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

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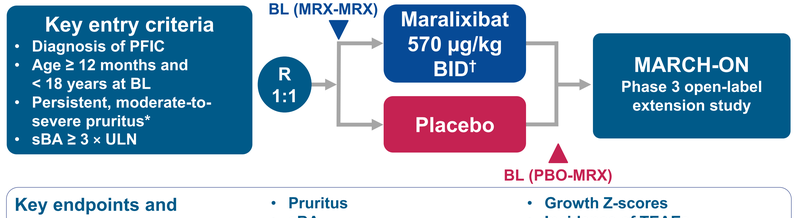
Introduction

- 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 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 ≥ 2 months of age in the EU and ≥ 3 months of age in the US.[2,3]
- In the MARCH-PFIC (MARCH) trial, a Phase 3, 26-week, randomised trial of maralixibat vs placebo, maralixibat achieved significant improvements in pruritus, levels of serum bile acids (sBA), bilirubin and growth in patients across the broadest range of PFIC types studied to date.[4,5]
- MARCH-ON is an open-label, long-term extension study for patients who completed the MARCH study.[6]

Aim

- To assess the long-term maintenance response to maralixibat in patients who were randomised to receive maralixibat (MRX-MRX) or placebo (PBO-MRX) in MARCH and continued treatment with maralixibat in MARCH-ON.

Methods



Key endpoints and assessments

- Pruritus
- sBA
- Bilirubin
- Growth Z-scores
- Incidence of TEAEs

*ItchRO(Obs) score ≥ 1.5; †Maralixibat 570 µg/kg is equivalent to 600 µg/kg maralixibat chloride.
BL, baseline; MRX, maralixibat; PBO, placebo; R, randomised; TEAE, treatment-emergent adverse event.

- Eighty-five patients from MARCH enrolled in MARCH-ON (data cut-off = 23 Jun 2022); of these patients, 47 had received maralixibat (MRX-MRX) and 38 had received placebo (PBO-MRX) in MARCH.*
- PFIC subtypes of patients included in the study were: non-truncated bile salt export pump (nt-BSEP, n = 27); familial intrahepatic cholestasis-associated protein type 1 (FIC1, n = 13); multidrug-resistance 3 protein (MDR3, n = 9); tight junction protein 2 (TJP2, n = 6); myosin VB (MYO5B, n = 2); heterozygosis (n = 2); truncated BSEP (t-BSEP, n = 9); variant not found (n = 8); fluctuating sBA (n = 2); and surgery (n = 7).†
- Baseline was defined as the start of maralixibat treatment for each group.

*Efficacy analyses included n = 33 in the MRX-MRX group and n = 24 patients in the PBO-MRX group; †Subtypes nt-BSEP, FIC1, MDR3, TJP2 and MYO5B were included in the efficacy analyses.

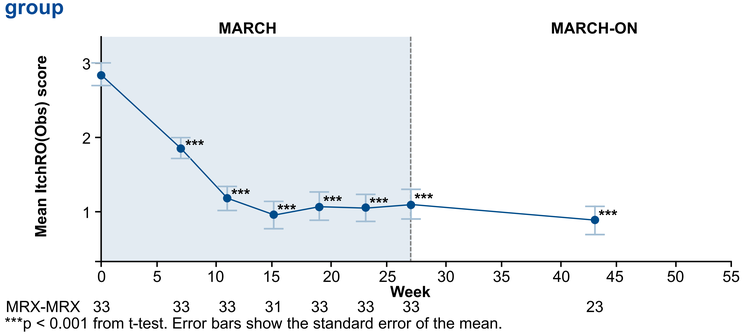
Baseline characteristics were well balanced between treatment arms

Variable	MRX-MRX (n = 47)	PBO-MRX (n = 38)
Age, years	4.8	5.1
Male, %	43	42
Pruritus, ItchRO(Obs) score	2.8	2.5
Total sBA, µmol/L	263	253
UDCA usage, %	83	82
Rifampicin usage, %	55	58
Alanine aminotransferase, U/L	108	102
Total bilirubin, µmol/L	70	77
Direct bilirubin, µmol/L	51	57
Height Z-score	-1.9	-2.0
Weight Z-score	-1.5	-1.2

All data are mean unless otherwise indicated. Percentages are 100 × n/N.
UDCA, ursodeoxycholic acid.

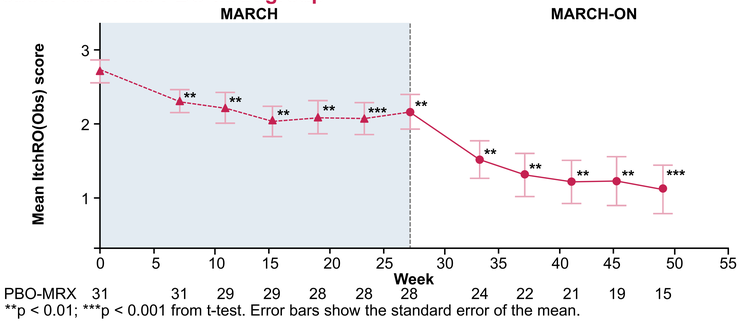
Results

Significant improvements in pruritus severity were sustained in the MRX-MRX group



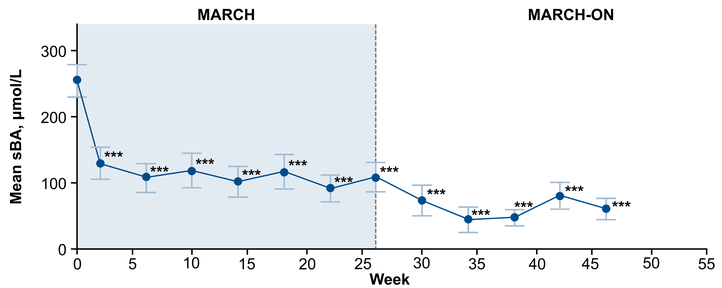
MRX-MRX 33 33 33 31 33 33 33 23
***p < 0.001 from t-test. Error bars show the standard error of the mean.

Newly gained statistically significant reductions in pruritus severity were observed in the PBO-MRX group



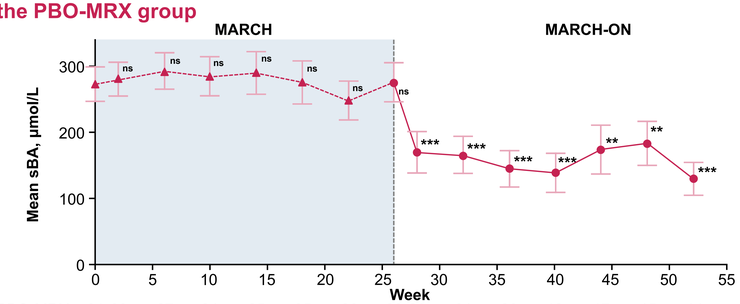
PBO-MRX 31 31 29 29 28 28 28 24 22 21 19 15
**p < 0.01; ***p < 0.001 from t-test. Error bars show the standard error of the mean.

Significant improvements in sBA levels were sustained in the MRX-MRX group



MRX-MRX 31 28 31 30 31 29 30 31 23 17 19 20 20
***p < 0.001 from t-test. Error bars show the standard error of the mean.

Newly gained statistically significant reductions in sBA levels were observed in the PBO-MRX group



PBO-MRX 31 30 27 24 25 25 26 28 22 21 20 18 17 15 14
**p < 0.01; ***p < 0.001 from t-test. Error bars show the standard error of the mean. ns, not significant.

Significant improvements in key endpoints were observed from Baseline to Week 52 in the MRX-MRX group and Baseline to Week 26 in the PBO-MRX group

Mean change from Baseline	MRX-MRX (n = 20)[a]	PBO-MRX (n = 15)[b]
Pruritus, ItchRO(Obs) score	-2.13 (p < 0.0001)	-1.05 (p = 0.0017)
sBA, µmol/L	-200 (p = 0.0004)	-141 (p = 0.0003)
Total bilirubin, µmol/dL	-45 (p = 0.0084)	-27 (p = 0.1878)
Height Z-score	+0.54 (p < 0.0001)	+0.46 (p = 0.0152)
Weight Z-score	+0.44 (p = 0.0010)	+0.09 (p = 0.5134)

[a]Analysis includes n = 20 patients in the MRX-MRX group with follow-up to Week 52; [b]Analysis includes n = 15 patients in the PBO-MRX group with follow-up to Week 26.

- In the MRX-MRX group, the median (min, max) exposure was 394 (108, 836) days. Significant improvements observed in the first 26 weeks of the MARCH study were sustained from Baseline to Week 52 in MARCH-ON for pruritus severity, sBA levels, total bilirubin, height Z-score and weight Z-score.
- In the PBO-MRX group, the median (min, max) exposure was 250 (29, 569) days. Newly gained statistically significant reductions in pruritus severity and sBA levels were observed in the key efficacy endpoints from Baseline to Week 26, in line with observations from the initial MARCH maralixibat group.

No new safety signals were identified during treatment with maralixibat

TEAEs, n (%)	MRX-MRX (n = 47)	PBO-MRX (n = 38)
Any TEAE	47 (100)	35 (92.1)
Severe TEAE	5 (10.6)	2 (5.3)
Serious TEAE	8 (17.0)	6 (15.8)
TEAE leading to discontinuation	3 (6.4)	0
TEAE leading to death	1 (2.1)	0
Most common TEAE: diarrhoea	30 (63.8)	13 (34.2)

Percentages are 100 × n/N. TEAE, treatment-emergent adverse event.

- No new safety signals were identified.
- The most frequent TEAEs were gastrointestinal-related, with early onset of diarrhoea (51%) in line with the mechanism of IBAT inhibition, mostly mild and transient.
  - Patients who previously received MRX in MARCH were less likely to have events in MARCH-ON compared with MARCH.

Conclusions

- **Significant and sustained responses in pruritus severity, sBA levels and bilirubin, as well as growth, were observed with 52 weeks 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.**
- **These data suggest overall improved liver health with maralixibat treatment in patients with PFIC, which can be maintained over time.**

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