Maralixibat Improves Cholestatic Pruritus and Bile Acids in Children With FIC1: Data From the MARCH-PFIC Trial

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Faculty Disclosure

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	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						
GenerationBio		x			x			
Rectify Therapeutics		x			x			
Alnylam		x						

Richard J Thompson

- Professor of Molecular Hepatology at King's College London, and Honorary Consultant Paediatric Hepatologist at King's College Hospital, London
- Specialises in genetic liver disease in both children and adults
- Through worldwide collaborations, his laboratory continues to identify new causes of genetic liver disease
- Clinical lead for a diagnostic laboratory specialising in liver and gastrointestinal disease

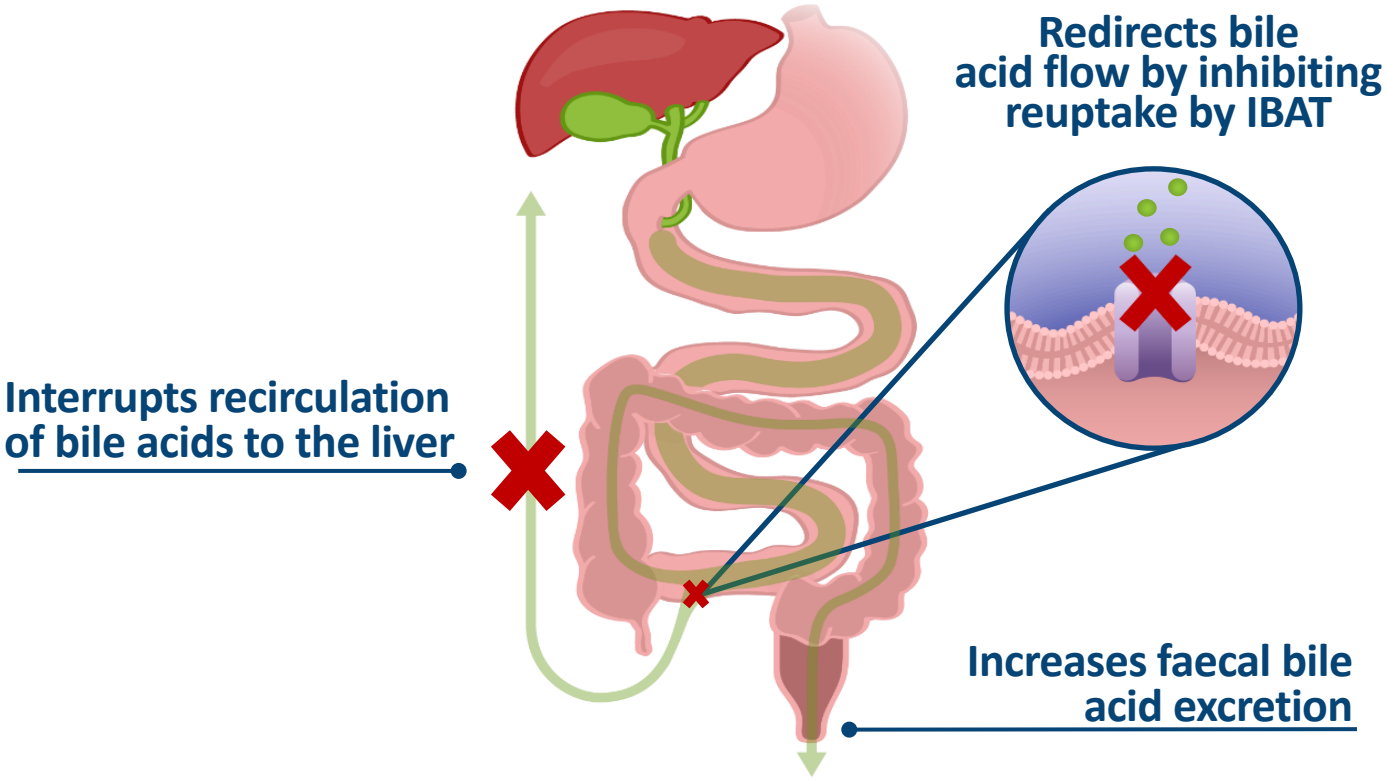
Progressive Familial Intrahepatic Cholestasis (PFIC)

- Disrupted bile composition and chronic cholestasis[1]
- Debilitating pruritus, impaired growth, reduced QoL, most children undergoing liver transplant[2-5]
  - FIC1 (*ATP8B1*) is widely expressed
- Treatments include off-label antipruritics, surgical biliary diversion, transplant and IBAT inhibitors[6-8,*]
- MARCH, the largest Phase 3 trial conducted in children with PFIC:[9]
  - Met primary and secondary endpoints, demonstrating rapid improvements in pruritus and sBA levels
  - Improvements observed in patients with BSEP (primary cohort) and across all PFIC types

The effect of higher doses of maralixibat has not been evaluated in patients with FIC1 deficiency

*Odevixibat is an IBAT inhibitor that has received FDA approval for the treatment of pruritus in patients 3 months of age and older with PFIC and is approved in the EU for the treatment of PFIC in patients 6 months of age and older.[7,8]
BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis-associated protein 1; IBAT, ileal bile acid transporter; PFIC, progressive familial intrahepatic cholestasis; QoL, quality of life; sBA, serum bile acid.
1. Jacquemin E, et al. *Clin Res Hepatol Gastroenterol.* 2012;36(Suppl 1):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. doi: 10.1186/1750-1172-4-1;
7. Albireo Pharma, Inc. BYLVAY® (odevixibat). [prescribing information]. 2021. 8. Albireo Pharma, Inc. BYLVAY ® (odevixibat). [summary of product characteristics]. Boston, MA; Albireo Pharma, Inc. Jul 2021.
9. Thompson RJ, et al. Presented at AASLD 2022.

Maralixibat: IBAT Inhibitor That Interrupts Enterohepatic Circulation



Clinical effects of maralixibat in cholestasis:

- ✓ Improvements in pruritus[1-3]
- ✓ Reduction in peripheral sBA[1-3]
- ✓ Five-year transplant-free survival in sBA responders with BSEP deficiency[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[4,5]

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

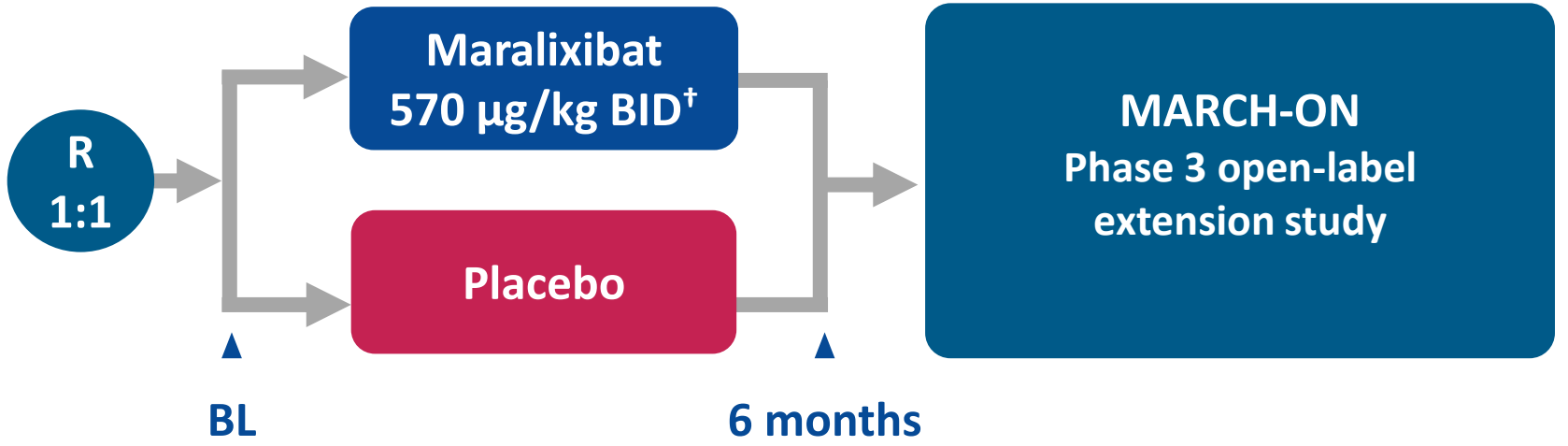
1. Thompson RJ, et al. Presented at EASL 2020; 2. Loomes MK, et al. *Hepatol Commun.* 2022;6:2379-2390; 3. Gonzales E, et al. *Lancet.* 2021;398:1581-1592;
4. Mirum Pharmaceuticals, Inc. LIVMARLI® (maralixibat) [prescribing information]. Foster City, CA; Mirum Pharmaceuticals, Inc. Mar 2023;
5. LIVMARLI™ (maralixibat) [summary of product characteristics]. Amsterdam, Netherlands; Mirum Pharmaceuticals, Inc. Dec 2022.

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.

MARCH-PFIC: Phase 3 Study Design

MARCH STUDY

Key Entry Criteria*
- Diagnosis of PFIC
- Age ≥ 12 months and < 18 years at time of Baseline
- Persistent, moderate to severe pruritus
- Cholestasis



*sBA ≥ 3 x ULN required for patients with BSEP deficiency (primary cohort). †Maralixibat 570 µg/kg is equivalent to 600 µg/kg maralixibat chloride.
BID, twice daily; BL, baseline; BSEP, bile salt export pump; PFIC, progressive familial intrahepatic cholestasis; R, randomised; sBA, serum bile acid; ULN, upper limit of normal.
ClinicalTrials.gov ID: NCT03905330. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT03905330 on 24 Mar 2023.

MARCH-PFIC: Study Populations and Key Endpoints

Full-Study Population (N = 93)

All-PFIC cohort (n = 64)

BSEP cohort: nt-BSEP (n = 31)

FIC1 (n = 13), MDR3 (n = 9), TJP2 (n = 7) and MYO5B (n = 4) (n = 33)

Exploratory cohort (n = 29)

Heterozygosis* (n = 2), t-BSEP (n = 9), variants not found (n = 8), fluctuating sBA (n = 2) and surgery (n = 8)

Key efficacy endpoints: improvements in pruritus, serum bile acids, and bilirubin

*One subject had a heterozygous *ABCB11* mutation and another had a heterozygous *ATP8B1* mutation.
BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis-associated protein 1; MDR3, multidrug-resistance 3 protein; MYO5B, myosin VB; nt, non-truncated mutations; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid; t, truncated mutations; TJP2, tight junction protein 2.

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MARCH: Key Demographics and Baseline Characteristics of Patients With FIC1 Deficiency

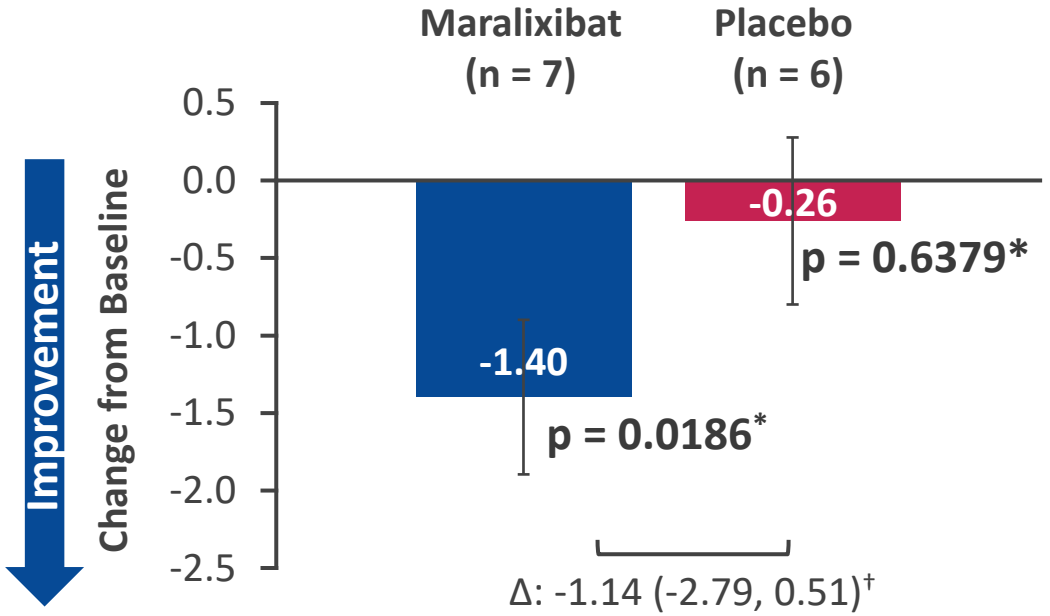
Variable	Maralixibat (n = 7)	Placebo (n = 6)	Overall (N = 13)
Age, years	3.3	1.8	2.6
Male, %	85.7	50.0	69.2
Pruritus, ItchRO(Obs)	3.18	3.39	3.27
Total sBA, μmol/L	206	206	206
UDCA usage, %	100	83.3	92.3
Rifampicin usage, %	71.4	66.7	69.2
Alanine aminotransferase, U/L	61	90	75
Total bilirubin, mg/dL	5.29	9.73	7.34
Direct bilirubin, mg/dL	3.79	7.28	5.40
Height Z-score	-2.86	-2.88	-2.87
Weight Z-score	-2.49	-1.93	-2.23

Baseline characteristics and demographics were generally balanced between groups

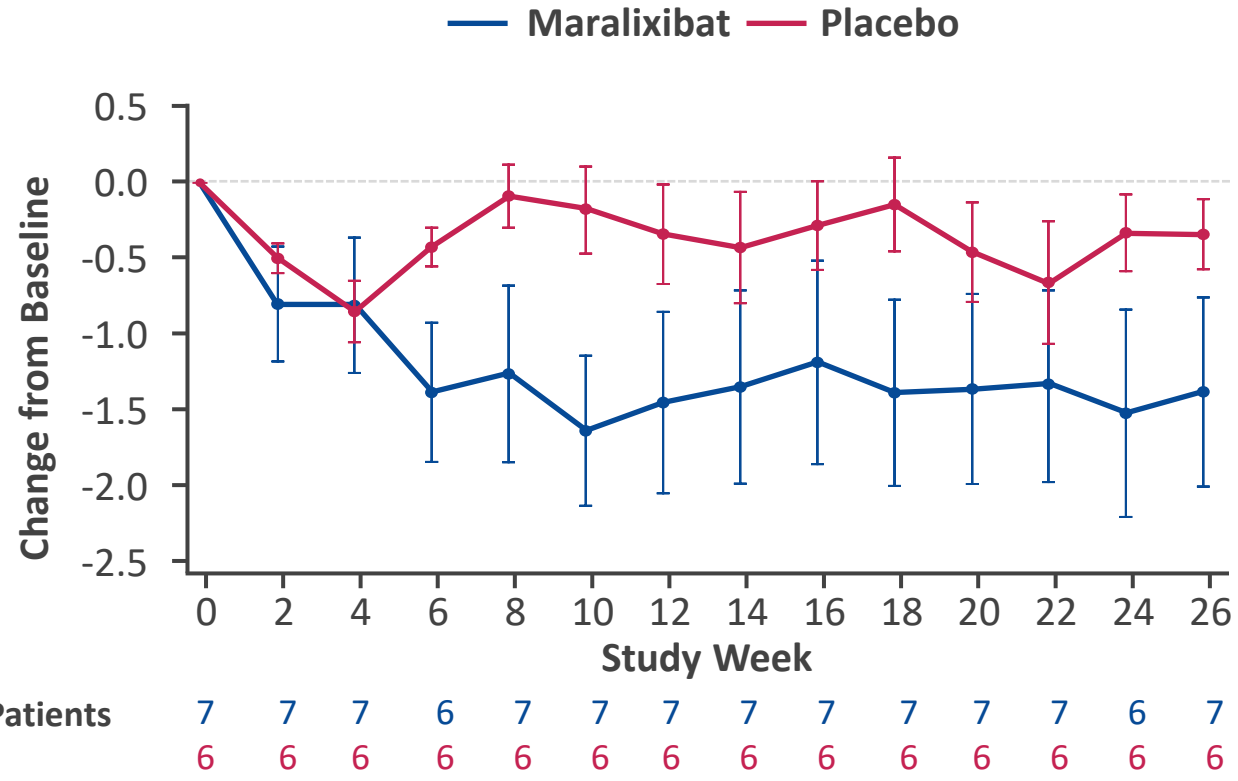
Note: All data are mean unless otherwise indicated. Percentages are 100 x n/N.
ItchRO(Obs), Itch-Reported Outcome (Observer); sBA, serum bile acid; UDCA, ursodeoxycholic acid.

MARCH: Change in Weekly ItchRO(Obs) Score in FIC1 Deficiency Cohort

Pruritus Score (ItchRO[Obs]) MMRM Analysis



Weekly Average ItchRO(Obs) Score Over Time



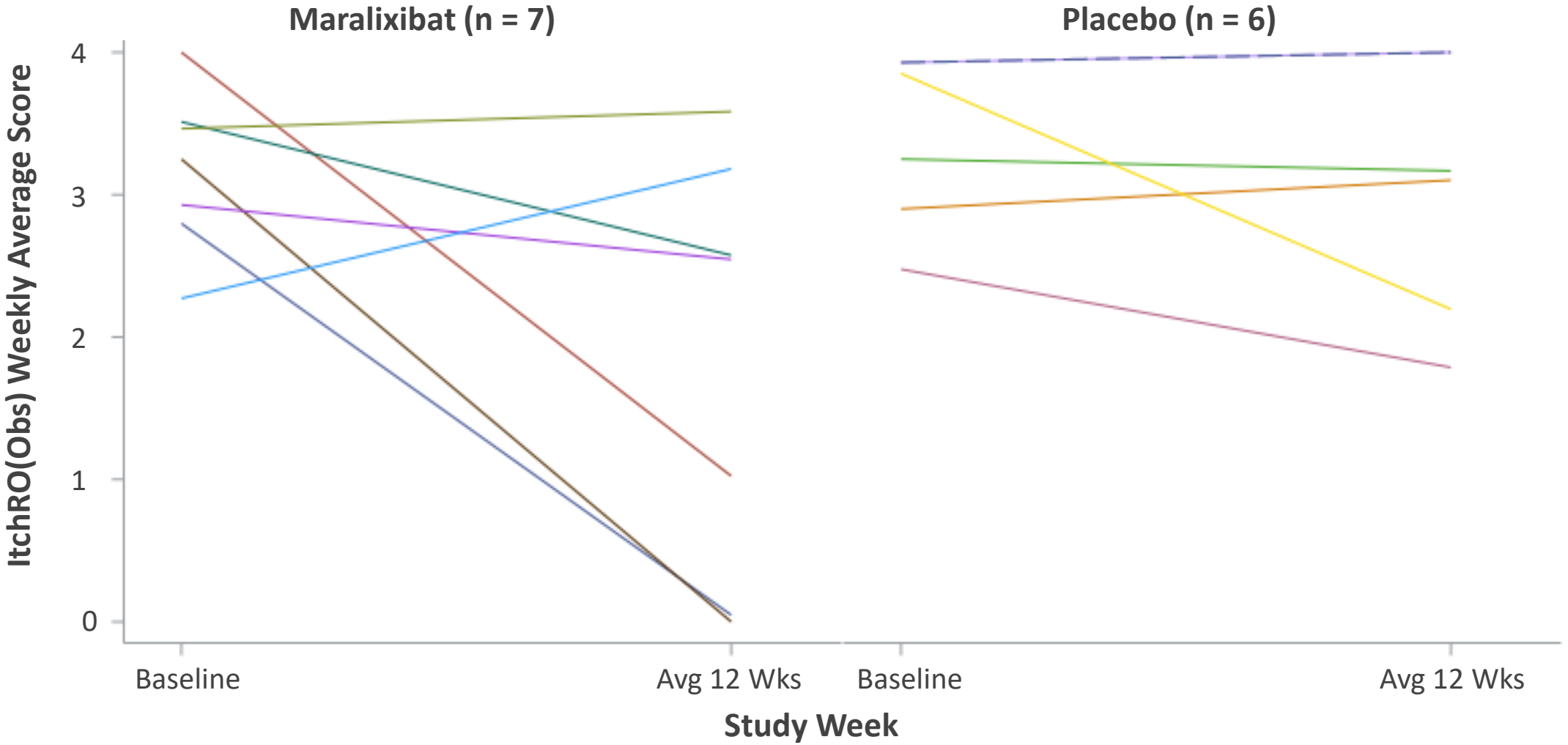
Patients														
	7	7	7	6	7	7	7	7	7	7	7	7	6	7
	6	6	6	6	6	6	6	6	6	6	6	6	6	6

Maralixibat resulted in improvements in pruritus

Data are LS mean with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals) using an MMRM.
*LS mean = 0. †LS mean delta with 95% CI.
FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer); LS, least squares; MMRM, mixed-model repeated measures.

MARCH: Individual Changes in Weekly ItchRO(Obs) Scores in FIC1 Deficiency Cohort

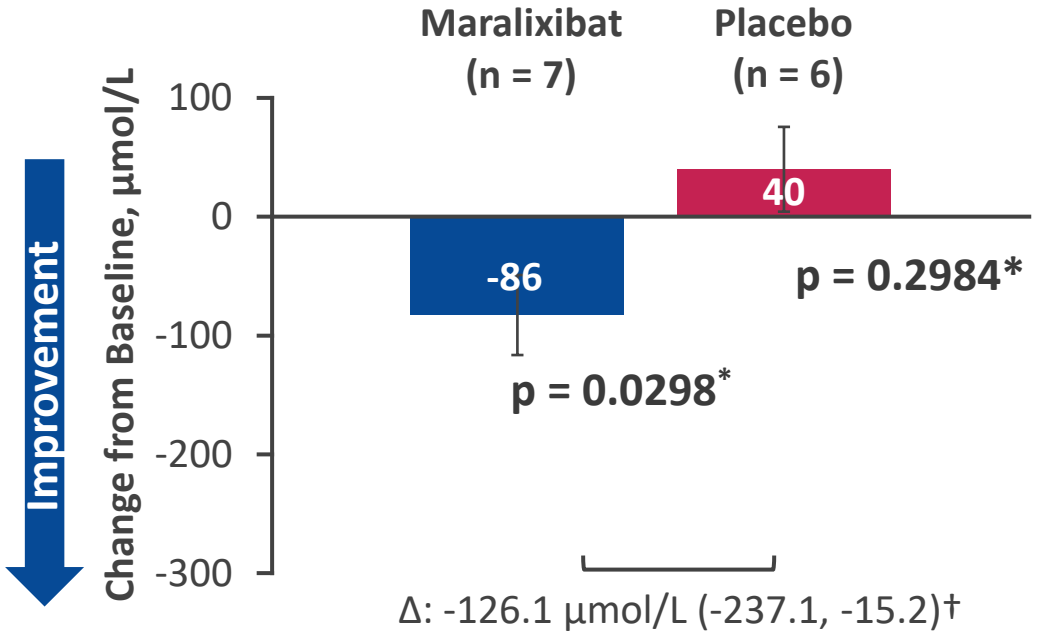
Pruritus Score (ItchRO[Obs]) by Patient



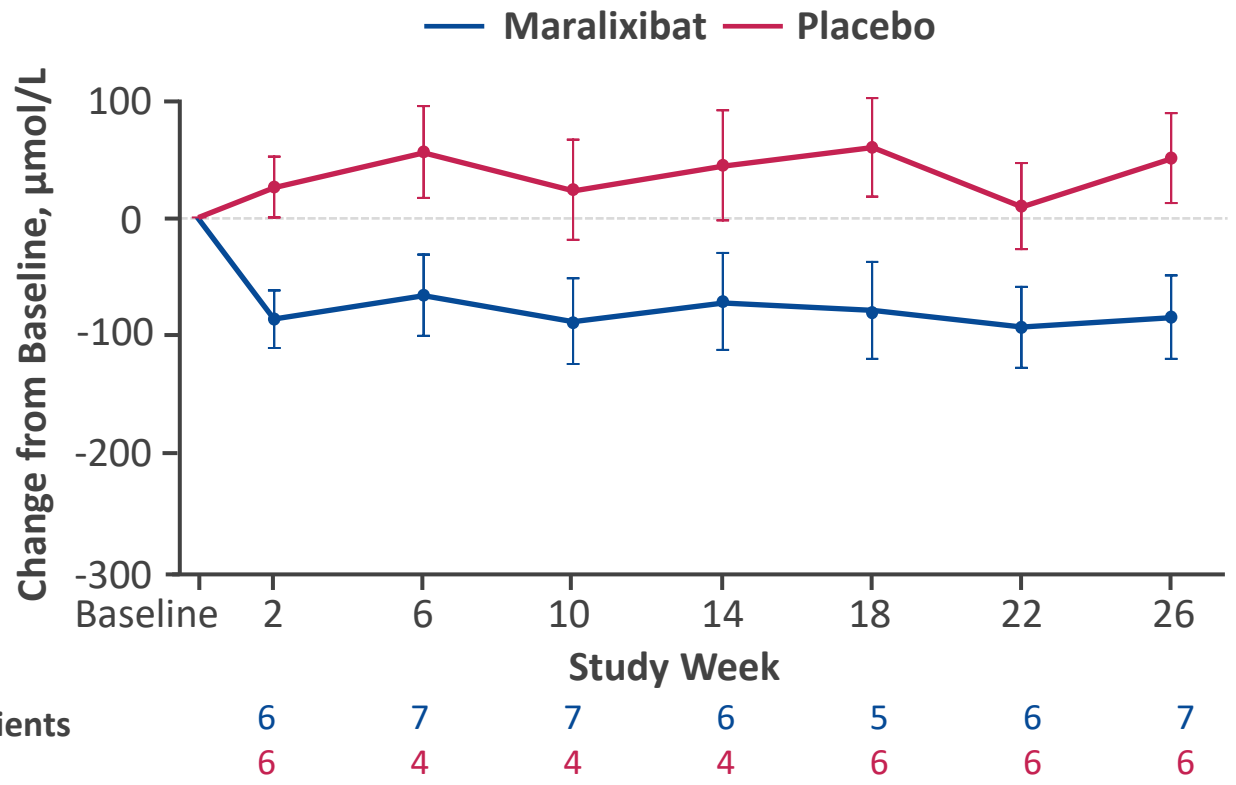
Data are baseline or the average of the three 4-week timepoints (Weeks 15-18, Weeks 19-22, Weeks 23-26).
FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer).

MARCH: Change in Serum Bile Acid Levels in FIC1 Deficiency Cohort

sBA MMRM Analysis



Average sBA Over Time

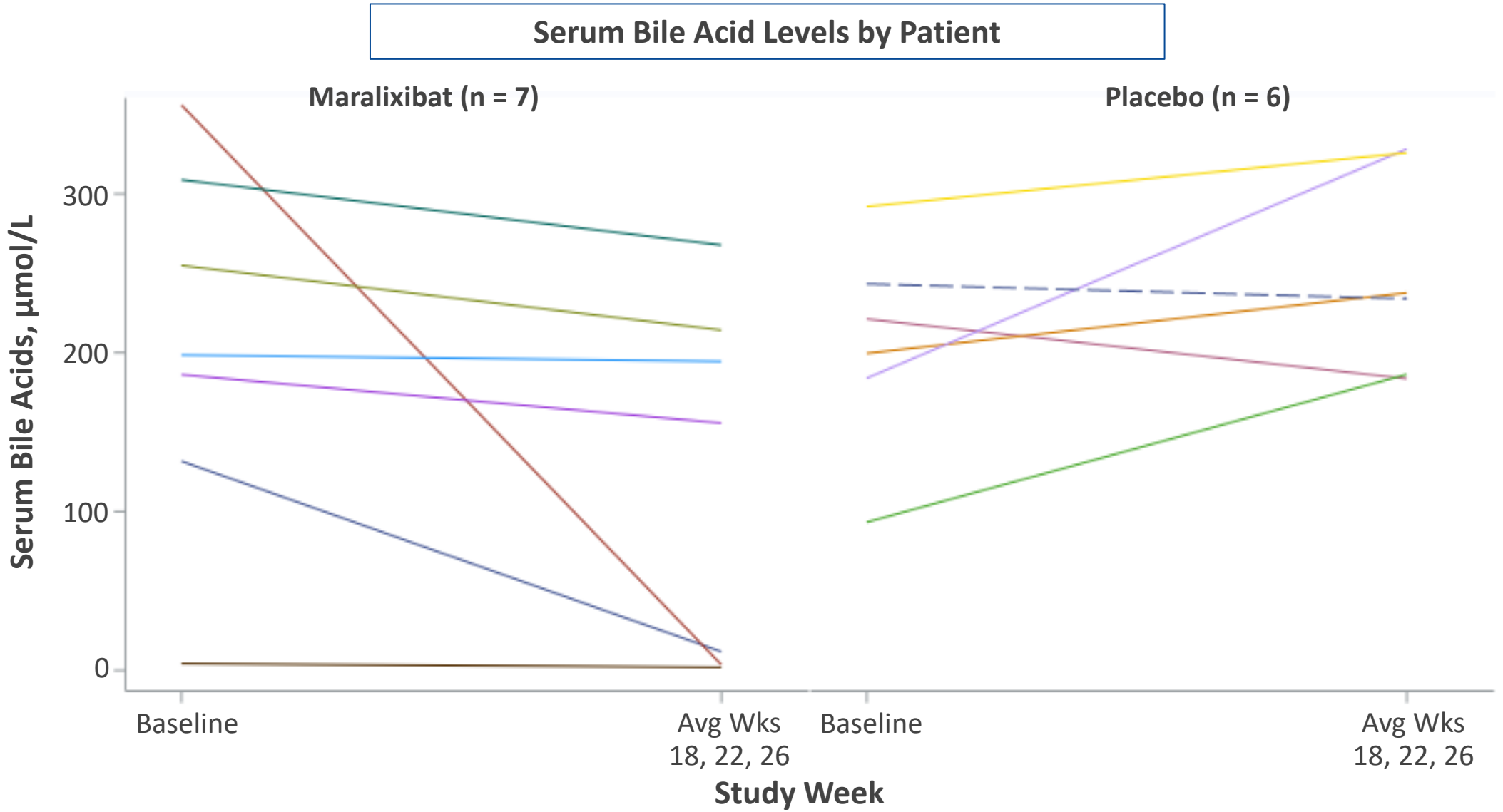


Maralixibat resulted in statistically significant improvements in serum bile acid levels

Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (Weeks 18, 22 and 26) using an MMRM. *LS mean = 0. †LS mean delta with 95% CI. ‡Maralixibat LS mean = placebo LS mean.

CI, confidence interval; FIC1, familial intrahepatic cholestasis-associated protein 1; LS, least squares; MMRM, mixed-model repeated measures; sBA, serum bile acid.

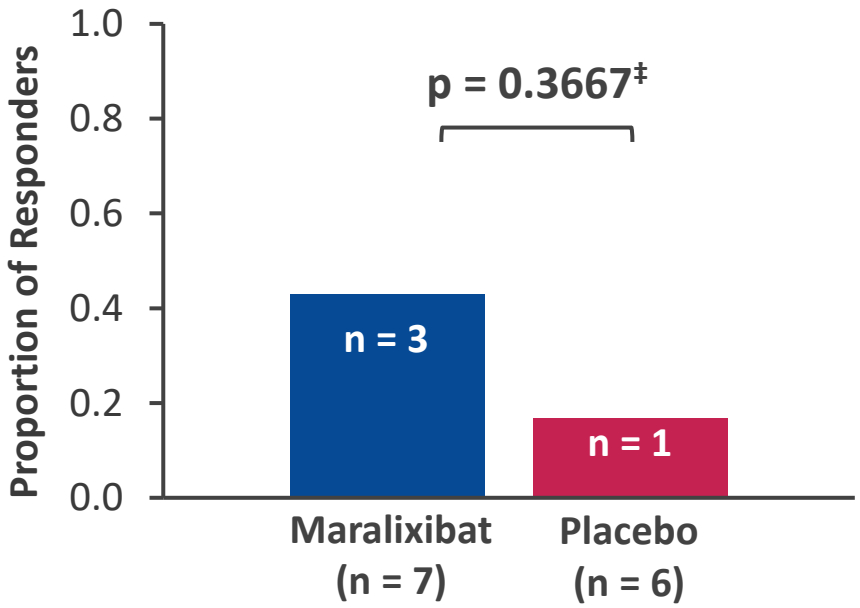
MARCH: Individual Changes in Serum Bile Acid Levels in FIC1 Deficiency Cohort



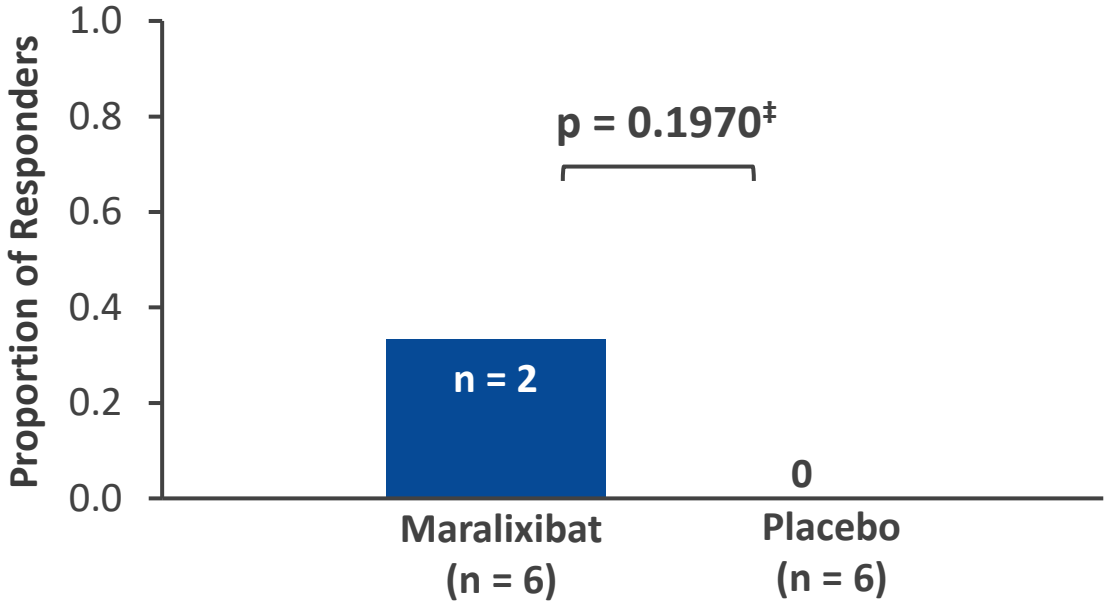
Data are baseline or the average of Weeks 18, 22, 26.
FIC1, familial intrahepatic cholestasis-associated protein 1

MARCH: Proportion of Patients with FIC1 Deficiency Achieving a Clinically Meaningful Response to Pruritus and Serum Bile Acids

Pruritus Responders*
≥ 1-point reduction OR score of ≤ 1.0 on ItchRO(Obs)



Proportion of Patients Who Achieved sBA Response* of < 65 µmol/L[1,†]

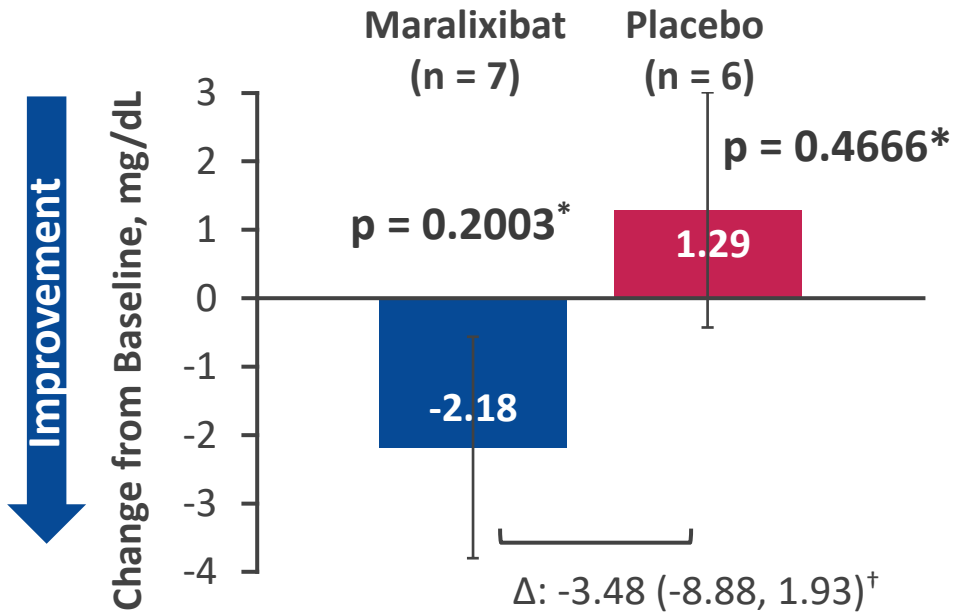


A greater number of maralixibat-treated patients achieved clinically meaningful improvements in pruritus as well as serum bile acid reduction associated with improved transplant-free survival

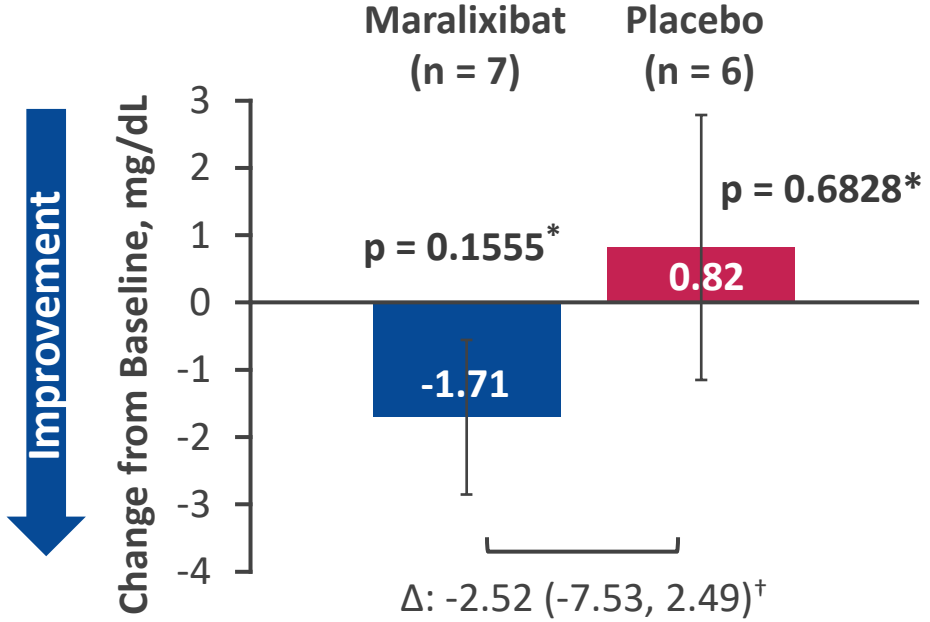
Note: Percentages are 100 x n/N. Data are LS mean with standard error bars, unless stated otherwise.
*To determine response: the average pruritus severity score from the three 4-week periods (Weeks 15-18, 19-22 and 23-26) was used. A subject was defined an ItchRO(Obs) non-responder if the 4-week average baseline score was missing OR all three 4-week average (post-baseline) scores were missing. For sBA: the average sBA value from Weeks 18, 22 and 26 values was used. †NAPPED threshold for FIC1 deficiency associated with TFS. Only those with sBA ≥65 µmol/L at baseline were included. ‡Morning and evening were used in the calculation of the proportion. ‡p-values comparing maralixibat with placebo treatment groups were calculated using a Barnard's exact test.
FIC1, familial intrahepatic cholestasis-associated protein 1; LS, least squares; ItchRO(Obs), Itch-Reported Outcome (Observer); MMRM, mixed-model repeated measures.
1. Van Wessel DBE, et al. *Hepatology*. 2021;74:892-906.

MARCH: Change From Baseline in Total & Direct Bilirubin in FIC1 Deficiency Cohort

Serum Total Bilirubin MMRM Analysis



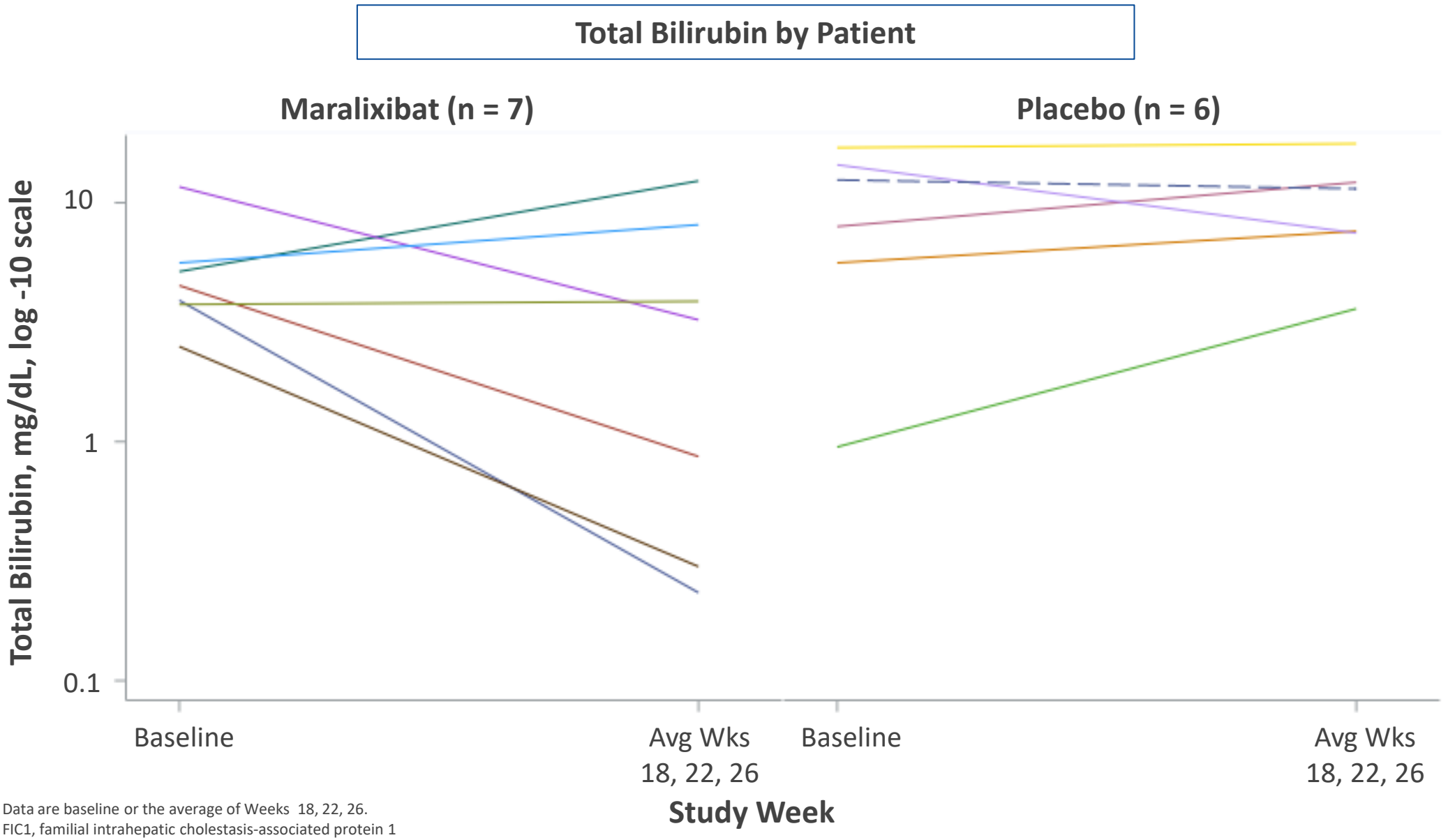
Serum Direct Bilirubin MMRM Analysis



Maralixibat resulted in improvements in total and direct bilirubin

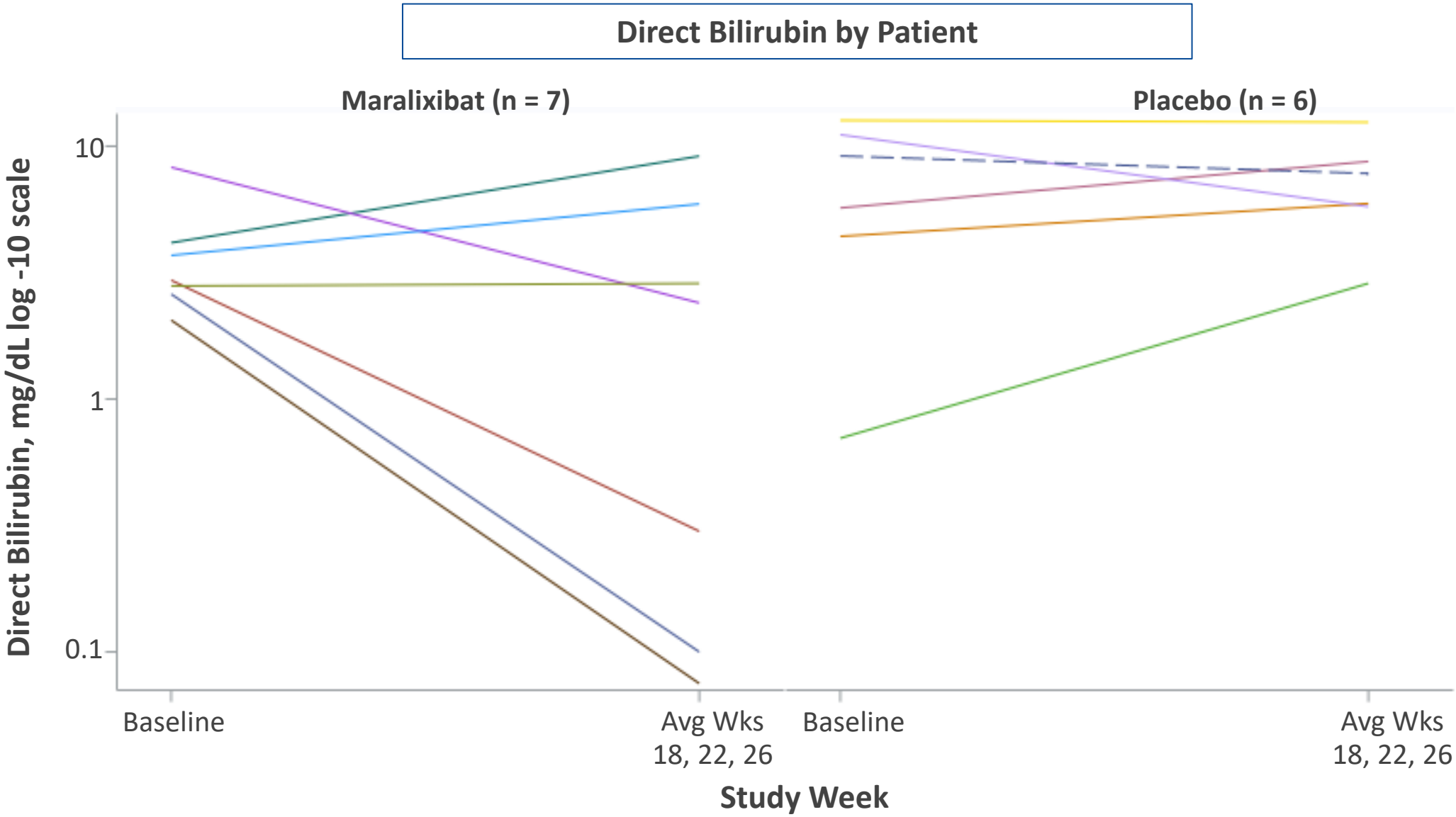
Data are LS mean with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (weeks 18, 22, and 26) using an MMRM.
*LS mean = 0. †LS mean delta with 95% CI.
CI, confidence interval; FIC1, familial intrahepatic cholestasis-associated protein 1; LS, least squares; MMRM, mixed-model repeated measures.

MARCH: Individual Changes in Total Bilirubin in FIC1 Deficiency Cohort



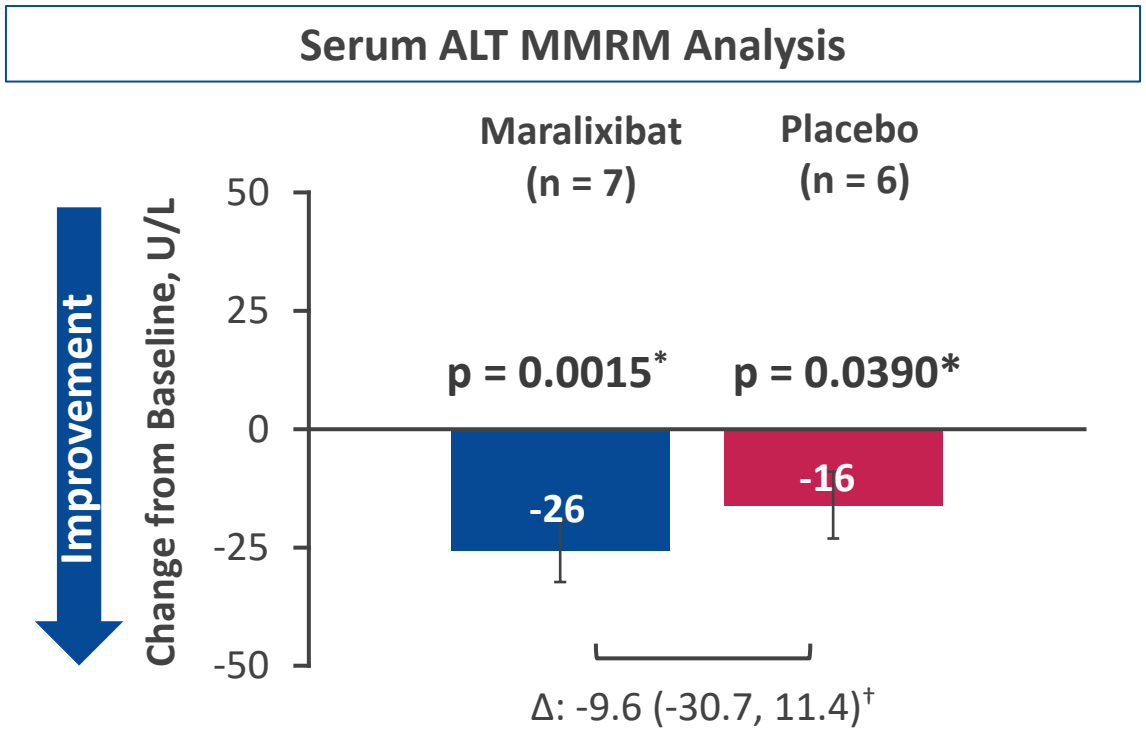
Data are baseline or the average of Weeks 18, 22, 26.
FIC1, familial intrahepatic cholestasis-associated protein 1

MARCH: Individual Changes in Direct Bilirubin in FIC1 Deficiency Cohort



Data are baseline or the average of Weeks 18, 22, 26.
FIC1, familial intrahepatic cholestasis-associated protein 1

MARCH: Change From Baseline in ALT in FIC1 Deficiency Cohort



No significant changes in ALT levels were observed following maralixibat treatment

Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (weeks 18, 22, and 26) using an MMRM.
*LS mean = 0. †LS mean delta with 95% CI.
ALT, alanine aminotransferase; CI, confidence interval; FIC1, familial intrahepatic cholestasis-associated protein 1; LS, least squares; MMRM, mixed-model repeated measures.

Summary of TEAEs

TEAE	Maralixibat (n = 7)	Placebo (n = 6)	Overall (N = 13)
Any TEAE, n (%)	7 (100)	6 (100)	13 (100)
Severe TEAE, n (%)	0	0	0
Serious TEAE, n (%)	0	2 (33.3)	2 (15.4)
TEAE leading to discontinuation, n (%)	0	0	0
TEAE leading to death, n (%)	0	0	0
Most common TEAE: pyrexia, n (%)	3 (42.9)	4 (66.7)	7 (53.8)
GI TEAE, n (%)	4 (57.1)	2 (33.3)	6 (46.2)

- **Frequency of TEAEs in the FIC1 deficiency similar to that in overall safety population (N = 93)**
- Diarrhoea (n = 4; 57.1%) in the maralixibat group was predominantly mild and transient with a median duration of 7 days; no severe events reported
- There were no serious TEAEs that were related to maralixibat
- No deaths

Note: Percentages are 100 x n/N. AEs were coded using MedRA version 22.1. Participants who reported > 1 AE within each category were only counted once.
AE, adverse event; FIC1, familial intrahepatic cholestasis-associated protein 1; MedRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Conclusions

- In MARCH-PFIC, patients with FIC1 deficiency had similar improvements in sBA, pruritus and bilirubin to the BSEP cohort and the All-PFIC cohort
- Statistically and clinically significant improvements observed in sBA for patients with FIC1 deficiency
  - Using the NAPPED threshold for FIC1 deficiency associated with transplant-free survival, one-third of the maralixibat-treated patients achieved an sBA response
- The study was not powered to identify changes in the FIC1 subgroup, but the magnitude of treatment effect for changes in pruritus and bilirubin was consistent with MARCH-PFIC for the BSEP cohort and the All-PFIC cohort
- Maralixibat was generally well tolerated
  - Frequency of diarrhoea was similar to that in the BSEP and All-PFIC cohorts
  - No new safety signals observed

BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis-associated protein 1 NAPPED, NAtural Course and Prognosis of PFIC and Effect of Biliary Diversion; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.

Acknowledgements

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

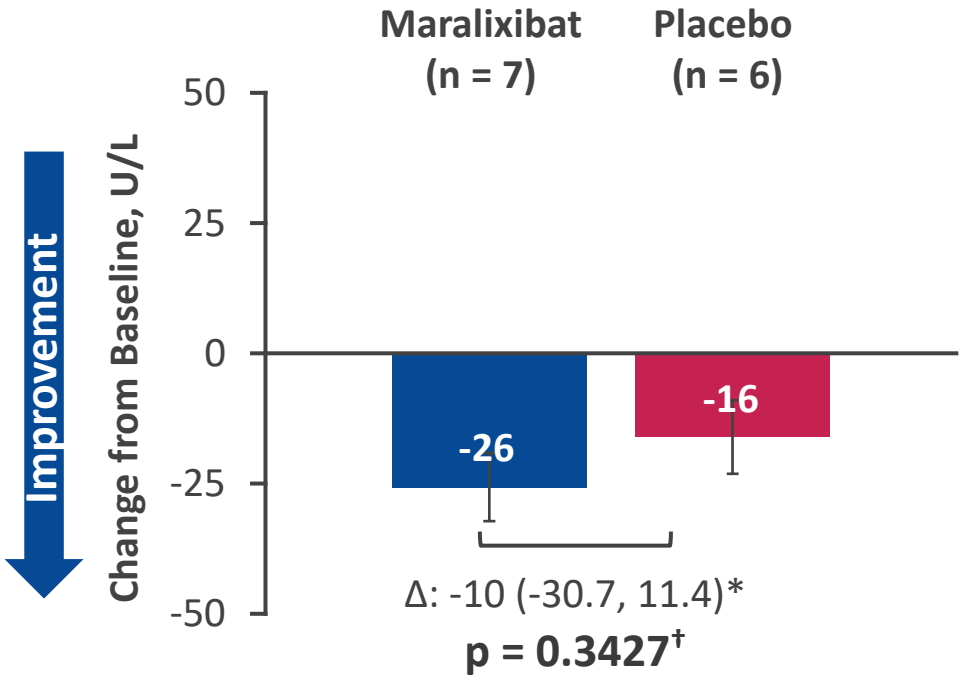
Author Disclosures

- A Miethke is a consultant and has a sponsored research agreement for Mirum Pharmaceuticals, Inc.
- A Aqul is a consultant for Mirum Pharmaceuticals, Inc., Albireo and Sarepta Therapeutics
- N Mittal is an investigator for Mirum Pharmaceuticals, Inc.
- T Nunes, A Lascau, D Mogul, W Garner and P Vig are employees of and shareholders in Mirum Pharmaceuticals, Inc.
- A Moukarzel, G Porta, J Covarrubias Esquer, R Squires, D D'Agostino, F K Chiou, W D Huber, J Hartley and N Laverdure have nothing to disclose

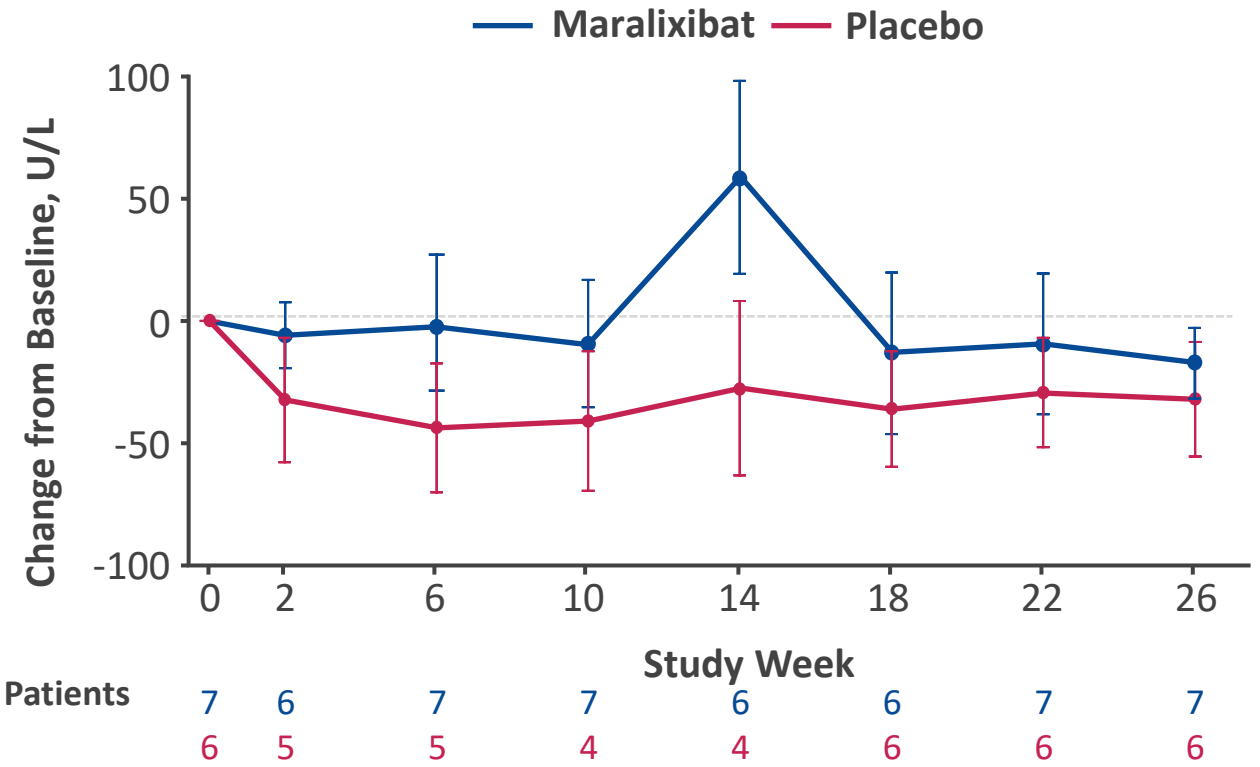
Back-up

MARCH: Change From Baseline in ALT in FIC1 Deficiency Cohort

Serum ALT MMRM Analysis



Average Serum ALT Over Time



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