Improvements in Pruritus Are Associated With Improvements in Growth in Patients With Progressive Familial Intrahepatic Cholestasis: Data From the MARCH-ON Trial

Alexander G. Miethke[1], Amal A. Aqul[2], Chuan-Hao Lin[3], Douglas B. Mogul[4], Tiago Nunes[4], Jolan Terner-Rosenthal[4], Marshall Baek[4], Pamela Vig[4], Richard J. Thompson[5]

[1]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [2]University of Texas Southwestern Medical Center, Dallas, Texas, USA; [3]Children's Hospital Los Angeles, Los Angeles, California, USA; [4]Mirum Pharmaceuticals, Inc., Foster City, California, USA; [5]Institute of Liver Studies, King's College London, London, UK

Presenter Disclosure: Richard J. Thompson

	No, Nothing to Disclose
x	Yes, Please Specify:

Company Name	Honoraria/ Expenses	Consulting / Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership/ Equity Position	Employee	Other (please specify)
Mirum Pharmaceuticals, Inc.		x						
Albireo		x						
Generation Bio		x				x		
Rectify Therapeutics		x				x		
Alnylam		x						
Integra Therapeutics		x				x		
Glycomine		x						
Spruce Bio		x						

[a]Products or services produced by this company are relevant to my presentation.

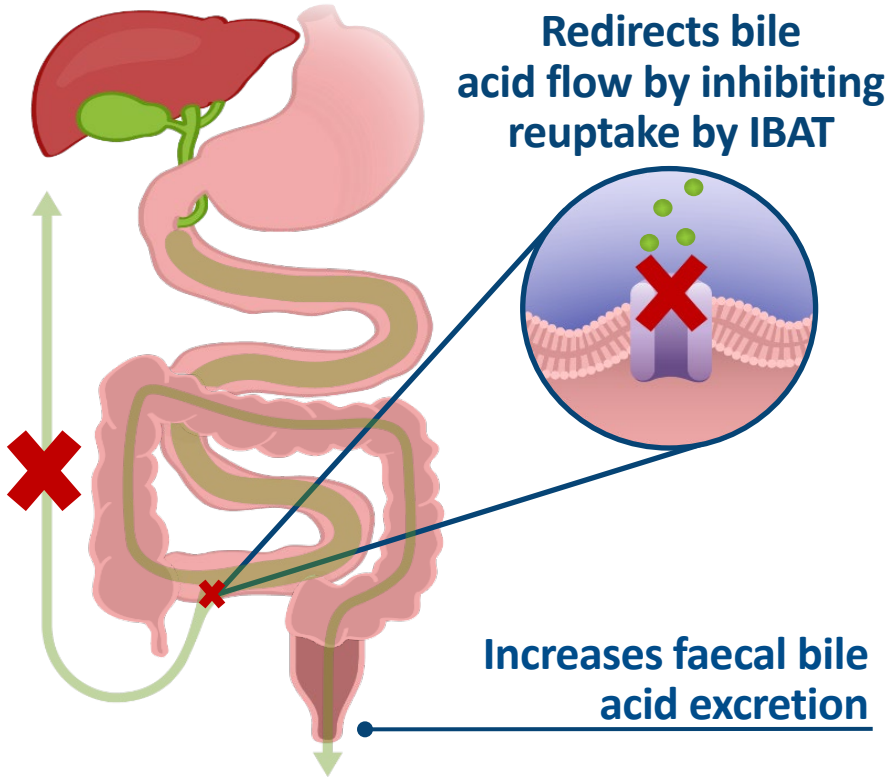
Progressive Familial Intrahepatic Cholestasis

- 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 approved for the treatment of cholestatic pruritus in PFIC[6-8,a,b]

EU, European Union; IBAT, ileal bile acid transporter; PFIC, progressive familial intrahepatic cholestasis; QoL, quality of life.
[a]Maralixibat is an IBAT inhibitor approved for the treatment of PFIC in patients 3 months of age and older in the EU.[7]
[b]Odevixibat is an IBAT inhibitor approved for the treatment of PFIC in patients 6 months of age and older in the EU.[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;**4**:**1**. **7.** LIVMARLI® (maralixibat) [summary of product characteristics]. Amsterdam, Netherlands; Mirum Pharmaceuticals International B.V. Dec 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 PFIC and Alagille syndrome

- ✓ Improvements in pruritus[1-4]
- ✓ Reduction in peripheral sBA[1-4]
- ✓ Improved transplant-free survival[1,2]

Maralixibat is approved for the treatment of PFIC in patients ≥3 months of age in the EU[4]

IBAT, ileal bile acid transporter; PFIC, progressive familial intrahepatic cholestasis; 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.** Miethke AG, et al. *Lancet Gastroenterol Hepatol*. 2024;9:620-631. **4.** LIVMARLI® (maralixibat) [summary of product characteristics]. Amsterdam, Netherlands; Mirum Pharmaceuticals International B.V. Dec 2024.

Study Overviews: MARCH and MARCH-ON

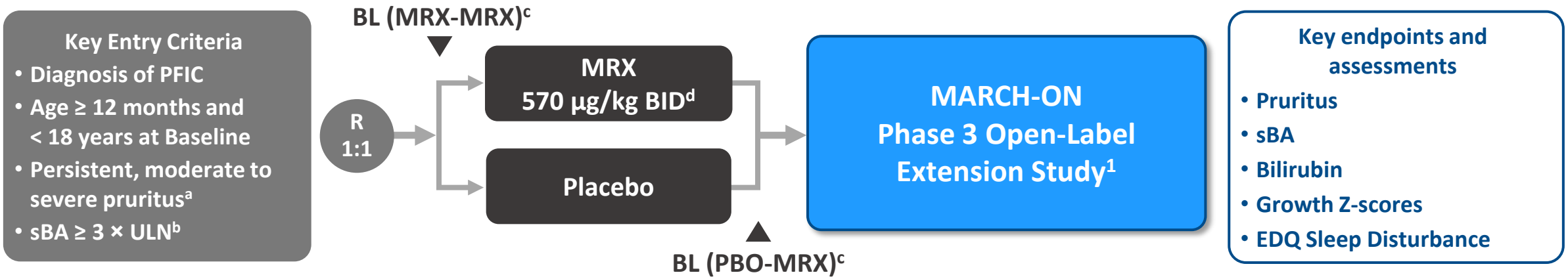
- MARCH (NCT03905330) was a phase 3, randomised, double-blind, placebo-controlled, 26-week trial investigating the efficacy and safety of maralixibat in participants with PFIC across the broadest range of PFIC types studied to date[1,2]
  - MARCH-ON (NCT04185363) was an open-label extension study for participants who completed the MARCH study[3]
- In MARCH, participants who received maralixibat had statistically significant improvements in weight that persisted through MARCH-ON and a trend for improvements in height Z-scores that reached statistical significance in MARCH-ON and persisted through 70 weeks of treatment[4]

Objective of current analysis: To report the relationship between pruritus response and growth improvement in participants with PFIC who received maralixibat in the MARCH/MARCH-ON trials

PFIC, progressive familial intrahepatic cholestasis.

1. ClinicalTrials.gov identifier: NCT03905330. Updated December 11, 2023. Accessed March 24, 2025. https://clinicaltrials.gov/ct2/show/NCT03905330 **2.** Miethke AG, et al. *Lancet Gastroenterol Hepatol*. 2024;9:620-631.
3. ClinicalTrials.gov identifier: NCT04185363. Updated February 14, 2025. Accessed March 24, 2025. https://www.clinicaltrials.gov/study/NCT04185363 **4.** Gonzalez-Peralta RP, et al. Presented at EASL 2024.

MARCH-ON: Study Design



- Pruritus response was defined as having a ≥ 1-point reduction in ItchRO(Obs) from Baseline to the average of the three 4-week periods in MARCH or MARCH-ON (Weeks 15-18, Weeks 19-22, and Weeks 23-26) or an average score of ≤ 1[e]
  - ItchRO(Obs) is a 0 to 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
- Height and weight Z-scores based on a participant's sex and age at each scheduled trial visit were analysed
- Change from Baseline (CFB) within groups and between groups was determined using Wilcoxon signed-rank test and rank sum test, respectively
  - Results were combined from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively

BID, twice daily; BL, baseline; BSEP, bile salt export pump; EDQ, electronic diary questionnaire; ItchRO(Obs); Itch-Reported Outcome (Observer); MRX, maralixibat; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; R, randomisation; sBA, serum bile acid; ULN, upper limit of normal.

[a]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]A participant was defined as a nonresponder if the 4-week average Baseline score was missing or all 3 of the postbaseline scores were missing.

1. ClinicalTrials.gov identifier: NCT04185363. Updated February 14, 2025. Accessed March 24, 2025. https://www.clinicaltrials.gov/study/NCT04185363 **2.** Kamath BM, et al. *Hepatol Commun*. 2020;4:1012-1018.

Baseline Demographic Characteristics

Parameter[a]	BSEP (n = 28)		FIC1/TJP2/MYO5B (n = 23)	
	ItchRO(Obs) responders (n = 18) 64%	ItchRO(Obs) nonresponders (n = 10)	ItchRO(Obs) responders (n = 11) 48%	ItchRO(Obs) nonresponders (n = 12)
Age, y	6.2	5.2	5.2	2.8
Sex, male, %	27.8	50.0	54.6	58.3
Pruritus, ItchRO(Obs) score[b]	2.6	2.2	2.9	2.9
Total sBA, µmol/L	302	331	179	240
ALT, U/L	94	139	78	60
AST, U/L	116	138	75	77
Total bilirubin, µmol/L	46.2	66.7	36.8	149.8
Direct bilirubin, µmol/L	32.5	49.6	26.3	112.6
Height Z-score	-1.9	-2.4	-1.3	-3.1
Weight Z-score	-1.0	-1.4	-1.1	-2.3

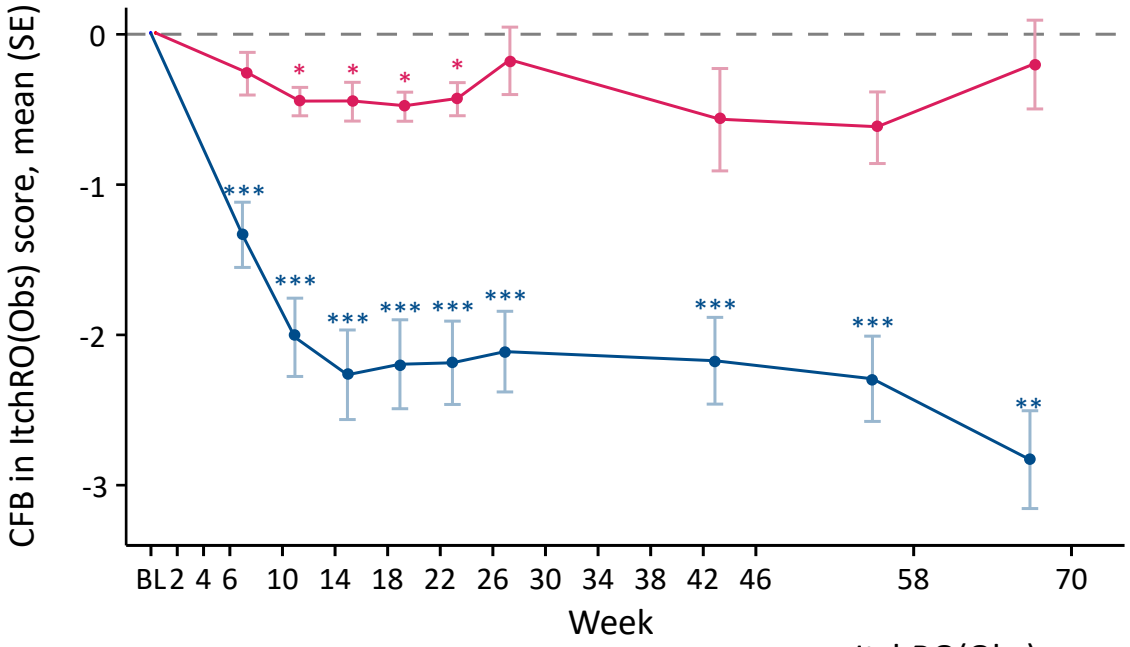
Growth was stunted at Baseline across pruritus responders and non-responders in both cohorts

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer); MDR3, multidrug resistance protein 3; MRX, maralixibat; MYO5B, myosin Vb; nt, nontruncated; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid; TJP2, tight junction protein 2.
[a]All data are mean unless otherwise indicated. Values are based on non-missing assessments. [b]ItchRO(Obs) is the 4-week morning average severity score.

Sustained Significant Improvements in ItchRO(Obs) Were Observed in Pruritus Responders in the BSEP and FIC1/TJP2/MYO5B Cohorts

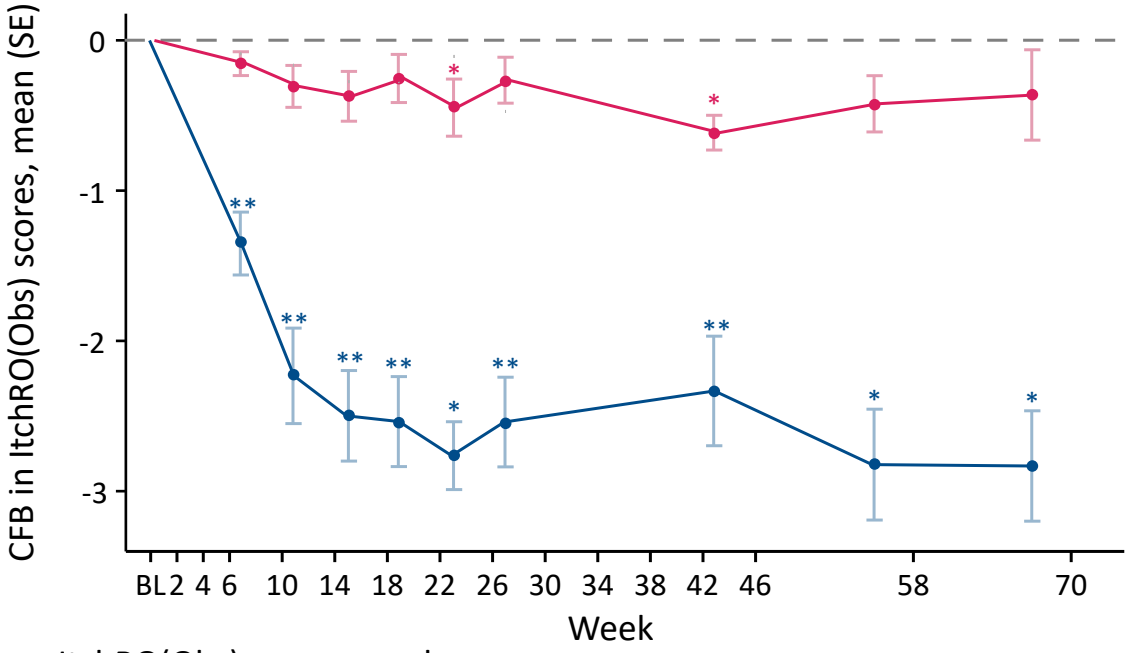
Mean CFB in Monthly Average Morning ItchRO(Obs) Scores Over Time[a,b]

BSEP Cohort



Responders	18	18	18	18	18	18	18	18	16	11
Nonresponders	10	10	10	9	10	8	9	9	6	7

FIC1/TJP2/MYO5B Cohort



Responders	11	11	11	11	11	10	11	11	9	9
Nonresponders	12	12	12	11	11	11	11	9	9	6

ItchRO(Obs) responders — ItchRO(Obs) nonresponders

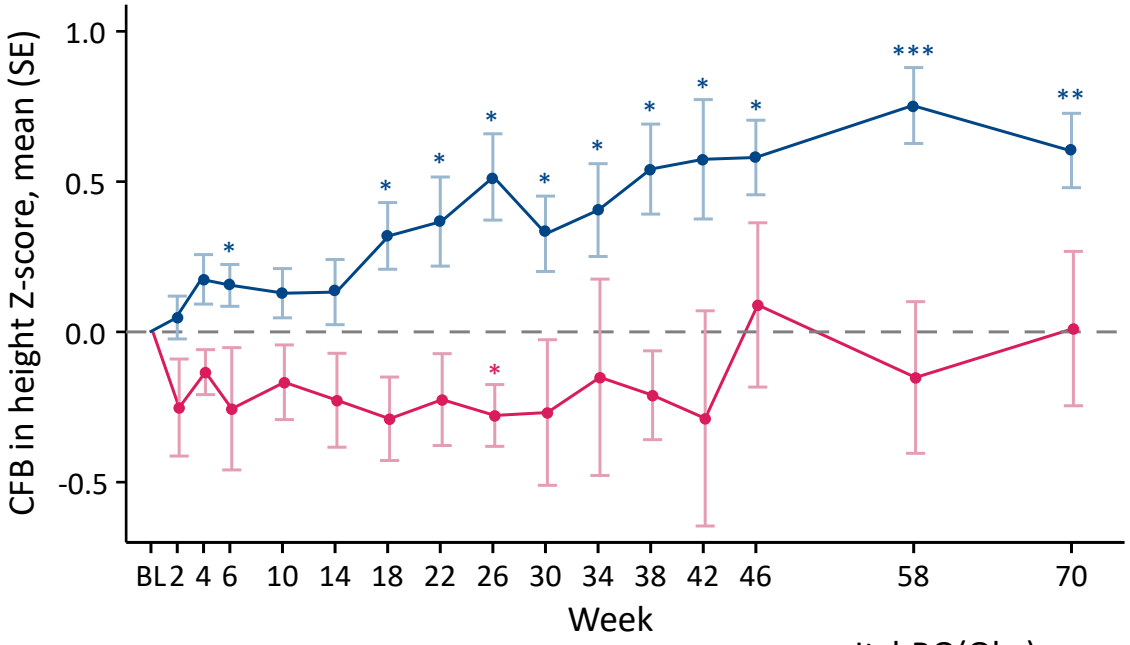
In both cohorts, significant improvements in ItchRO(Obs) from Baseline were observed in pruritus responders at Week 26 in MARCH ($P < 0.0001$; $P < 0.001$) and sustained in MARCH-ON out to 70 weeks of treatment ($P < 0.001$; $P < 0.05$)

BL, baseline; BSEP, bile salt export pump; CFB, change from baseline; FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; MYO5B, myosin Vb; PBO, placebo; SE, standard error; TJP2, tight junction protein 2. [a]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively. [b]Two-tailed *P* value for Student's t test: * ≤ 0.05, ** ≤ 0.001, *** ≤ 0.0001.

Sustained Significant Improvements in Height Were Observed in Pruritus Responders in the BSEP and FIC1/TJP2/MYO5B Cohorts

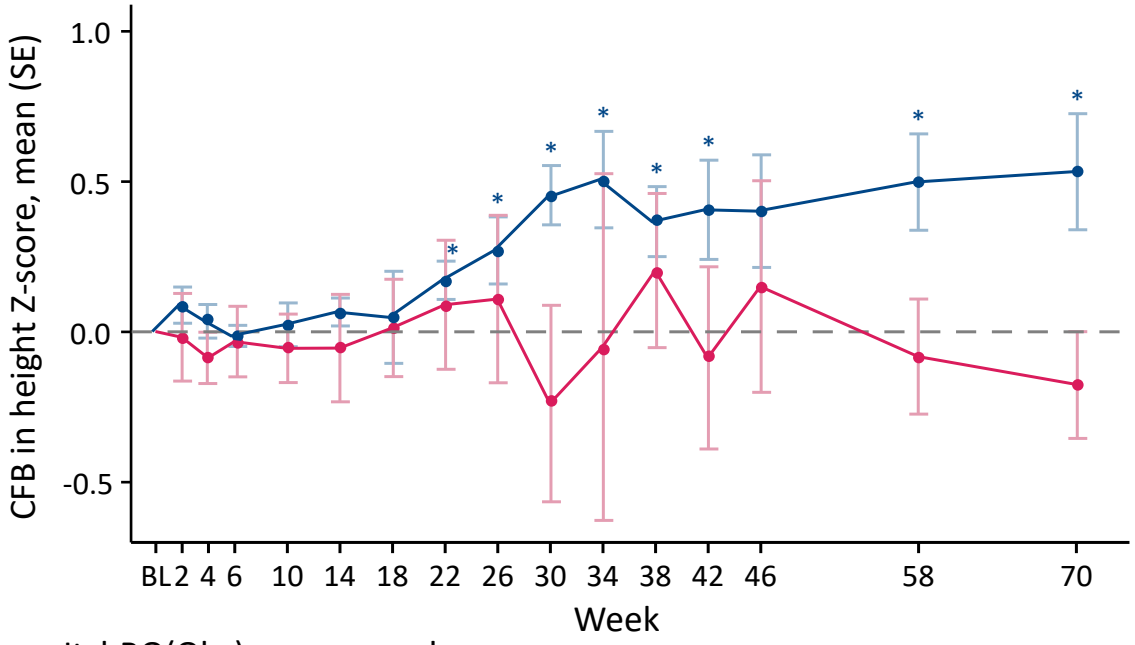
Mean CFB in Height Z-Score Over Time[a,b]

BSEP Cohort



Responders	18	17	15	17	17	17	17	17	18	8	6	16	6	9	17	12
Nonresponders	10	9	8	9	8	9	8	9	9	5	4	8	4	4	7	5

FIC1/TJP2/MYO5B Cohort



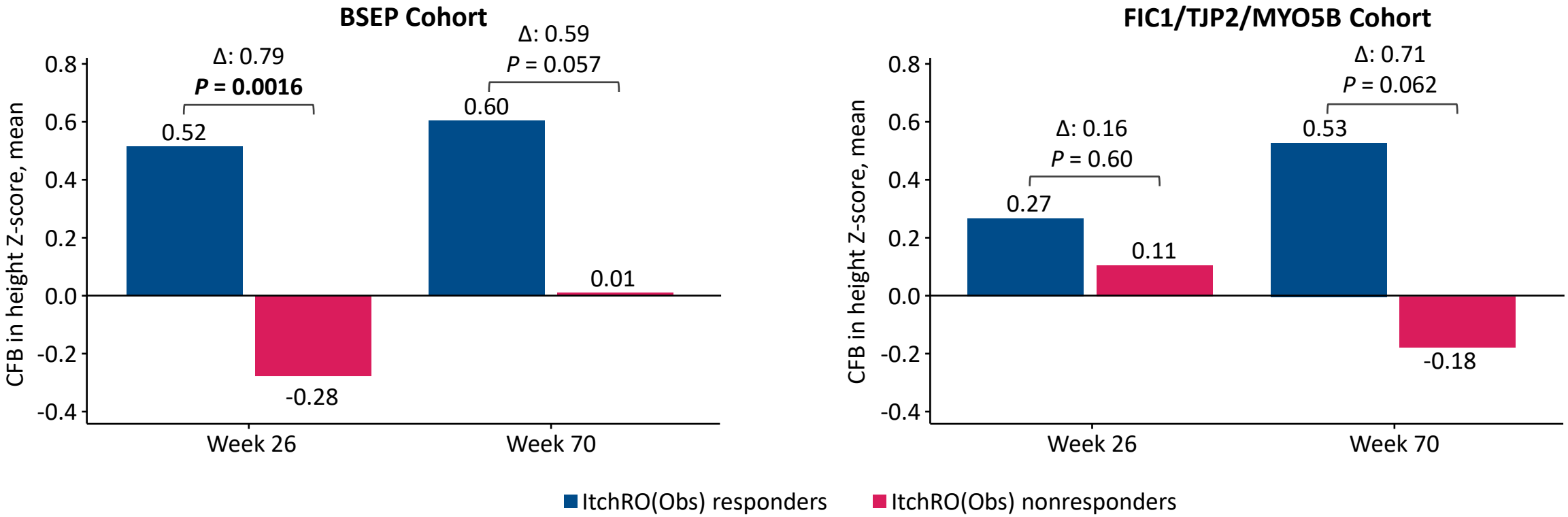
Responders	11	9	9	11	11	10	9	11	11	9	8	10	8	9	9	8
Nonresponders	12	8	10	11	10	9	10	10	11	3	2	7	5	5	8	7

In both cohorts, significant improvements in height Z-score from Baseline were observed in pruritus responders at Week 26 in MARCH ($P < 0.05$) and sustained in MARCH-ON out to 70 weeks of treatment ($P < 0.05$)

BL, baseline; BSEP, bile salt export pump; CFB, change from baseline; FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; MYO5B, myosin Vb; PBO, placebo; SE, standard error; TJP2, tight junction protein 2. [a]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively. [b]Two-tailed *P* value for Student's t test: * ≤ 0.05, ** ≤ 0.001, *** ≤ 0.0001.

Height Z-Score by Analysis Timepoints in the BSEP and FIC1/TJP2/MYO5B Cohorts

Mean CFB in Height Z-Score by Analysis Timepoints[a]



	Week 26	Week 70
Responders	18	12
Nonresponders	9	5

	Week 26	Week 70
Responders	11	8
Nonresponders	11	7

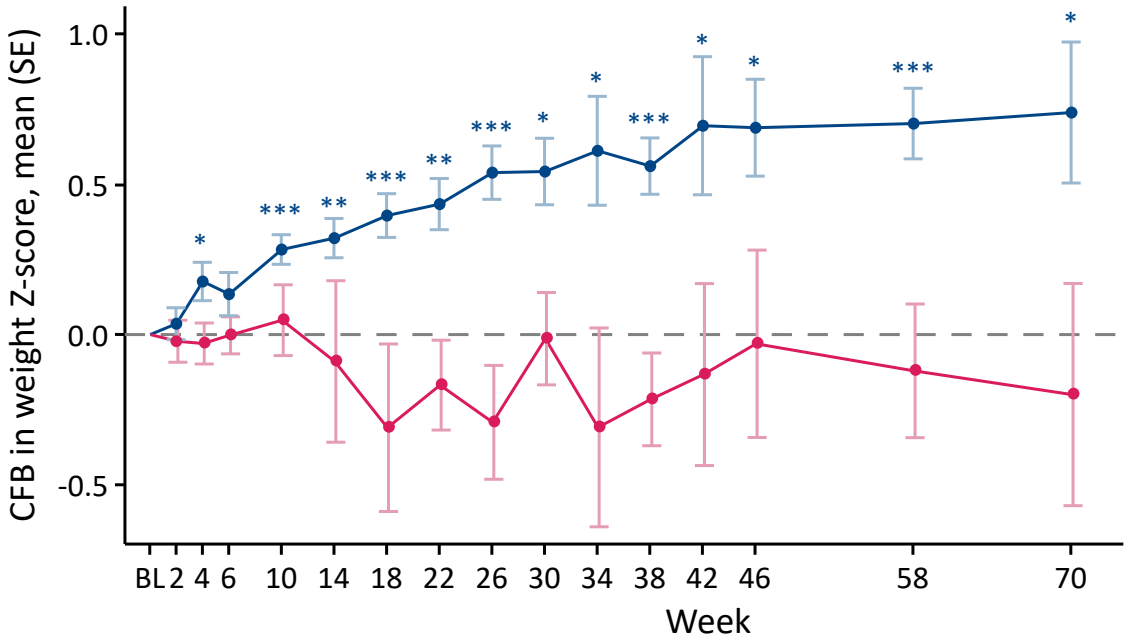
In both cohorts, greater improvements in height Z-scores in pruritus responders versus nonresponders were sustained out to 70 weeks

BSEP, bile salt export pump; CFB, change from baseline; FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; MYO5B, myosin Vb; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; TJP2, tight junction protein 2. [a]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively.

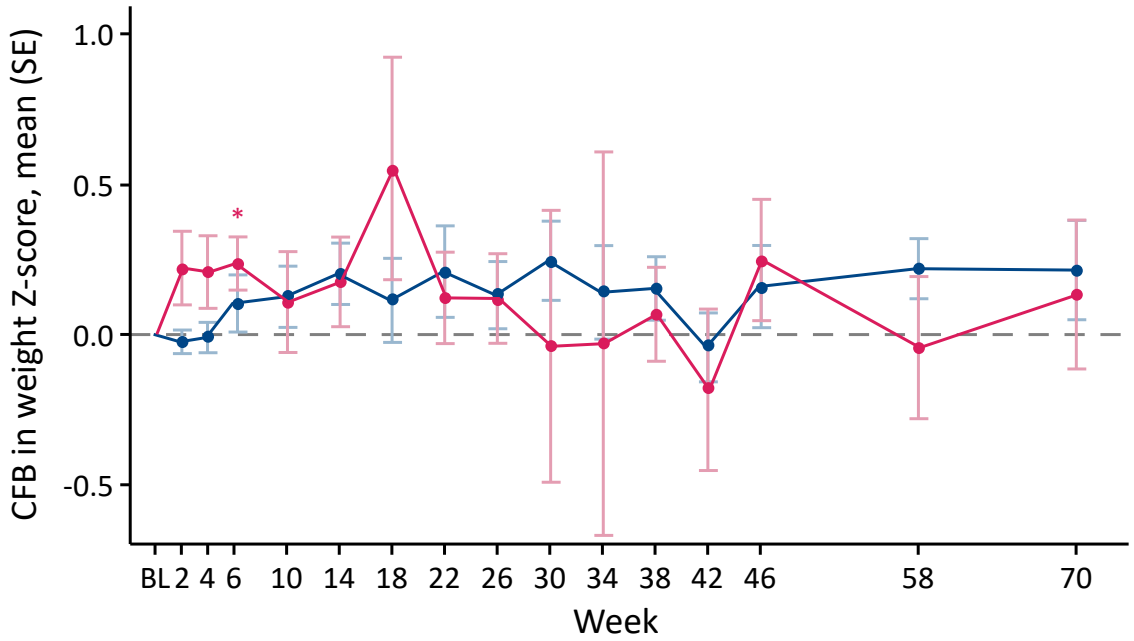
Sustained Significant Improvements in Weight Were Observed in Pruritus Responders in the BSEP Cohort

Mean CFB in Weight Z-Score Over Time[a,b]

BSEP Cohort



FIC1/TJP2/MYO5B Cohort



ItchRO(Obs) responders — ItchRO(Obs) nonresponders

Responders	18	17	15	17	17	17	17	17	18	8	6	16	6	9	17	12	
Nonresponders	10	9	8	9	8	9	8	9	9	5	4	8	4	4	7	5	

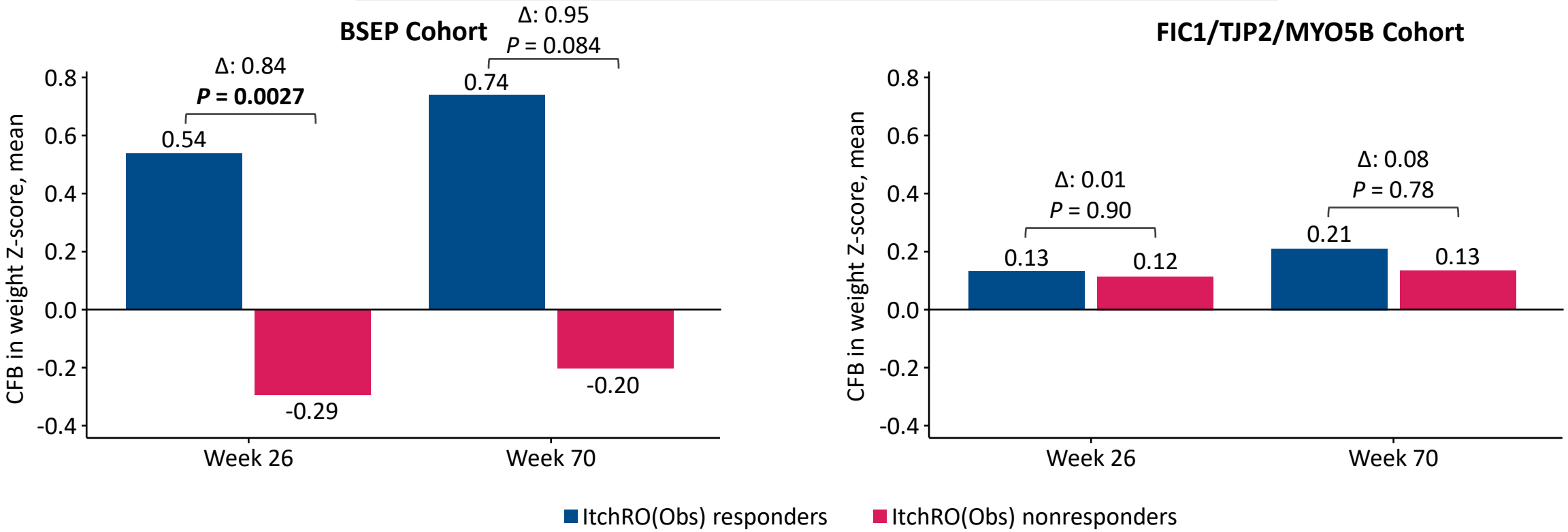
Responders	11	9	9	11	11	11	10	11	11	9	8	10	8	9	9	8	
Nonresponders	12	8	10	11	10	11	10	11	11	3	2	8	5	5	8	7	

In the BSEP cohort, significant improvements in weight Z-score from Baseline were observed in pruritus responders at Week 26 in MARCH ($P < 0.0001$) and sustained in MARCH-ON out to 70 weeks of treatment ($P < 0.05$)

BL, baseline; BSEP, bile salt export pump; CFB, change from baseline; FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; MYO5B, myosin Vb; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; SE, standard error; TJP2, tight junction protein 2. [a]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively. [b]Two-tailed *P* value for Student's t test: * ≤ 0.05, ** ≤ 0.001, *** ≤ 0.0001.

Weight Z-Score by Analysis Timepoints in the BSEP and FIC1/TJP2/MYO5B Cohorts

Mean CFB in Weight Z-Score by Analysis Timepoints[a]



	Week 26	Week 70
Responders	18	12
Nonresponders	9	5

	Week 26	Week 70
Responders	11	8
Nonresponders	11	7

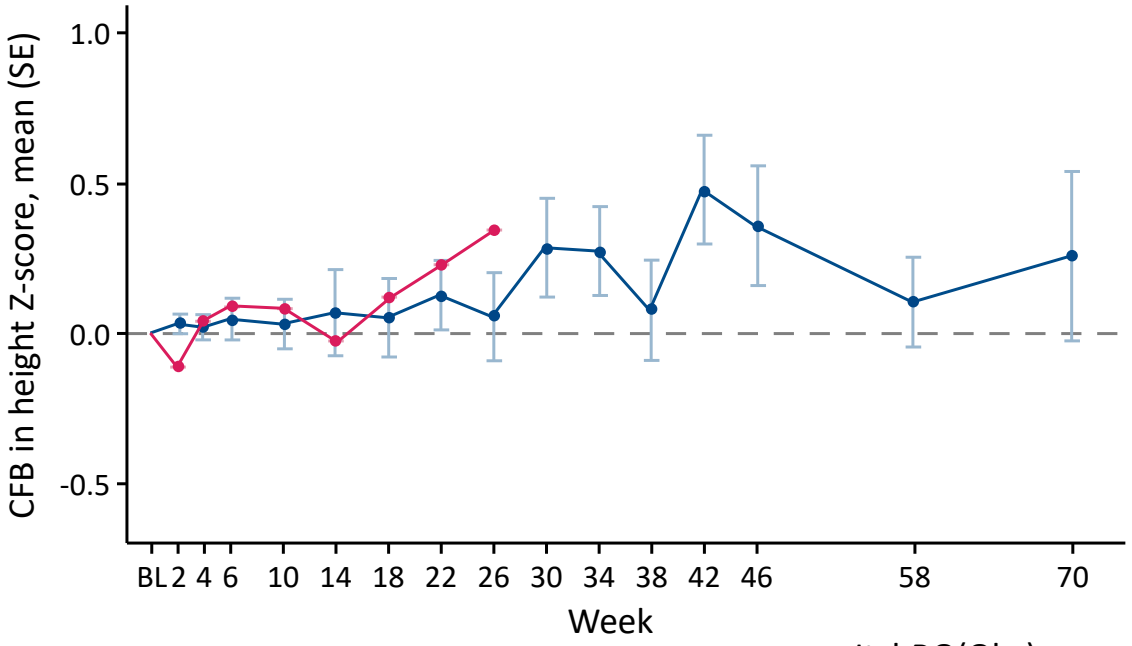
In the BSEP cohort, significant differences between pruritus responders and nonresponders in weight Z-score were observed at Week 26 (*P* = 0.0027) and numerical improvements were sustained out to Week 70

BSEP, bile salt export pump; CFB, change from baseline; FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; MYO5B, myosin Vb; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; TJP2, tight junction protein 2. [a]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively.

Mean Height and Weight Score Over Time in the MDR3 Cohort

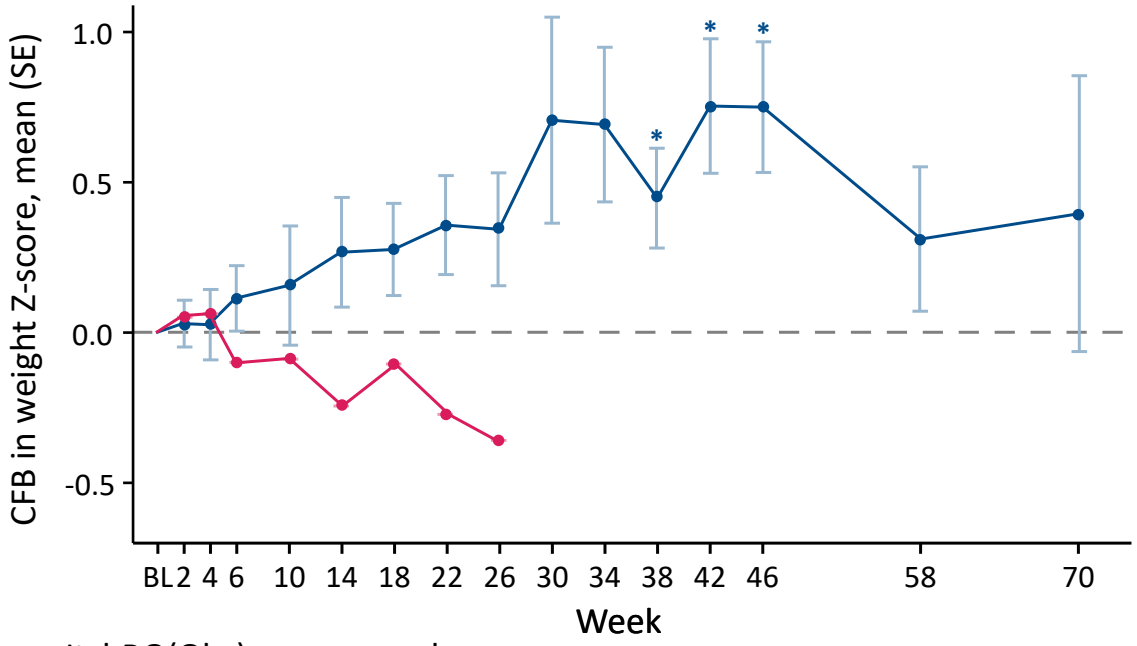
Mean CFB in Height and Weight Z-Score Over Time[a,b]

Height MDR3 Cohort



Responders	8	7	8	8	8	8	8	8	7	4	4	8	4	4	7	3	
Nonresponders	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	

Weight MDR3 Cohort



Responders	8	7	8	8	8	8	8	8	7	4	4	8	4	4	7	3	
Nonresponders	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	

ItchRO(Obs) responders — ItchRO(Obs) nonresponders

Improvements in height and weight Z-scores in pruritus responders in the MDR3 cohort were sustained out to Week 70

BL, baseline; CFB, change from baseline; ItchRO(Obs), Itch-Reported Outcome (Observer); MDR3, multidrug resistance protein 3; MRX, maralixibat; PBO, placebo; SE, standard error.
[a]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively. [b]Two-tailed *P* value for Student's t test: * ≤ 0.05.

Potential Mechanisms for Improved Growth After Maralixibat Treatment in PFIC

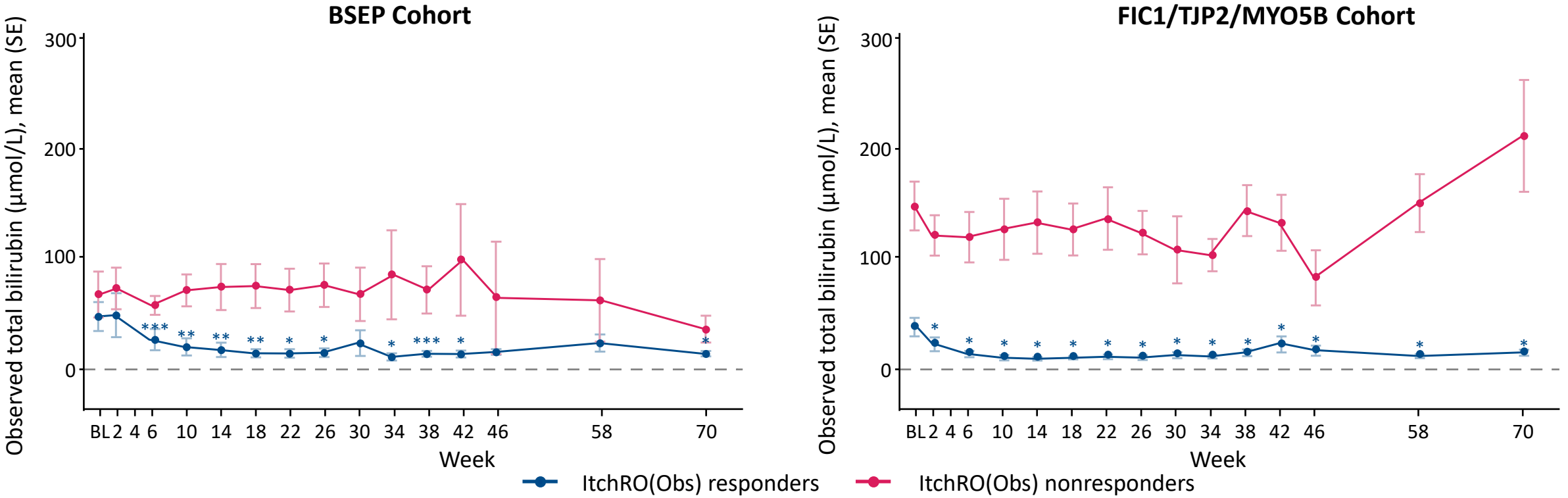
- Disease-modifying effects
- Improvement in sleep which has been linked to growth hormone release and healthy body composition[1]
- Improvements in caloric utilisation

PFIC, progressive familial intrahepatic cholestasis.

1. Stich FM, et al. *Neuroendocrinology*. 2022;112:673-701.

Mean Total Bilirubin Over Time in the BSEP and FIC1/TJP2/MYO5B Cohort[a,b]

Mean Observed Total Bilirubin Score Over Time



Responders	18	17	17	17	18	18	17	18	9	7	17	7	10	18	12	
Nonresponders	10	9	10	8	10	8	9	9	5	4	9	5	4	7	5	

Responders	11	10	11	11	10	10	11	11	9	8	11	8	9	9	8	
Nonresponders	12	8	10	10	10	11	11	11	4	4	8	5	5	8	6	

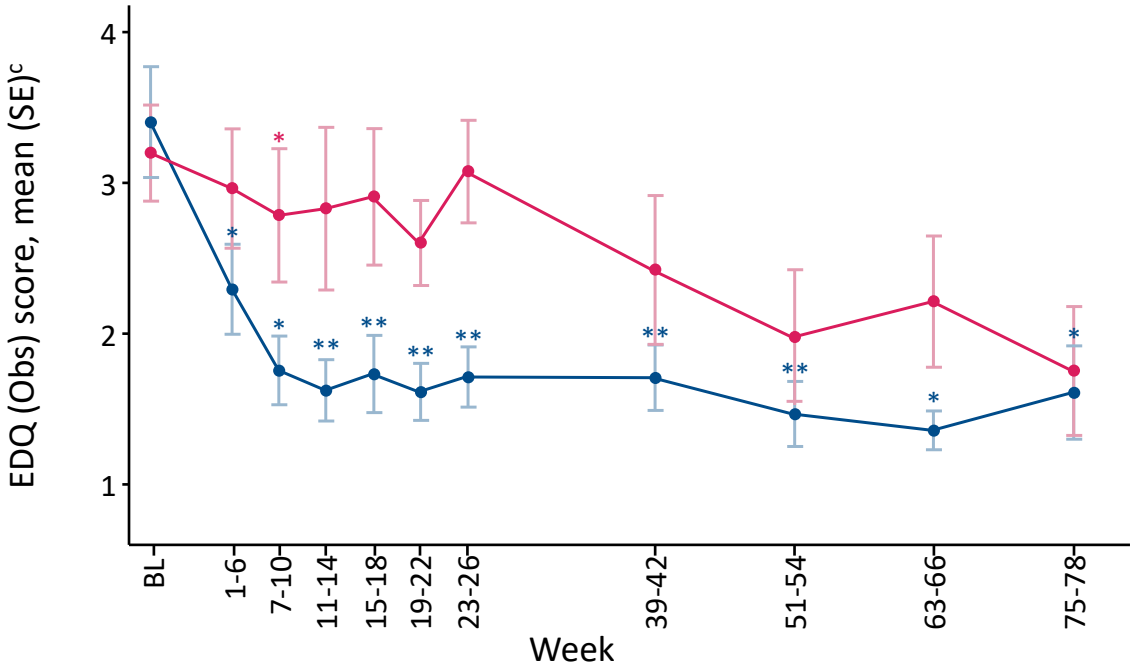
In both cohorts, lower levels of bilirubin were sustained out to Week 70 in pruritus responders compared with non-responders

BL, baseline; BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; MYO5B, myosin Vb; PBO, placebo; SE, standard error; TJP2, tight junction protein 2.[a]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively.
[b]Two-tailed *P* value for Student's t test: * ≤ 0.05, ** ≤ 0.001, *** ≤ 0.0001.

Mean Sleep Disturbance Score Over Time in the BSEP and FIC1/TJP2/MYO5B Cohorts[a,b]

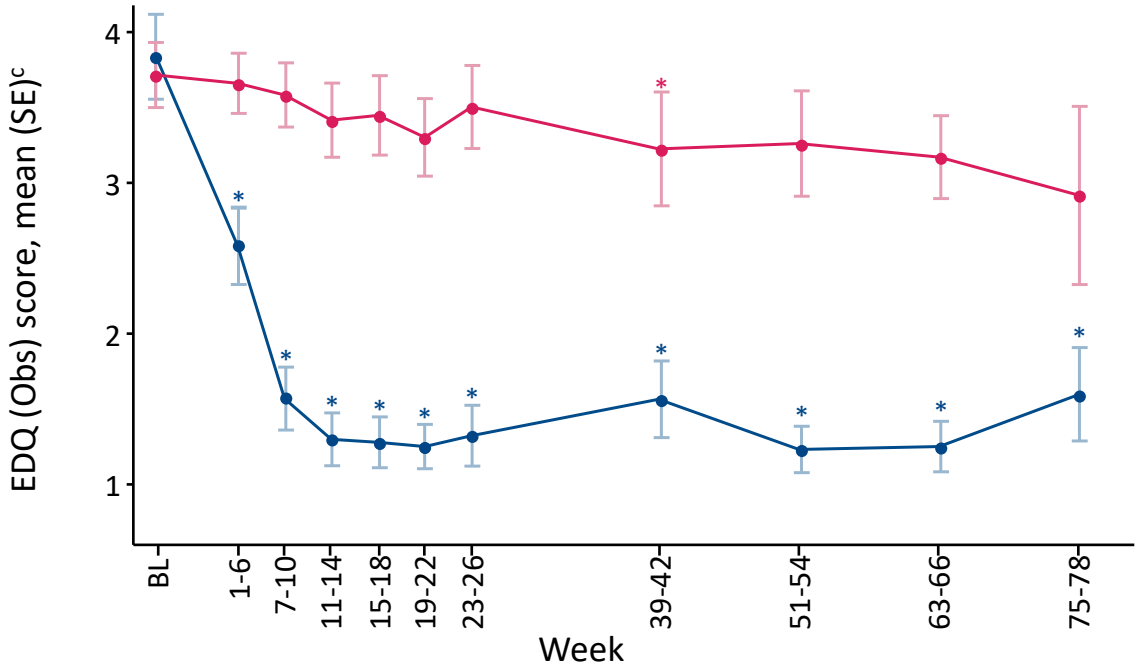
Mean Observed EDQ(Obs) Score Over Time

BSEP Cohort



Responders	13	13	13	13	13	13	13	13	12	10	9
Nonresponders	8	8	8	7	8	7	8	8	5	6	4

FIC1/TJP2/MYO5B Cohort



Responders	9	9	9	9	9	9	9	9	9	9	7
Nonresponders	12	12	12	11	11	11	11	9	9	7	4

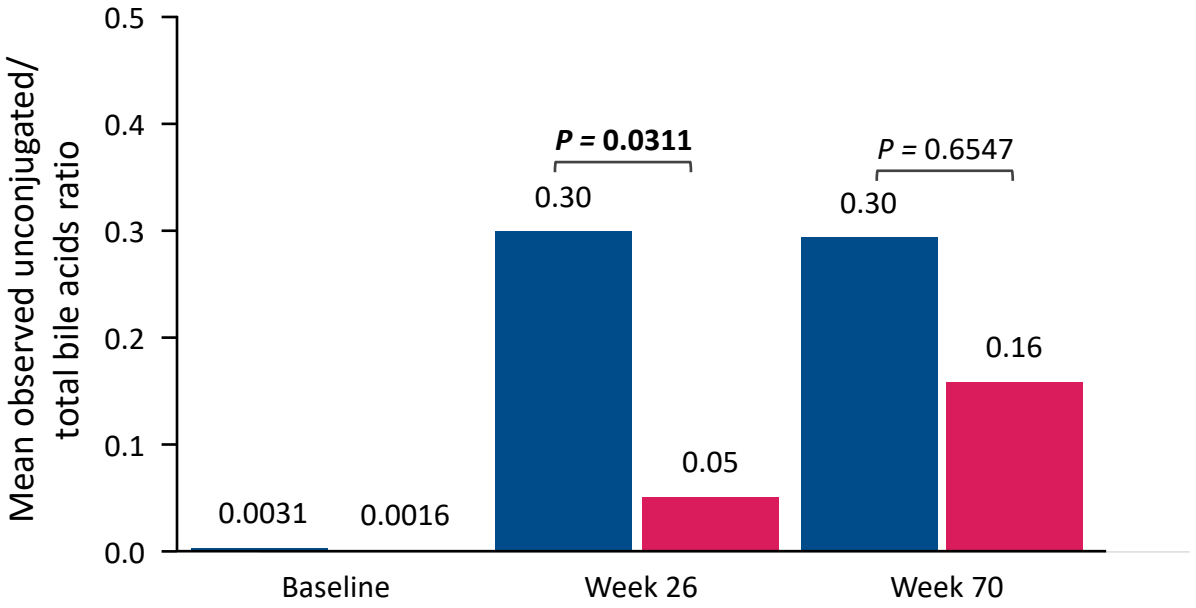
ItchRO(Obs) responders ItchRO(Obs) nonresponders

In both cohorts, significant improvements in sleep were obsevered in pruritus responders versus non-responders and sustained out to Week 70 ($P < 0.05$)

BL, baseline; BSEP, bile salt export pump; EDQ(Obs), exploratory diary questionnaire (observer); FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; MYO5B, myosin Vb; PBO, placebo; SE, standard error; TJP2, tight junction protein 2. [a]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively. [b]Two-tailed *P* value for Student's t test: * ≤ 0.05, ** ≤ 0.001. [c]EDQ(Obs) is a 1-5 scale (1 = never to 5 = almost always) that includes questions focused on sleep disturbances related to pruritus.

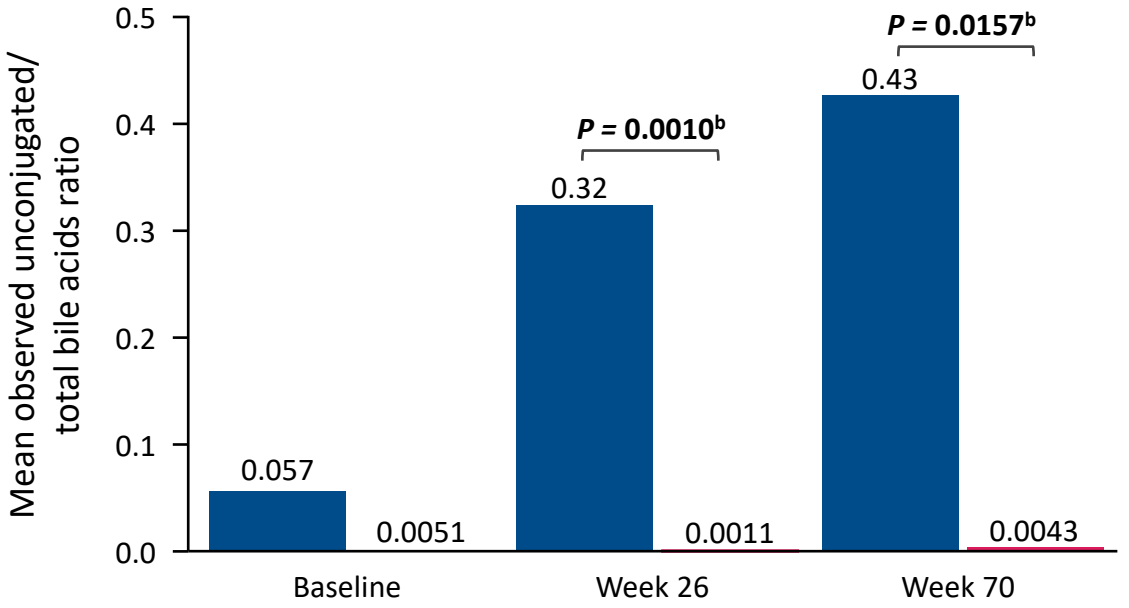
Unconjugated BA/Total BA by Analysis Timepoints in the BSEP and FIC1/TJP2/MYO5B Cohorts[a]

BSEP Cohort



	Baseline	Week 26	Week 70
Responders	16	18	13
Nonresponders	9	9	5

FIC1/TJP2/MYO5B Cohort



	Baseline	Week 26	Week 70
Responders	11	10	8
Nonresponders	12	11	6

ItchRO(Obs) responders ■ ItchRO(Obs) nonresponders

In both cohorts serum bile acid analysis revealed a significant increase in unconjugated/total BA in pruritus responders versus non-responders which was sustained out to Week 70

BA, bile acid; BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; MYO5B, myosin Vb; PBO, placebo; TJP2, tight junction protein 2.
[a]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline for the PBO-MRX group is from MARCH-ON, respectively.

Conclusions

- Among participants who were treated with maralixibat in MARCH/MARCH-ON, significant improvements in growth were observed in pruritus responders compared to non-responders that were sustained out to 70 weeks of treatment
- The consistent trends in growth observed for participants who received maralixibat and were pruritus responders indicate a potential disease-modifying effect of maralixibat treatment in PFIC
- Additional research is needed to better understand the relationship between pruritus response and improvements in growth

PFIC, progressive familial intrahepatic cholestasis.

Acknowledgements

- The authors would like to thank the clinical trial participants, their families, and investigators for their participation in the MARCH and MARCH-ON clinical studies

Disclosures

- AGM is a consultant and has a sponsored research agreement for Mirum Pharmaceuticals, Inc.
- AAA is a consultant for Mirum Pharmaceuticals, Inc., Albireo/Ipsen, and Sarepta Therapeutics.
- CHL has nothing to disclose.
- DBM, TN, JTR, MB, and PV are employees of and shareholders in Mirum Pharmaceuticals, Inc.

Thank You!