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

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Progressive Familial Intrahepatic Cholestasis

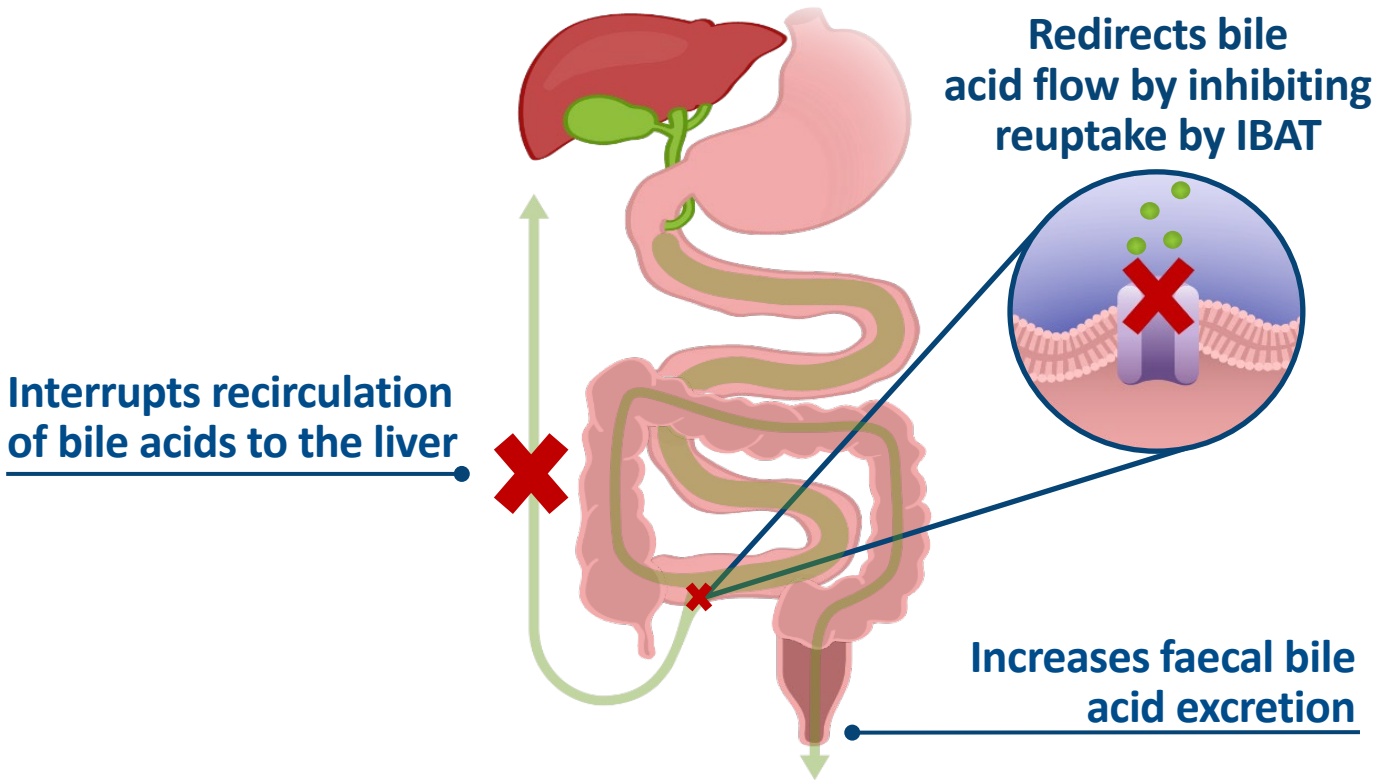
- Genetic disorders resulting in disrupted bile composition and chronic cholestasis[1]
- Debilitating pruritus, impaired growth, reduced QoL and progressive liver disease, with many children undergoing liver transplantation[2-5]
- PFIC types include deficiencies of[1-3]:
  - Bile salt export pump (BSEP)
  - Familial intrahepatic cholestasis-associated protein type 1 (FIC1)
  - Multidrug-resistance 3 protein (MDR3)
  - Tight junction protein 2 (TJP2)
  - Myosin VB (MYO5B)
- Current treatments include off-label antipruritic treatments, surgical biliary diversion, liver transplantation and IBAT inhibitors[6-8,a]
  - sBA control (reduction of sBA to <102 µmol/L or ≥75% reduction) after surgical biliary diversion is associated with native liver survival to 15 years (NAPPED)[2]

The efficacy of IBAT inhibitors has not been studied across every PFIC type

FDA, US Food and Drug Administration; IBAT, ileal bile acid transporter; NAPPED, NAtural course and Prognosis of PFIC and Effect of biliary Diversion; PFIC, progressive familial intrahepatic cholestasis; QoL, quality of life; sBA, serum bile acid.
[a]Odevixibat is an IBAT inhibitor approved for the treatment of PFIC in patients 6 months of age and older in the EU and approved by the FDA for the treatment of pruritus in patients with PFIC 3 months of age and older in the US.[7,8]

1. Jacquemin E. *Clin Res Hepatol Gastroenterol*. 2012;36:S26-S35. **2.** van Wessel D, et al. *J Hepatol*. 2020;73:84-93. **3.** Kamath BM, et al. *Liver Int*. 2020;40:1812-1822. **4.** Kamath BM, et al. *Patient*. 2018;11:69-82. **5.** Loomes MK, et al. *Hepatol Commun*. 2022;6:2379-2390. **6.** Davit-Spraul A, et al. *Orphanet J Rare Dis*. 2009 Jan 8;4:1. **7.** BYLVAY® (odevixibat) [prescribing information]. Cambridge, MA; Ipsen Biopharmaceuticals, Inc.; Jan 2024. **8.** BYLVAY® (odevixibat). [summary of product characteristics]. Göteborg, Sweden; Albireo AB.; July 2021.

Maralixibat: IBAT Inhibitor That Interrupts Enterohepatic Circulation



Clinical effects of maralixibat in ALGS

- ✓ Improvements in pruritus[1-3]
- ✓ Reduction in peripheral sBA[1-3]
- ✓ Improved transplant-free survival[1,2]

Maralixibat is approved for the treatment of cholestatic pruritus in patients with ALGS ≥2 months of age in the EU and ≥3 months of age in the US[3,4]

ALGS, Alagille syndrome; BSEP, bile salt export pump; IBAT, ileal bile acid transporter; sBA, serum bile acid.

1. Gonzales E, et al. *Lancet*. 2021;398:1581-1592. **2.** Sokol RJ, et al. *Hepatology*. 2023;78:1698-1710. **3.** LIVMARLI® (maralixibat) [prescribing information]. Foster City, CA; Mirum Pharmaceuticals, Inc. Mar 2024. **4.** LIVMARLI® (maralixibat) [summary of product characteristics]. Amsterdam, Netherlands; Mirum Pharmaceuticals International B.V. Jan 2024.

Figure reprinted from *Lancet*, 398, Gonzales E, et al., 'Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study', 1581-1592, Copyright (2021), with permission from Elsevier.

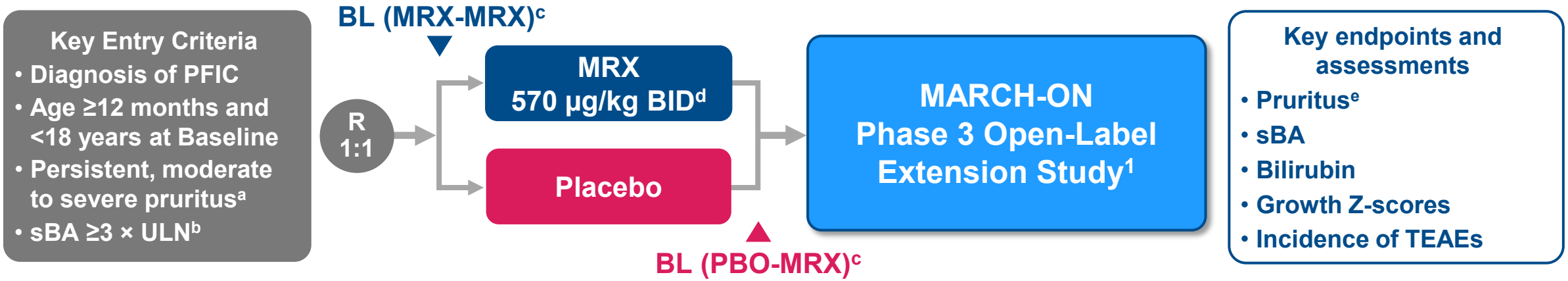
MARCH-ON: Open-Label Long-Term Extension Study of Maralixibat in Patients With PFIC

OBJECTIVE

To report the long-term maintenance of response for up to 2 years of treatment in participants with PFIC who were randomised to receive maralixibat (MRX-MRX) or placebo (PBO-MRX) in MARCH and continued treatment with maralixibat in MARCH-ON

MRX, maralixibat; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis.
ClinicalTrials.gov identifier: NCT04185363. Updated October 5, 2023. Accessed April 19, 2024. https://www.clinicaltrials.gov/study/NCT04185363

MARCH-ON: Study Design



- Eighty-eight participants received maralixibat in either MARCH or MARCH-ON[f]
  - 47 received maralixibat in MARCH and could continue to receive maralixibat in MARCH-ON (MRX-MRX)
  - 41 received placebo in MARCH and initiated maralixibat in MARCH-ON (PBO-MRX)
- PFIC subtypes 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)[g]

BID, twice daily; BL, baseline; FIC1, familial intrahepatic cholestasis-associated protein 1; MDR3, multidrug resistance protein 3; MYO5B, myosin Vb; MRX, maralixibat; nt, nontruncated; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; R, randomisation; sBA, serum bile acid; t, truncated; TEAE, treatment-emergent adverse event; TJP2, tight junction protein 2; ULN, upper limit of normal.
[a]Itch-Reported Outcome (Observer) (ItchRO[Obs]) score ≥1.5. [b]Criteria for primary BSEP cohort only. [c]Baseline was defined as the last assessment before the start of maralixibat treatment for each group. [d]Maralixibat 570 µg/kg is equivalent to 600 µg/kg maralixibat chloride. [e]ItchRO(Obs) is a 0-4 scale, where 0 = no itch, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe.[2] A ≥1-point reduction in ItchRO(Obs) is considered clinically meaningful. [f]As of June 10, 2023. Efficacy analyses included n=33 in the MRX-MRX group and n=27 patients in the PBO-MRX group. [g]Subtypes nt-BSEP, FIC1, MDR3, TJP2, and MYO5B were included in the efficacy analyses.
1. ClinicalTrials.gov identifier: NCT04185363. Updated October 5, 2023. Accessed April 19, 2024. https://www.clinicaltrials.gov/study/NCT04185363 **2.** Kamath BM, et al. *Hepatol Commun*. 2020;4:1012-1018.

Key Demographics and Baseline Characteristics

Variable[a]	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, µmol/L	70.1	72.7
Direct bilirubin, µmol/L	51.1	54.0
Height Z-score	-2.0	-1.9
Weight Z-score	-1.6	-1.1

- 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

Baseline characteristics were well balanced between treatment arms

ALT, alanine aminotransferase; BSEP, bile salt export pump; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid; UDCA, ursodeoxycholic acid.
[a]All data are mean unless otherwise indicated.

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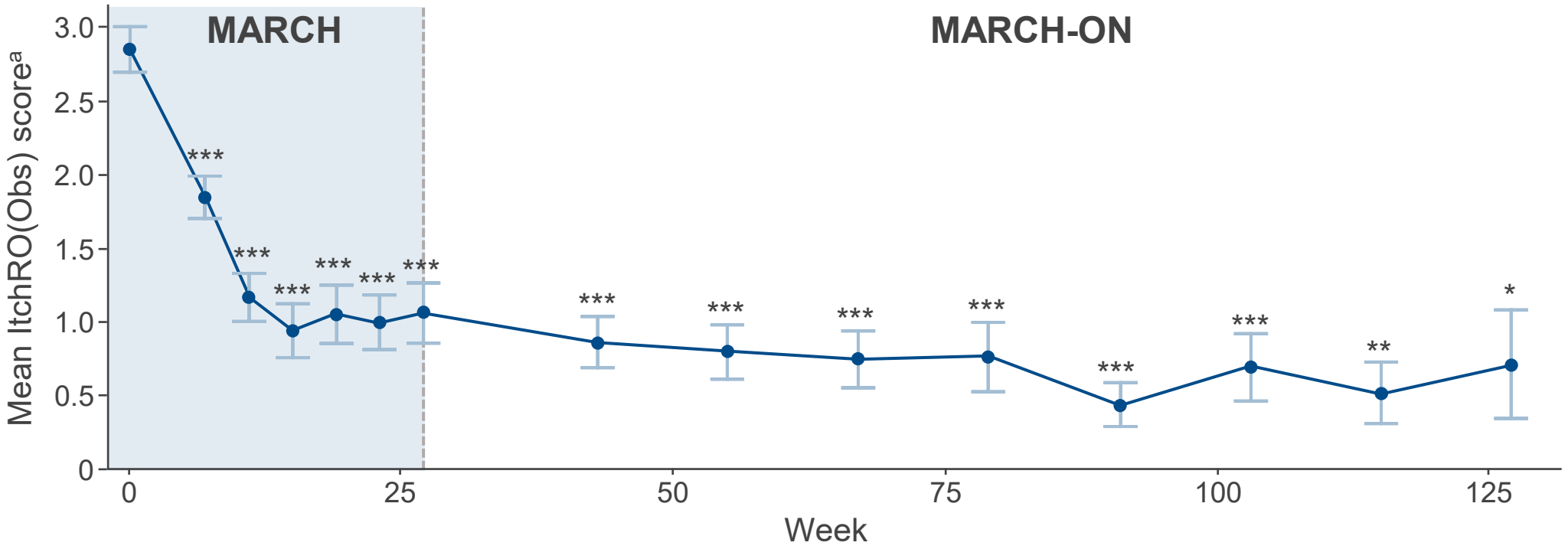
Significant Improvements in Pruritus Severity Were Sustained in the MRX-MRX Group

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



MRX-MRX	33	33	33	31	33	32	32	30	29	28	19	14	13	8	6

ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat.
[a]Error bars show standard error of the mean. *P<0.05, **P<0.01, ***P<0.001.

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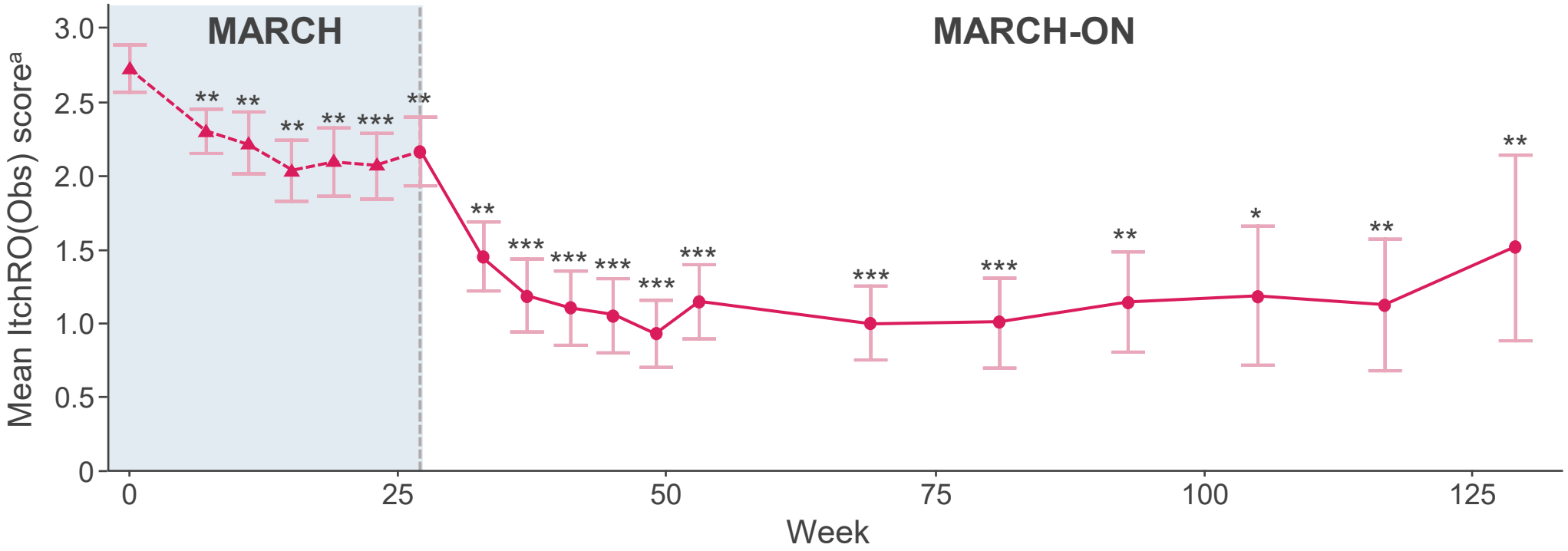
Significant Reductions in Pruritus Severity Were Observed in the PBO-MRX Group

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



PBO-MRX	31	31	29	29	28	28	28	27	27	26	26	24	26	25	18	12	9	8	5

ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; PBO, placebo.
[a]Error bars show standard error of the mean. Baseline is reassessed when treatment changes. *P<0.05, **P<0.01, ***P<0.001.

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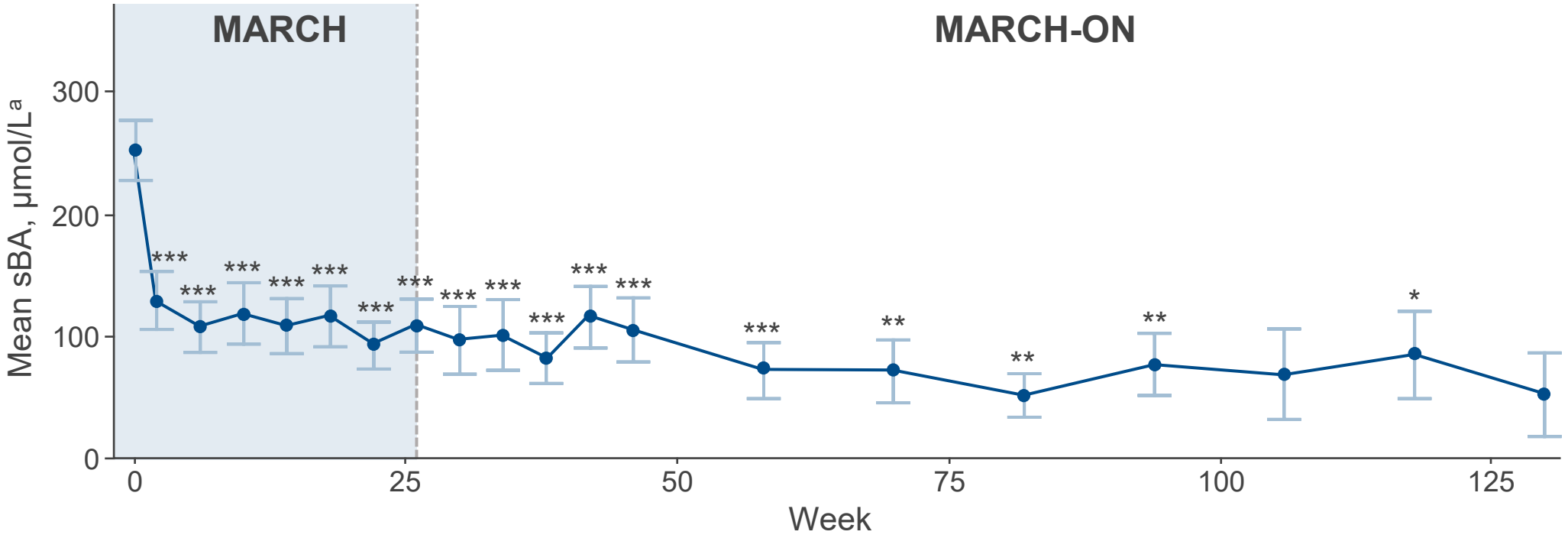
Significant Improvements in sBA Levels Were Sustained in the MRX-MRX Group

Mean sBA Over Time in the MRX-MRX Group



MRX-MRX	31	28	31	30	32	29	30	31	26	25	27	27	29	26	22	15	15	8	9	5

MRX, maralixibat; sBA, serum bile acid.

[a]Error bars show standard error of the mean. *P<0.05, **P<0.01, ***P<0.001. Data after Week 130 is not shown due to small sample sizes (n<5).

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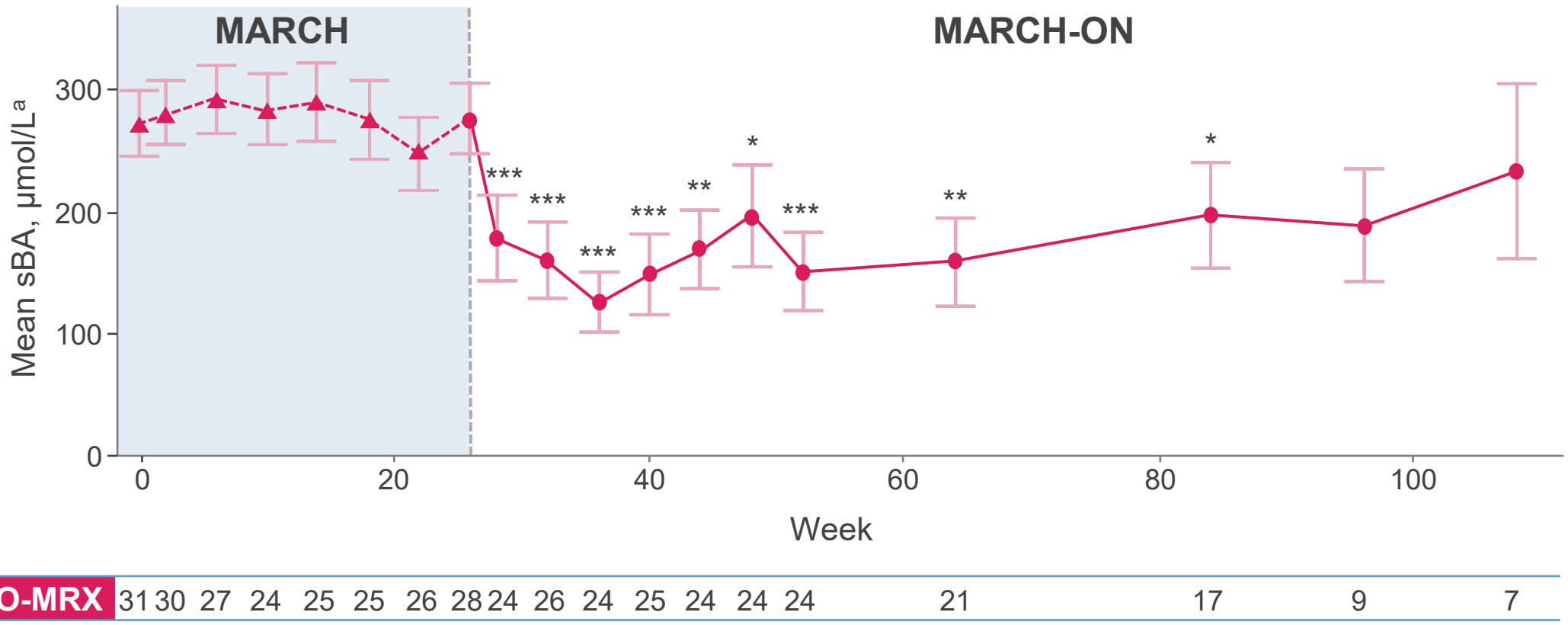
Significant Reductions in sBA Levels Were Observed in the PBO-MRX Group

Mean sBA Over Time in the PBO-MRX Group



MRX, maralixibat; PBO, placebo; sBA, serum bile acid.
[a]Error bars show standard error of the mean. Baseline is reassessed when treatment changes. *P<0.05, **P<0.01, ***P<0.001. Data after Week 108 is not shown due to small sample sizes (n<5).

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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, µmol/L	-27.7 (***P*=0.0153**)	-6.4 (*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**)

- In the MRX-MRX group, significant improvements in laboratory parameters of interest observed in the first 26 weeks of the MARCH study were sustained from Baseline to Week 104 in MARCH-ON
- In the PBO-MRX group, newly gained statistically significant reductions in laboratory parameters of interest were observed from Baseline to Week 52, in line with observations from the initial MARCH MRX group

ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; PBO, placebo.
[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 are presented.

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Summary of TEAEs in 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)
TRAE leading to death	0	0
Most common TEAE: diarrhoea	30 (63.8)	19 (46.3)

- No new safety signals were identified
- The most frequent TEAEs were gastrointestinal related, with diarrhoea (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

MRX, maralixibat; PBO, placebo; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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Conclusions

- Significant and sustained improvements 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

MRX, maralixibat; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.

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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 Cellaïon; an investigator for Mirum Pharmaceuticals, Inc., Albireo, and Intercept; and an advisor for Mirum Pharmaceuticals, Inc., and 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.
- SG is an advisor for Mirum Pharmaceuticals, Inc., and Medison Pharma, and is a clinical trials site lead for AbbVie, Mirum Pharmaceuticals, Inc., and Intercept Pharma
- 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, advisor, and speaker for and has received research support to his institution from Mirum Pharmaceuticals, Inc. He is also a consultant for Albireo, Generation Bio, Rectify Therapeutics, and Alnylam and a shareholder in Generation Bio and Rectify Therapeutic

Thank You!