), MDR3 (n=9), TJP2 (n=7), MYO5B (n=3), heterozygosis (n=2), t-BSEP (n=9), variant not found (n=8), fluctuating sBA (n=2), and surgery (n=7).[b]
- The median (min, max) exposure to maralixibat was 638 (10, 1135) days for the MRX-MRX group and 456 (22, 720) days for the PBO-MRX group.

[a]Efficacy analyses included n=33 in the MRX-MRX group and n=27 patients in the PBO-MRX group. [b]Subtypes nt-BSEP, FIC1, MDR3, TJP2, and MYO5B were included in the efficacy analyses.

Results

Significant Improvements in Pruritus Severity Were Sustained in the MRX-MRX Group

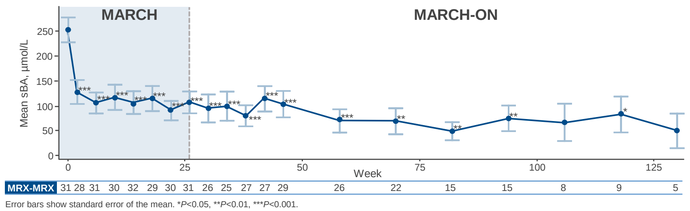
Figure 2. Mean Morning ItchRO(Obs) Over Time in the MRX-MRX Group



Error bars show standard error of the mean. *P<0.05, **P<0.01, ***P<0.001.

Significant Improvements in sBA Levels Were Sustained in the MRX-MRX Group

Figure 3. Mean sBA Over Time in the MRX-MRX Group



Error bars show standard error of the mean. *P<0.05, **P<0.01, ***P<0.001.

Significant Improvements in Key Endpoints Were Observed From Baseline to Week 104 in the MRX-MRX Group and Baseline to Week 52 in the PBO-MRX Group

Table 2. Change From Baseline in Laboratory Parameters of Clinical Interest

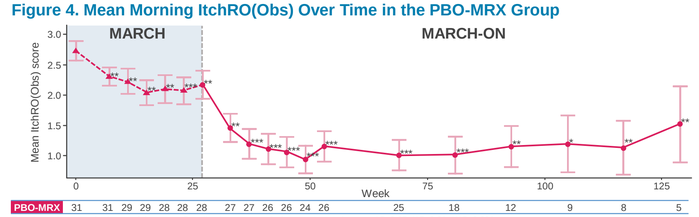
Mean change from Baseline	MRX-MRX (n=13)[a]	PBO-MRX (n=18)[b]
Pruritus, ItchRO(Obs) score	-2.0 (P<0.0001)	-1.1 (P=0.0001)
sBA, µmol/L	-166 (P=0.0031)[c]	-71 (P=0.0333)
Total bilirubin, mg/dL	-1.6 (P=0.0153)	-0.4 (P=0.6651)
Height Z-score	+0.40 (P=0.0458)	+0.37 (P=0.0115)
Weight Z-score	+0.52 (P=0.0108)	+0.32 (P=0.0278)

[a]Analysis includes n=13 patients in the MRX-MRX group with follow-up to Week 104. [b]Analysis includes n=18 patients in the PBO-MRX group with follow-up to Week 52. [c] Data from Week 94 is presented.

- In the MRX-MRX group, significant improvements observed in the first 26 weeks of the MARCH study were sustained from Baseline to Week 104 in MARCH-ON for pruritus severity, sBA levels, total bilirubin, height Z-score, and weight Z-score.
- In the PBO-MRX group, newly gained statistically significant reductions in pruritus severity, sBA levels, height Z-score, and weight Z-score were observed from Baseline to Week 52, in line with observations from the initial MARCH MRX group.

Newly Gained Statistically Significant Reductions in Pruritus Severity Were Observed in the PBO-MRX Group

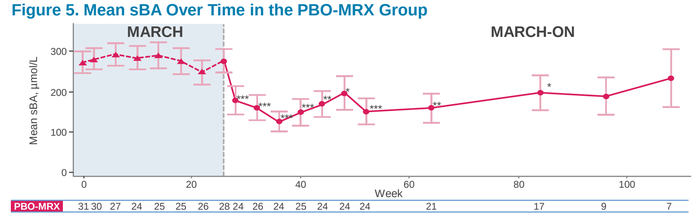
Figure 4. Mean Morning ItchRO(Obs) Over Time in the PBO-MRX Group



Error bars show standard error of the mean. Baseline is reassessed when treatment changes. *P<0.05, **P<0.01, ***P<0.001.

Newly Gained Statistically Significant Reductions in sBA Levels Were Observed in the PBO-MRX Group

Figure 5. Mean sBA Over Time in the PBO-MRX Group



Error bars show standard error of the mean. Baseline is reassessed when treatment changes. *P<0.05, **P<0.01, ***P<0.001.

No New Safety Signals Were Identified During Treatment With MRX

Table 3. Summary of TEAEs in the Full Study Cohort

TEAEs, n (%)	MRX-MRX (n=47)	PBO-MRX (n=41)
Any TEAE	47 (100)	40 (97.6)
Severe TEAE	9 (19.1)	7 (17.1)
Serious TEAE	13 (27.7)	9 (22.0)
TEAE leading to discontinuation	3 (6.4)	1 (2.4)
TEAE leading to death	0	0
Most common TEAE: diarrhea	30 (63.8)	19 (46.3)

- No new safety signals were identified.
- The most frequent TEAEs were gastrointestinal related, with diarrhea (56%) being mostly mild and transient.
  - Patients who previously received maralixibat in MARCH were less likely to have events in MARCH-ON compared with MARCH.

Conclusions

- Significant and sustained responses in pruritus severity, sBA levels, total bilirubin, and growth were observed with up to 2 years of maralixibat treatment across the broadest range of genetic PFIC types studied to date.
- The PBO-MRX group demonstrated significant improvements in pruritus severity and sBA levels similar to those observed in the original MARCH maralixibat group.
- No new safety signals were observed following 2 years of treatment with maralixibat.
- These data suggest overall improved liver health with maralixibat treatment in patients with PFIC that can be maintained long-term.

Abbreviations

ALT, alanine aminotransferase; BID, twice daily; BL, Baseline; BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis-associated protein type 1; IBAT, ileal bile acid transporter; ItchRO(Obs), Itch-Reported Outcome (Observer); MDR3, multidrug-resistance 3 protein; MRX, maralixibat; MYO5B, myosin VB; nt-BSEP, nontruncated bile salt export pump; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; R, randomized; sBA, serum bile acid; t-BSEP, truncated BSEP; TEAE, treatment-emergent adverse event; TJP2, tight junction protein 2; ULN, upper limit of normal; UDCA, ursodeoxycholic acid.

Disclosures

AGM is a consultant and has a sponsored research agreement with Mirum Pharmaceuticals, Inc. FO is a speaker for Alexion Pharmaceuticals and Valentech Pharma. AAA is a consultant for Mirum Pharmaceuticals, Inc., Albireo, and Sarepta Therapeutics. ES 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. LD'A is a consultant and advisor for Mirum Pharmaceuticals, Inc., Albireo, Selecta, Vivet Pharmaceuticals, Tome, Spark, Genespire, and Alexion. NK is a consultant for Mirum Pharmaceuticals, Inc. NM is an investigator for Mirum Pharmaceuticals, Inc. SPH is a hepatic safety adjudication committee member at Albireo and has received a research grant from Mirum Pharmaceuticals, Inc. TN, AL, LL, DBM, MB, and PV are employees of and shareholders in Mirum Pharmaceuticals, Inc. RG-P has received a research grant from Mirum Pharmaceuticals, Inc., and is an advisor, teacher, and educator for Mirum Pharmaceuticals, Inc. and Albireo. UE is a steering committee member for Mirum Pharmaceuticals, Inc. NO is a consultant for Albireo and received research support to her institution from Mirum Pharmaceuticals, Inc., Albireo, and Travere. 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. AM, GP, JCE, PC, MC, RHS, DD'A, NL, CA, C-HL, SMG, FKC, W-DH, VFH, JH, and NL have nothing to disclose.

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References

1. Loomes KM, et al. *Hepatol Commun*. 2022;6(9):2379-2390. **2.** LIVMARLI. Prescribing information. Mirum Pharmaceuticals, Inc.; 2023. **3.** LIVMARLI. Summary of product characteristics. Mirum Pharmaceuticals, Inc.; 2022. **4.** ClinicalTrials.gov identifier: NCT03905330. Updated July 6, 2023. Accessed August 25, 2023. https://www.clinicaltrials.gov/study/NCT03905330?term=NCT03905330&rank=1. **5.** Miethke A, et al. Oral presentation at: North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) annual meeting; October 4-7, 2023; San Diego, California. **6.** ClinicalTrials.gov identifier: NCT04185363. Updated August 16, 2023. Accessed August 25, 2023. https://www.clinicaltrials.gov/study/NCT04185363?term=NCT04185363&rank=1. **7.** Kamath BM, et al. *Hepatol Commun*. 2020;4(7):1012-1018.

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