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

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Faculty Disclosure

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership/ Equity Position	Employee	Other (please specify)
Mirum Pharmaceuticals, Inc.[a]		X	X					

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

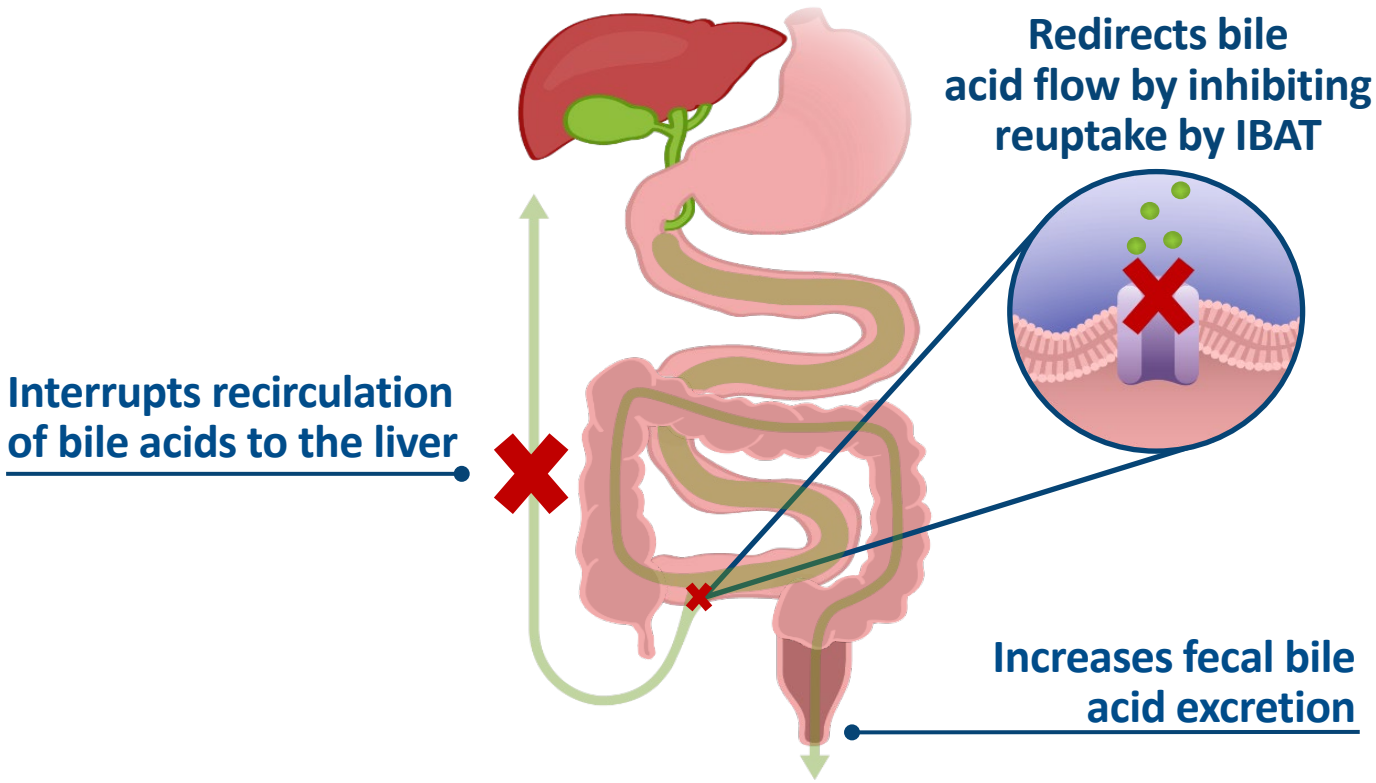
Progressive Familial Intrahepatic Cholestasis

- 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[6-10,a-b]

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]Maralixibat is an IBAT inhibitor approved by the FDA for the treatment of pruritus in patients with PFIC 12 months of age and older in the US and approved for the treatment of PFIC in patients 3 months of age and older in the EU.[7,8]
[b]Odevixibat is an IBAT inhibitor approved by the FDA for the treatment of pruritus in patients with PFIC 3 months of age and older in the US and approved for the treatment of PFIC in patients 6 months of age and older in the EU.[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;**4**:**1**. **7.** LIVMARLI® (maralixibat) [prescribing information]. Foster City, CA; Mirum Pharmaceuticals, Inc. July 2024. **8.** LIVMARLI® (maralixibat) [summary of product characteristics]. Amsterdam, Netherlands; Mirum Pharmaceuticals International B.V. July 2024. **9.** BYLVAY® (odevixibat) [prescribing information]. Cambridge, MA; Ipsen Biopharmaceuticals, Inc.; Jan 2024. **10.** 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 cholestatic pruritus in patients with PFIC ≥12 months of age in the US and for the treatment of PFIC in patients ≥3 months of age in the EU[4,5]

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) [prescribing information]. Foster City, CA; Mirum Pharmaceuticals, Inc. July 2024. **5.** LIVMARLI® (maralixibat) [summary of product characteristics]. Amsterdam, Netherlands; Mirum Pharmaceuticals International B.V. July 2024.

Study Overviews: MARCH and MARCH-ON

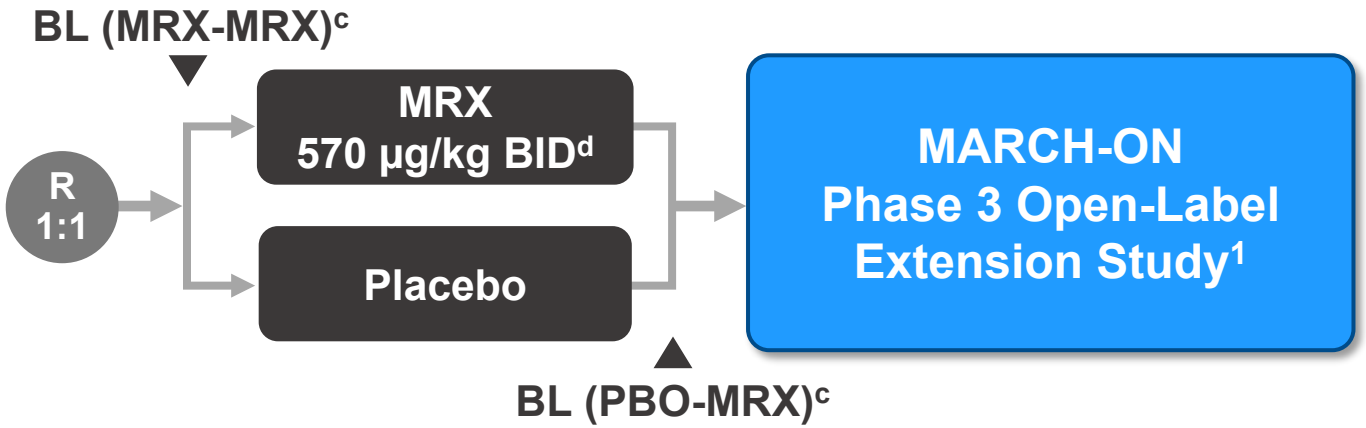
- MARCH (NCT03905330) was a phase 3, randomized, double-blind, placebo-controlled, 26-week trial investigating the efficacy and safety of maralixibat in participants with PFIC across the broadest range of PFIC types studied to date[1,2]
  - MARCH-ON (NCT04185363) was an open-label extension study for 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 September 13, 2024. https://clinicaltrials.gov/ct2/show/NCT03905330 **2.** Miethke AG, et al. *Lancet Gastroenterol Hepatol*. 2024;9:620-631.
3. ClinicalTrials.gov identifier: NCT04185363. Updated May 29, 2024. Accessed September 12, 2024. https://www.clinicaltrials.gov/study/NCT04185363 **4.** Gonzalez-Peralta RP, et al. Presented at EASL 2024.

MARCH-ON: Study Design

Key Entry Criteria
- Diagnosis of PFIC
- Age ≥12 months and <18 years at Baseline
- Persistent, moderate to severe pruritus[a]
- sBA ≥3 × ULN[b]



Key endpoints and assessments
- Pruritus
- sBA
- Bilirubin
- Growth Z-scores
- EDQ Sleep Disturbance

- 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 0-4 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 analyzed
- 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, randomization; sBA, serum bile acid.
TEAE, treatment-emergent adverse event; 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 May 29, 2024. Accessed September 12, 2024. https://www.clinicaltrials.gov/study/NCT04185363 **2.** Kamath BM, et al. *Hepatol Commun*. 2020;4:1012-1018.

Baseline Demographic Characteristics

Variable[a]	BSEP (n=28)		All-PFIC (N=60)	
	ItchRO(Obs) responders (n=18) 64%	ItchRO(Obs) nonresponders (n=10)	ItchRO(Obs) responders (n=37) 62%	ItchRO(Obs) nonresponders (n=23)
Age, y	6.2	5.2	6.0	3.9
Sex, male, %	27.8	50.0	40.5	52.2
Pruritus, ItchRO(Obs) score[b]	2.6	2.2	2.5	2.6
Total sBA, µmol/L	302	331	247	285
ALT, U/L	94	139	92	97
AST, U/L	116	138	106	107
Total bilirubin, mg/dL	2.7	3.9	3.0	6.4
Direct bilirubin, mg/dL	1.9	2.9	2.2	4.8
Height Z-score	-1.9	-2.4	-1.8	-2.6
Weight Z-score	-1.0	-1.4	-1.2	-1.8

- PFIC types included in the analysis were nt-BSEP (n=28 [responders, n=18; nonresponders, n=10]), FIC1 (n=13 [responders, n=3; nonresponders, n=10]), MDR3 (n=9 [responders, n=8; nonresponders, n=1]), TJP2 (n=7 [responders, n=5; nonresponders, n=2]), and MYO5B (n=3 [responders, n=3])

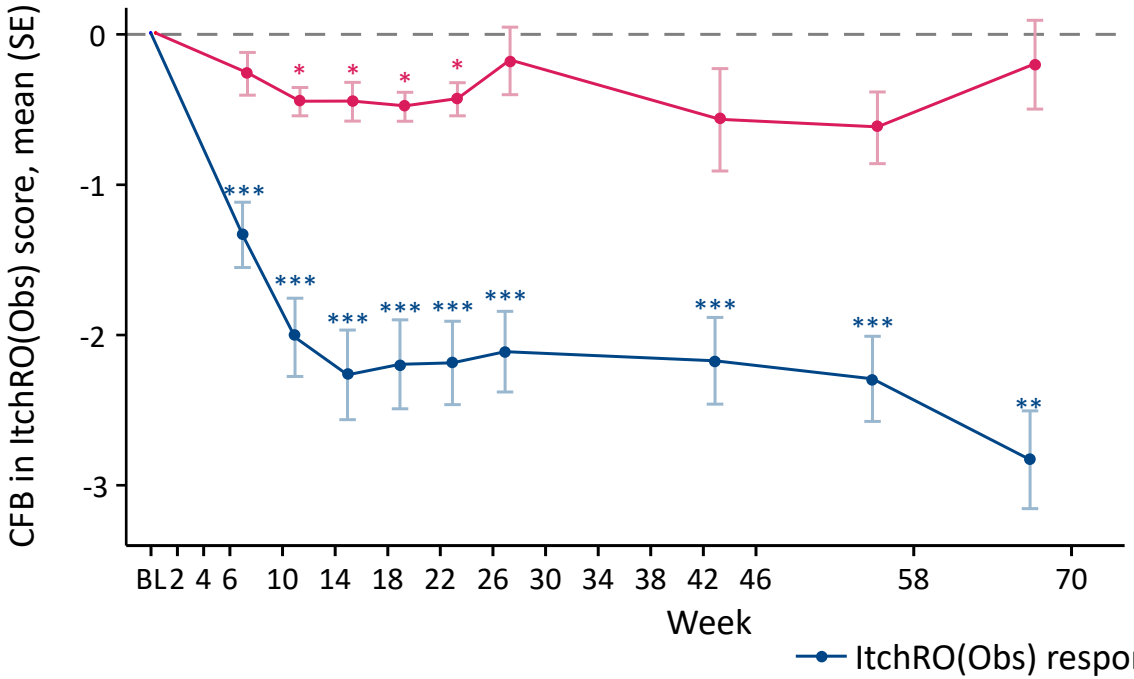
Growth was stunted at Baseline across all groups

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; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid; TJP2, tight junction protein 2; UDCA, ursodeoxycholic acid.
[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

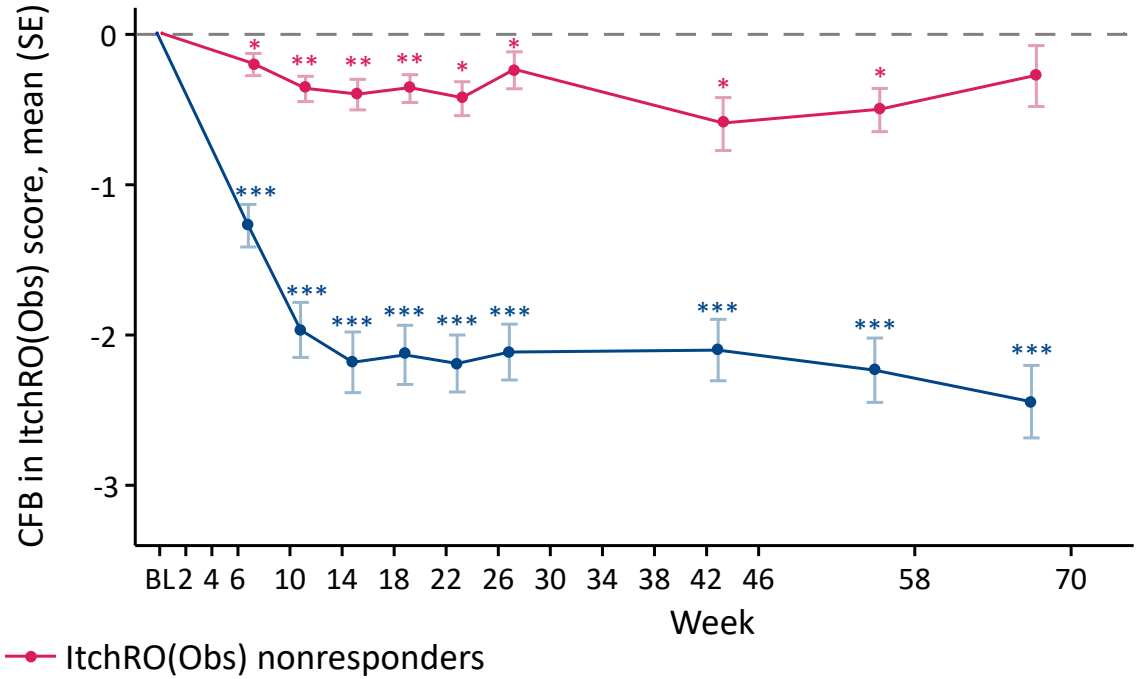
Mean CFB in Monthly Average Morning ItchRO(Obs) Scores Over Time[a,b]

BSEP Cohort



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

All-PFIC Cohort



Responders	37	37	37	36	37	36	37	37	32	27
Nonresponders	23	23	23	21	22	20	21	18	15	13

ItchRO(Obs) responders — ItchRO(Obs) nonresponders

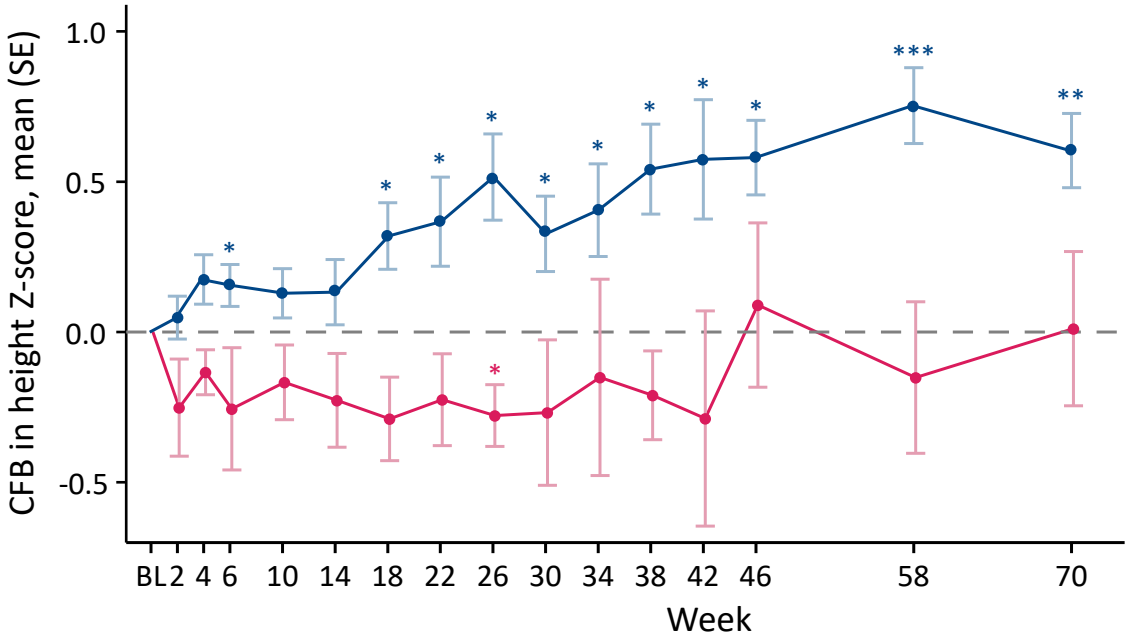
In both cohorts, significant improvements in ItchRO(Obs) from Baseline were observed in pruritus responders at Week 26 in MARCH (*P*<0.0001) and sustained in MARCH-ON out to 70 weeks of treatment (*P*<0.001)

BL, baseline; BSEP, bile salt export pump; CFB, change from baseline; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; 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, ** ≤0.001 , *** ≤0.0001.

Sustained Significant Improvements in Height Were Observed in Pruritus Responders

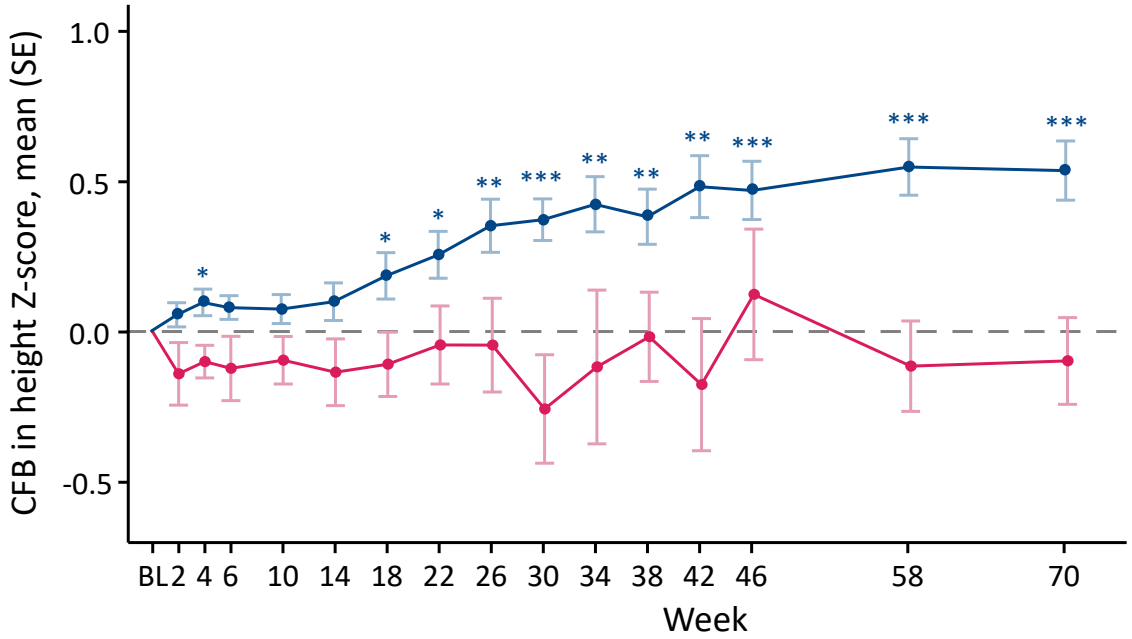
Mean CFB in Height Z-Score Over Time[a,b]

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

All-PFIC Cohort



Responders	37	33	32	36	36	35	34	36	36	21	18	34	18	22	33	23
Nonresponders	23	18	19	21	19	19	19	20	21	8	6	15	9	9	15	12

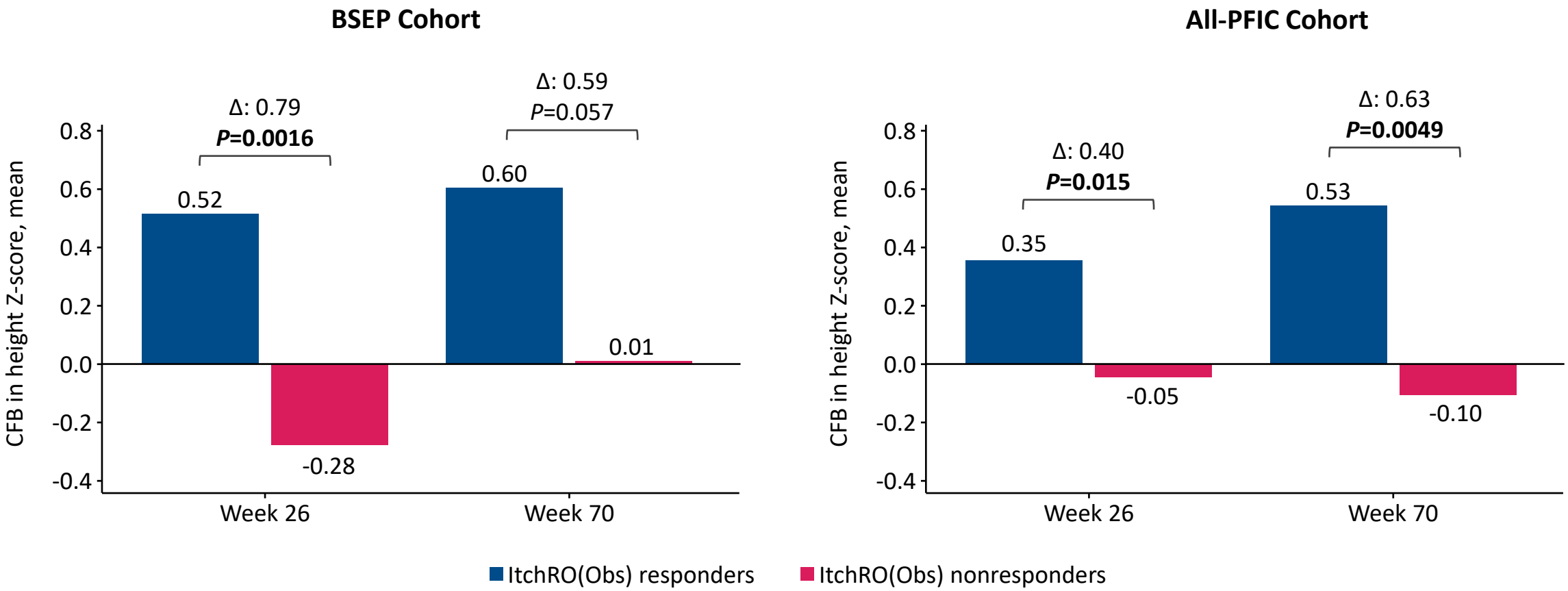
ItchRO(Obs) responders — ItchRO(Obs) nonresponders

In the All-PFIC cohort, significant improvements in height 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*<0.0001)

BL, baseline; BSEP, bile salt export pump; CFB, change from baseline; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; 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, ** ≤0.001 , *** ≤0.0001.

Pruritus Responders Had Improved Height Compared With Nonresponders

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



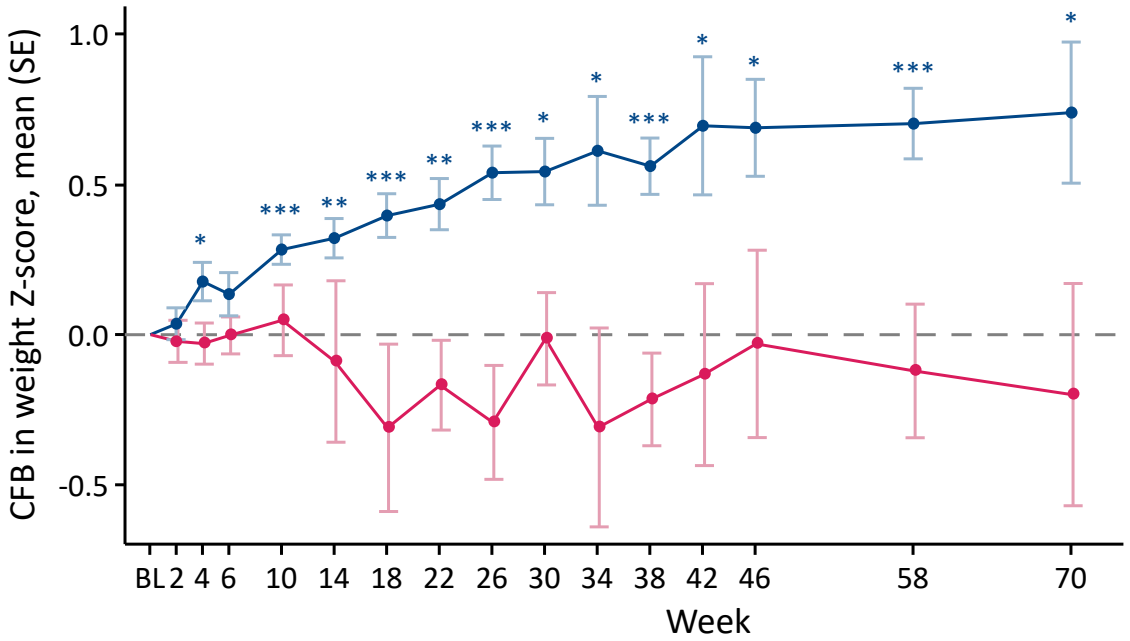
In the All-PFIC cohort, significant differences in height Z-score between pruritus responders and nonresponders were sustained out to 70 weeks (*P*=0.0049)

BSEP, bile salt export pump; CFB, change from baseline; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis.
[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.

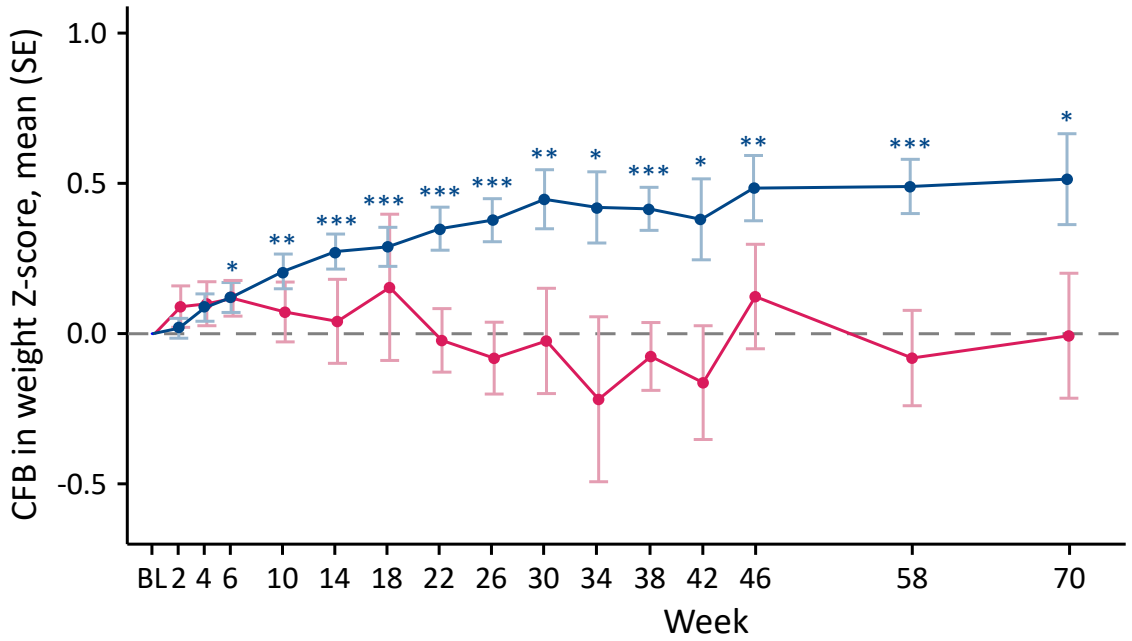
Sustained Significant Improvements in Weight Were Observed in Pruritus Responders

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

BSEP Cohort



All-PFIC 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	

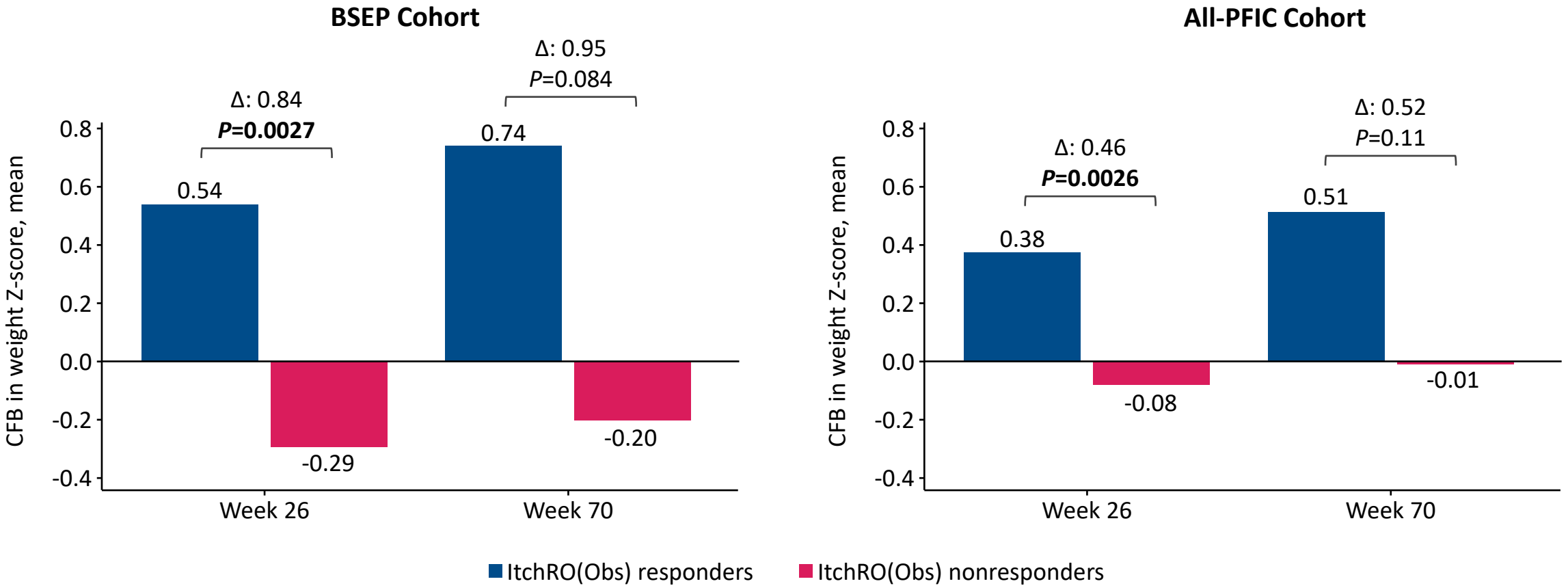
Responders	37	33	32	36	36	36	35	36	36	21	18	34	18	22	33	23	
Nonresponders	23	18	19	21	19	21	19	21	21	8	6	16	9	9	15	12	

In the All-PFIC 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*<0.0001)

BL, baseline; BSEP, bile salt export pump; CFB, change from baseline; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; 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, ** ≤0.001 , *** ≤0.0001.

Pruritus Responders Had Improved Weight Compared With Nonresponders

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



In the All-PFIC cohort, significant differences between pruritus responders and nonresponders in weight Z-score were observed at Week 26 (*P*=0.0026) and numerical improvements were sustained out to Week 70

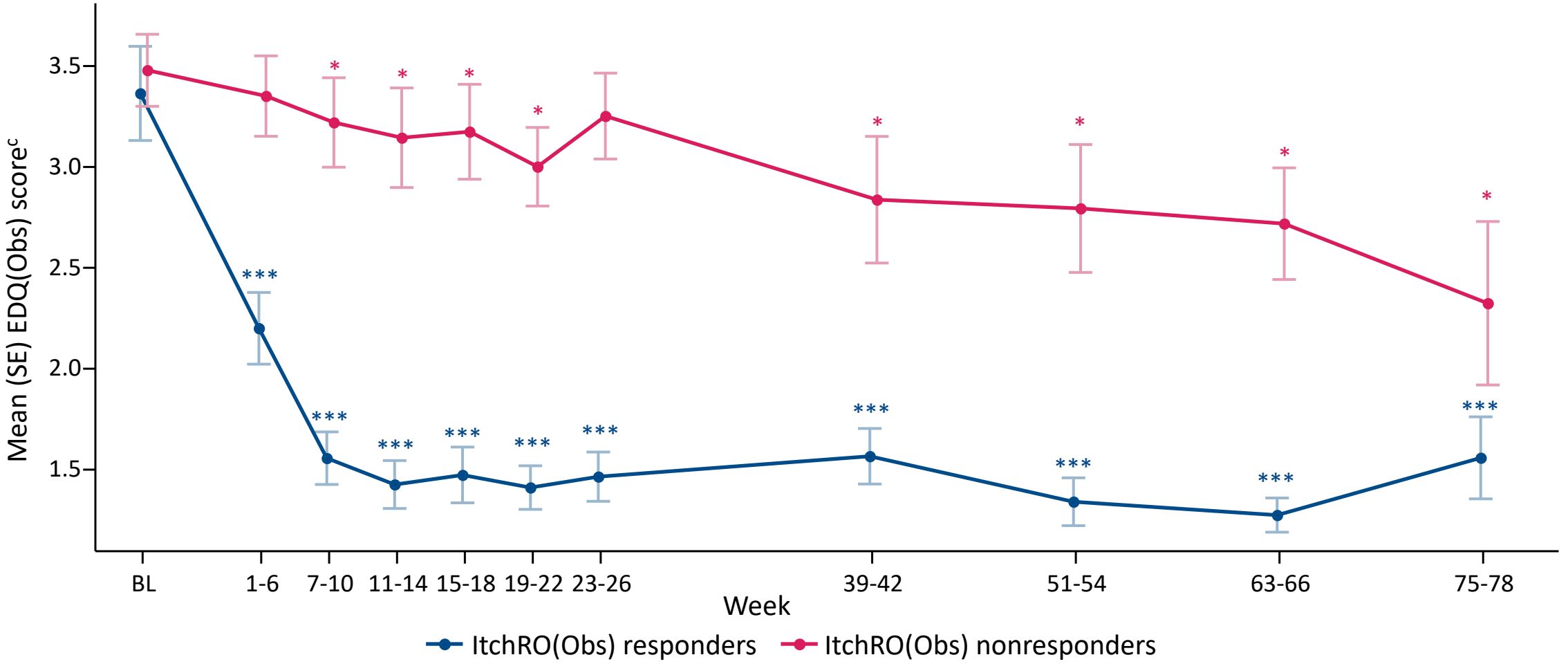
BSEP, bile salt export pump; CFB, change from baseline; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis.
[a]Combines results from MRX-MRX and PBO-MRX treatment groups. Baseline for the MRX-MRX group is from MARCH and Baseline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

Potential Mechanisms for Improved Growth After Maralixibat Treatment in PFIC

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

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

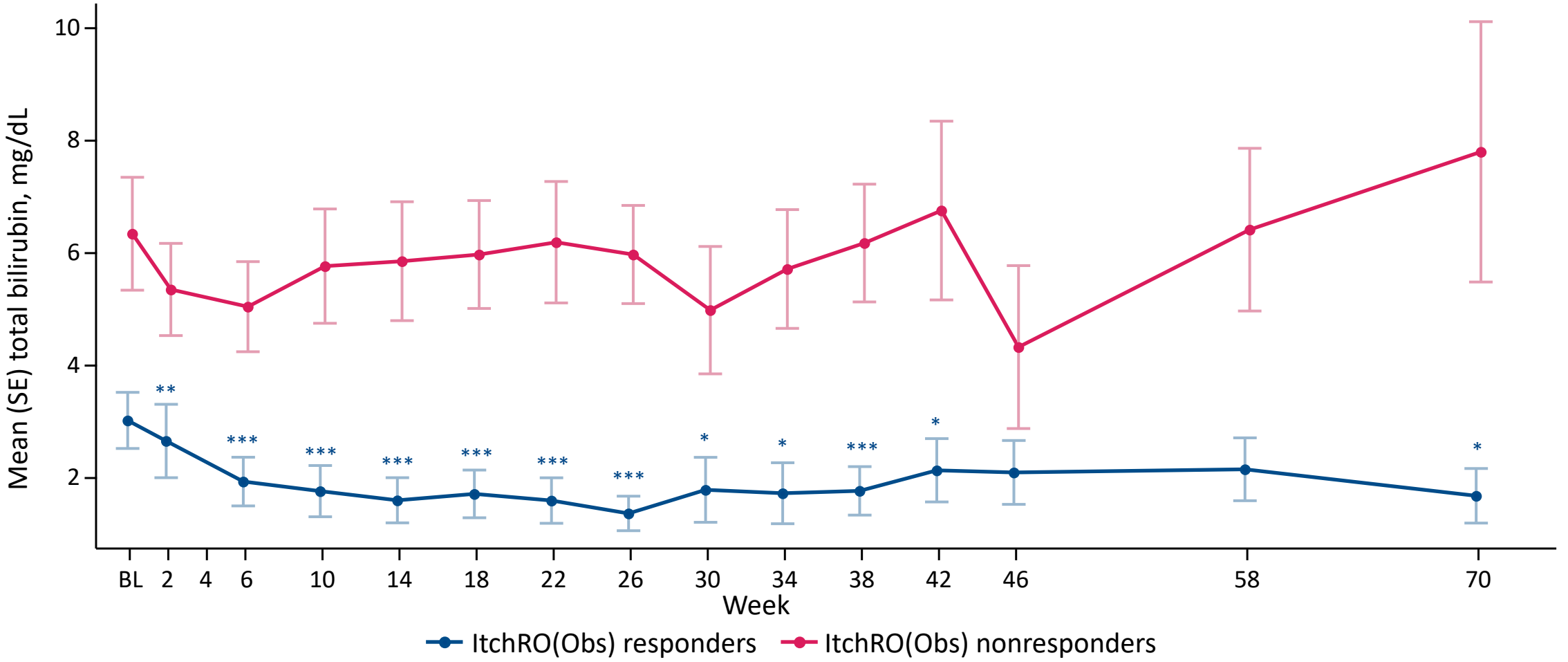
Mean Sleep Disturbance Score Over Time in the All-PFIC Cohort[a,b]



Responders	28	28	28	27	28	28	28	27	26	24	17
Nonresponders	21	21	21	19	20	19	20	17	14	13	8

BL, baseline; EDQ(Obs), exploratory diary questionnaire (observer); ItchRO(Obs), Itch-Reported Outcome (Observer); 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, *** ≤0.0001.
[c]EDQ(Obs) is a 1-5 scale (1=never to 5=almost always) that includes questions focused on sleep disturbances related to pruritus.

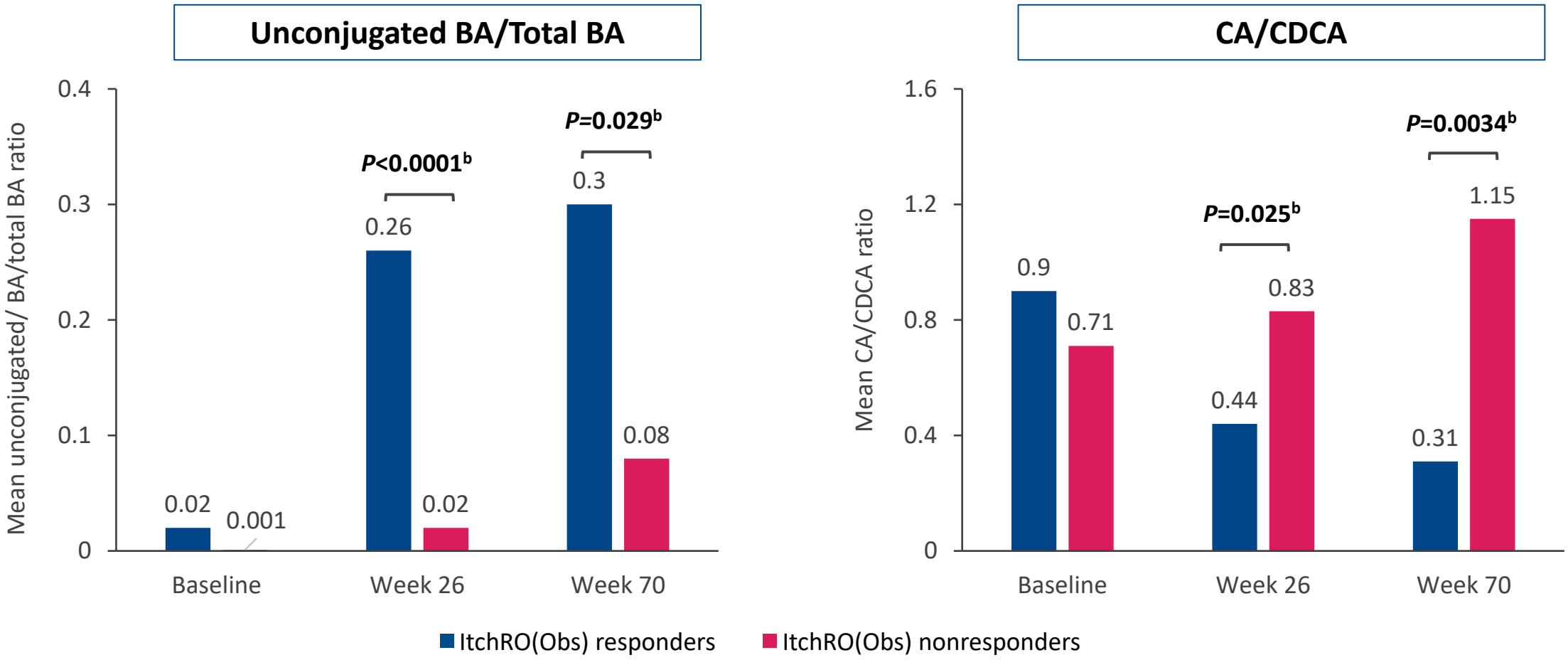
Mean Total Bilirubin Over Time in the All-PFIC Cohort[a,b]



Responders	37	34	36	36	36	36	36	36	23	21	36	21	25	34	25
Nonresponders	23	18	21	19	21	20	21	20	9	9	17	10	9	15	11

BL, baseline; ItchRO(Obs), Itch-Reported Outcome (Observer); 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, ** ≤0.001 , *** ≤0.0001.

Unconjugated BA/Total BA and CA/CDCA Ratios by Analysis Timepoints in the All-PFIC Cohort[a]



- **Serum BA analysis revealed a significant increase in unconjugated/total BA and decrease in CA/CDCA in responders[1]**
- **Activity of *CYP8B1* controls CA/CDCA and is linked to efficiency in fat absorption and whole-body insulin sensitization[2,3]**

BA, bile acid; CA, cholic acid; CDCA, chenodeoxycholic acid; ItchRO(Obs), Itch-Reported Outcome (Observer); MRX, maralixibat; PBO, placebo; sBA, serum bile acid.
[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]Wilcoxon rank sum test was used to determine if the difference between responders and nonresponders was statistically significant.

1. Verkade HJ, et al. Presented at AASLD; Nov 15-19, 2024, Poster 4436. **2.** Zhong S, et al. *J Clin Invest.* 2022;132(21):e152961. **3.** Bertaggia E, et al. *Am J Physiol Endocrinol Metab.* 2017;313(2):E121-E133.

Conclusions

- Among participants who were treated with maralixibat in MARCH/MARCH-ON, significant improvements in growth were observed in pruritus 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

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Disclosures

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- 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.
- RJT is a consultant for Mirum Pharmaceuticals, Inc., Albireo/Ipsen, Generation Bio, Rectify Therapeutics, and Alnylam and a shareholder in Generation Bio and Rectify Therapeutics.

Thank You!