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Efficacy and Safety of Maralixibat in Patients with Progressive Familial Intrahepatic Cholestasis (MARCH-PFIC): A Randomized Placebo-Controlled Phase 3 Study

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Richard J Thompson

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

Disclosures

- R J Thompson is a consultant for Mirum Pharmaceuticals, Inc., Albireo, GenerationBio, and Rectify Therapeutics, and is a shareholder in GenerationBio and Rectify Therapeutics

Progressive Familial Intrahepatic Cholestasis (PFIC)

- Genetic disorders resulting in disrupted bile composition and chronic cholestasis[1]
- Debilitating pruritus, impaired growth, reduced QoL, and progressive liver disease with most children undergoing liver transplantation[2–5]
- PFIC types include deficiencies of:[1-3]
  - Bile salt export pump (BSEP)
  - Familial intrahepatic cholestasis-associated protein 1 (FIC1)
  - Multidrug resistant 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[6–7]*

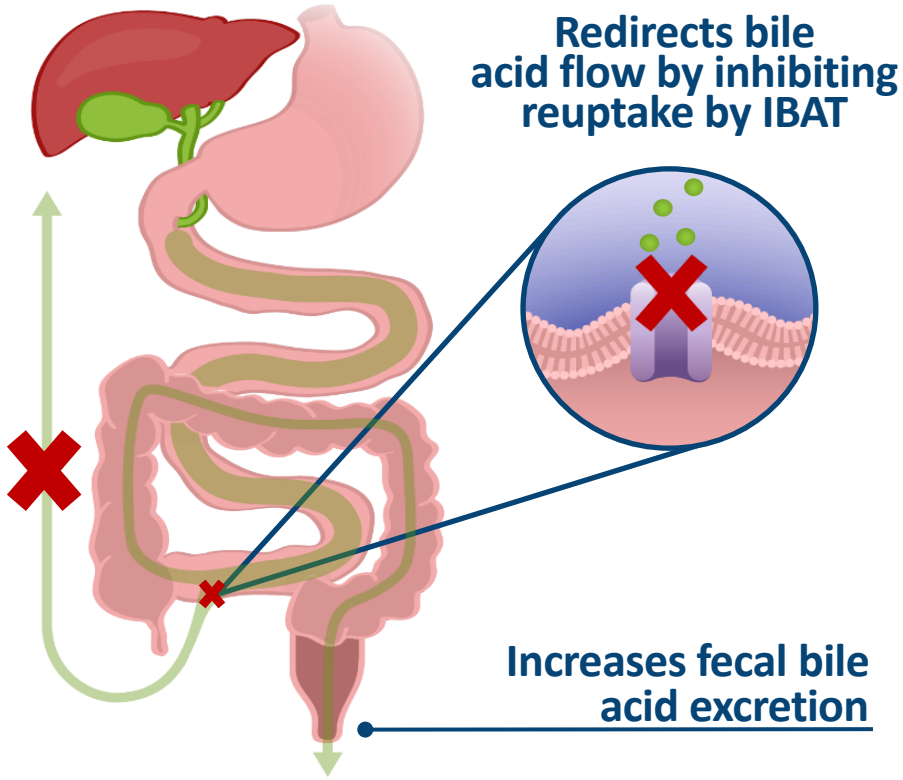
The efficacy of IBAT inhibitors has not been studied across every PFIC type

*Odevixibat is an IBAT inhibitor that 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.

IBAT, ileal bile acid transporter; PFIC, progressive familial intrahepatic cholestasis; QoL, quality of life.

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 Jan 8;4:1. doi: 10.1186/1750-1172-4-1; 7. Albireo Pharma, Inc. BYLVAY® (odevixibat). Prescribing Information. 2021.

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 received FDA approval in 2021 for the treatment of cholestatic pruritus in patients with ALGS 1 year of age and older[3,4]

BSEP, bile salt export pump; sBA, serum bile acid.

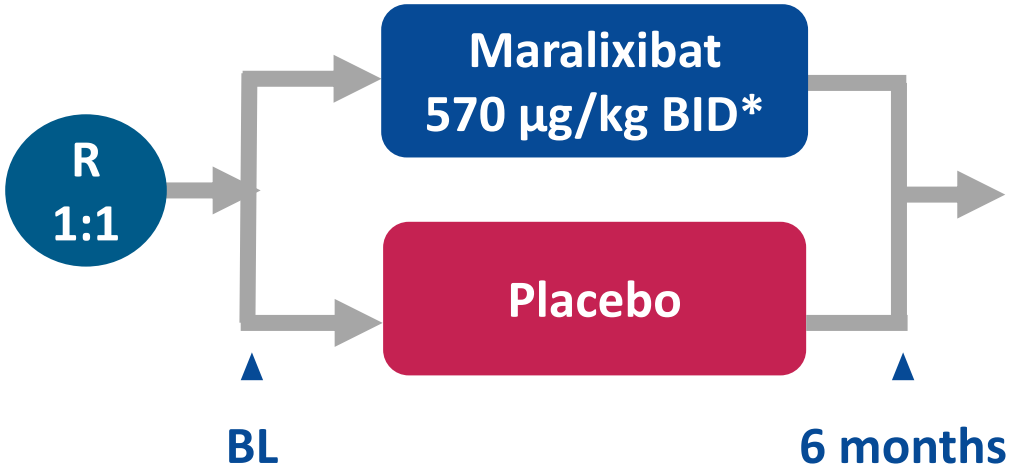
1. Thompson R, *et al*. EASL 2020. (Oral presentation, #LB08); 2. Loomes MK, *et al. Hepatol Commun.* 2022;6:2379-2390;
3. Gonzales E, *et al*. *Lancet.* 2021;398:1581-1592; 4. Mirum Pharmaceuticals, Inc. LIVMARLI® (maralixibat). Prescribing Information. 2021.

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
- sBA ≥3× ULN



MARCH-ON
Phase 3 open-label extension study

*Maralixibat 570 µg/kg is equivalent to 600 µg/kg maralixibat chloride.
BID, twice daily; BL ,baseline; R, randomized; ULN, upper limit of normal.
ClinicalTrials.gov ID: NCT03905330. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT03905330 on October 27, 2022.

MARCH-PFIC: Study Populations

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

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

MARCH-PFIC: Efficacy Endpoints

MARCH STUDY

Primary Endpoint (BSEP cohort):

Mean change in morning ItchRO(Obs) severity score between baseline and average of the last 12 weeks

Secondary Endpoints (BSEP and All-PFIC cohorts):

- Mean change in morning ItchRO(Obs) severity score between baseline and average of the last 12 weeks in the All-PFIC cohort
- Mean change in total sBA level between baseline and average of the last 12 weeks in the BSEP and All-PFIC cohorts
- Responder analyses of pruritus and sBA

Exploratory Endpoints (All-PFIC cohorts):

- Mean change from baseline in total and direct bilirubin
- Mean change from baseline in growth (height and weight Z-scores)

- Endpoints were analyzed using a repeated measures model (MMRM) considering data from all study visits
- ItchRO is a 0–4 scale; ≥1 point reduction is clinically meaningful
- The safety endpoints were assessed in the Full-Study population: incidence of AEs

AE, adverse event; ItchRO(Obs), Itch Reported Outcome (Observer); MMRM, mixed model repeated measures; NAPPED, NAtural Course and Prognosis of PFIC and Effect of Biliary Diversion.
ClinicalTrials.gov ID: NCT03905330. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT03905330 on October 27, 2022.

Key Demographics and Baseline Characteristics

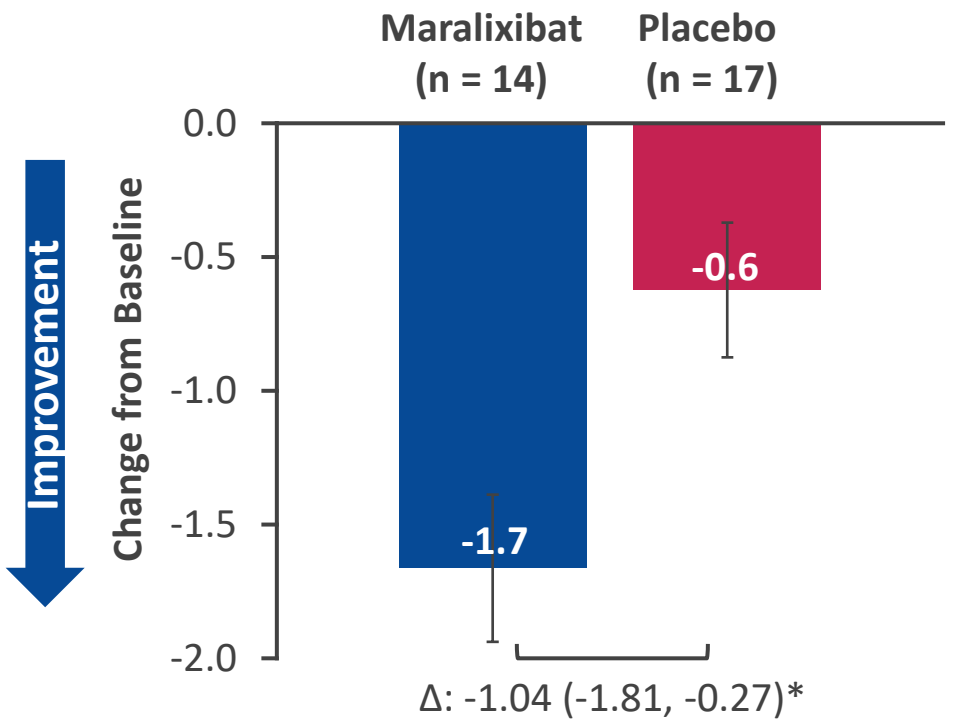
Variable	BSEP		All-PFIC		Full-Study	
	Maralixibat (n = 14)	Placebo (n = 17)	Maralixibat (n = 33)	Placebo (n = 31)	Maralixibat (n = 47)	Placebo (n = 46)
Age (years); mean	6.3	4.2	4.9	4.4	4.8	4.7
Sex (male); %	50	35	52	42	43	48
Pruritus (ItchRO[Obs]); mean	2.9	2.6	2.9	2.7	2.8	2.9
Total sBA (μmol/L); mean	312	312	254	272	263	243
UDCA usage (%)	79	100	82	97	83	85
Rifampicin usage (%)	43	53	55	48	55	50
Alanine aminotransferase (U/L); mean	98.4	154.9	87.8	127.3	107.9	121.2
Total bilirubin (mg/dL); mean	3.5	2.7	4.1	4.0	4.1	3.8
Direct bilirubin (mg/dL); mean	2.4	1.9	3.0	2.9	3.0	2.8
Height Z-score; mean	-2.0	-2.2	-2.1	-2.1	-2.0	-1.9
Weight Z-score; mean	-1.5	-1.2	-1.8	-1.3	-1.6	-1.2

Baseline characteristics and demographics were balanced between the cohorts

Note: Percentages are 100*n/N.
ItchRO(Obs), Itch Reported Outcome (Observer); sBA, serum bile acids; UDCA, ursodeoxycholic acid.

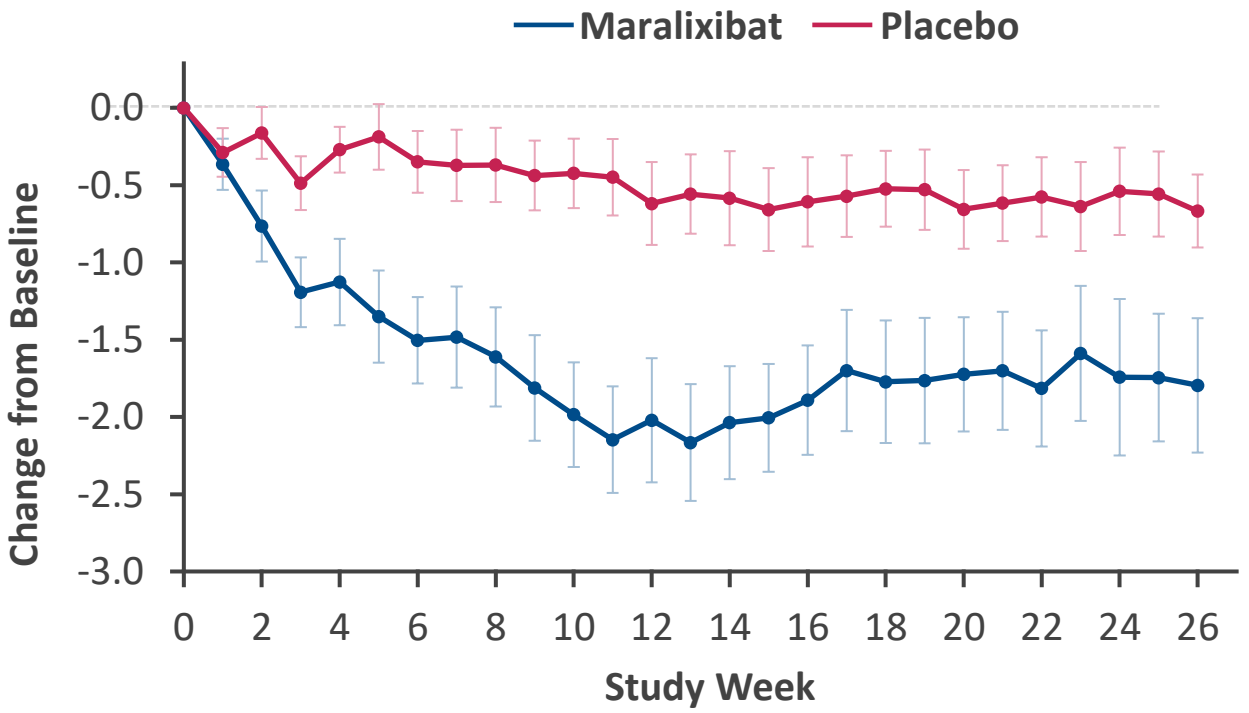
Primary Endpoint: Change in Weekly ItchRO(Obs) Score in BSEP Cohort

Pruritus Score (ItchRO[Obs]) MMRM Analysis



Primary endpoint **p=0.0098†**

Weekly Average Pruritus Score (ItchRO[Obs]) Over Time



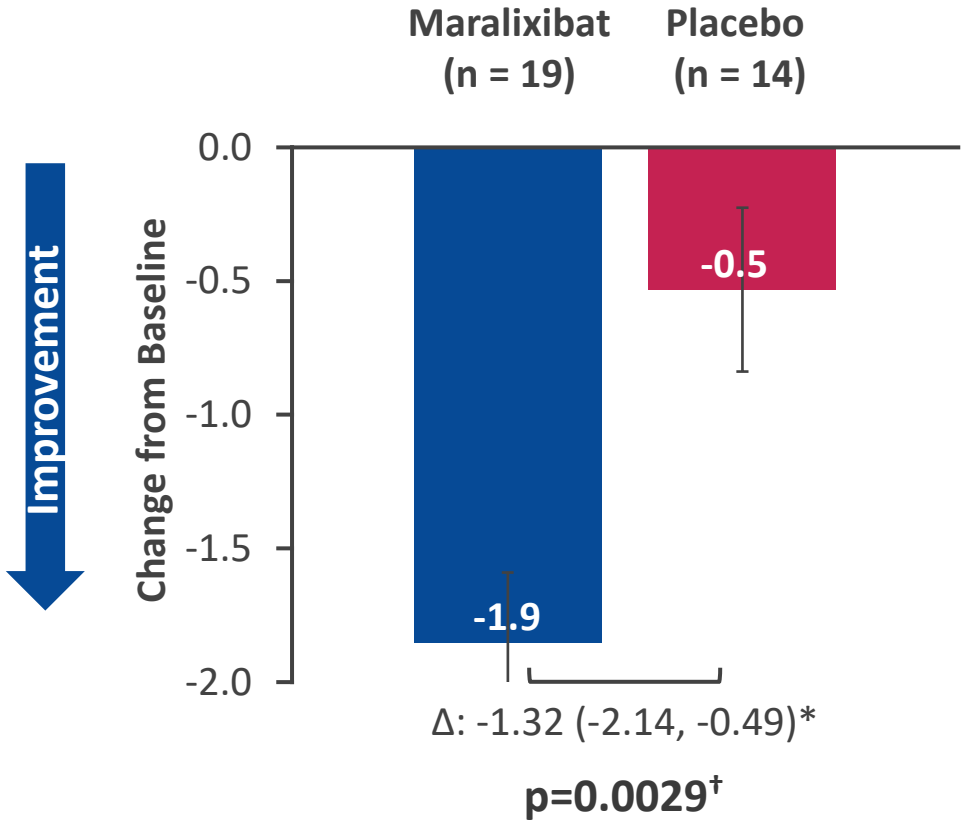
Patients														
	14	14	13	14	14	13	13	14	14	14	14	14	13	13
	17	17	17	17	17	17	16	15	15	15	15	15	15	15

Maralixibat resulted in statistically significant and clinically meaningful improvements in pruritus in the BSEP cohort

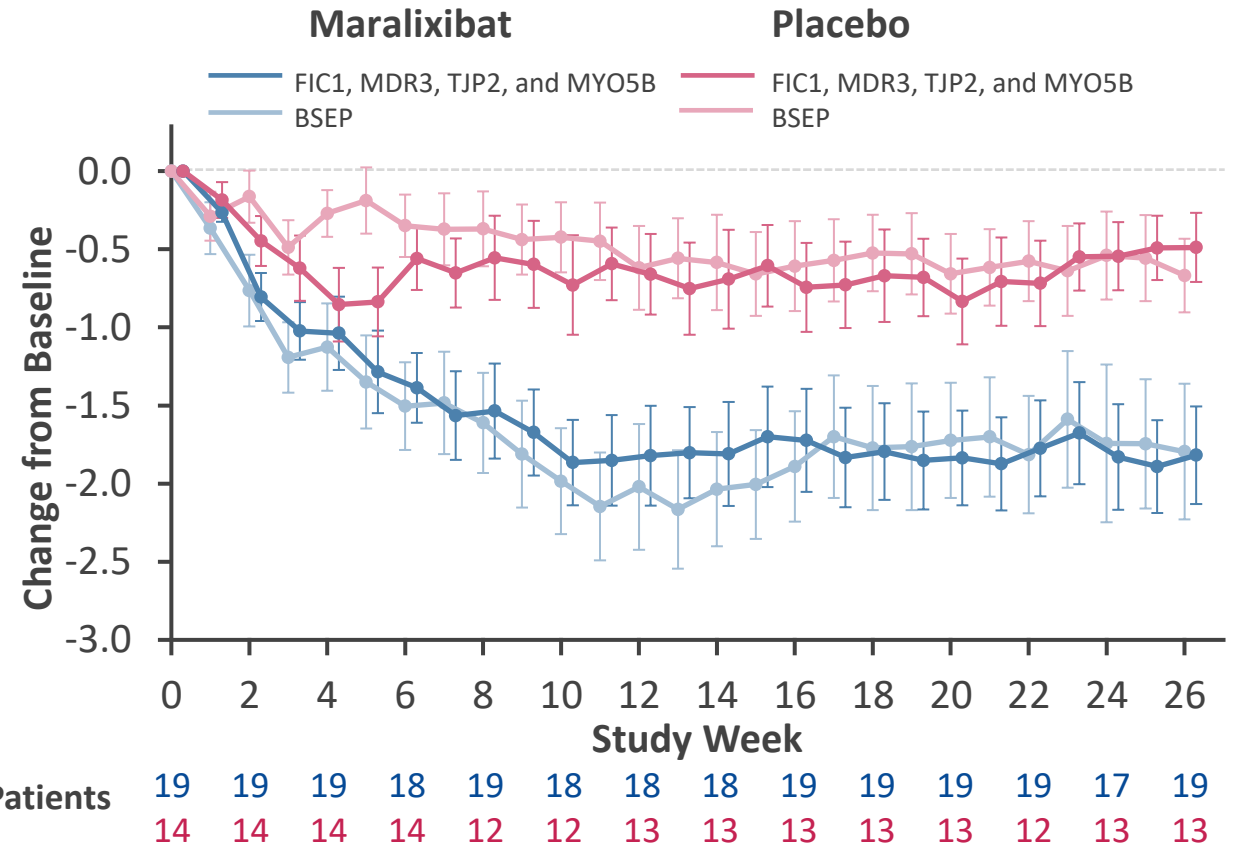
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals) using a MMRM. BSEP, bile salt export pump; ItchRO(Obs), Itch Reported Outcome (Observer); LS, least squares; MMRM, mixed model repeated measures.
*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean.

Change in Weekly ItchRO(Obs) Score in FIC1, MDR3, TJP2, and MYO5B

Pruritus Score (ItchRO[Obs]) MMRM Analysis



Weekly Average Pruritus Score (ItchRO[Obs]) Over Time

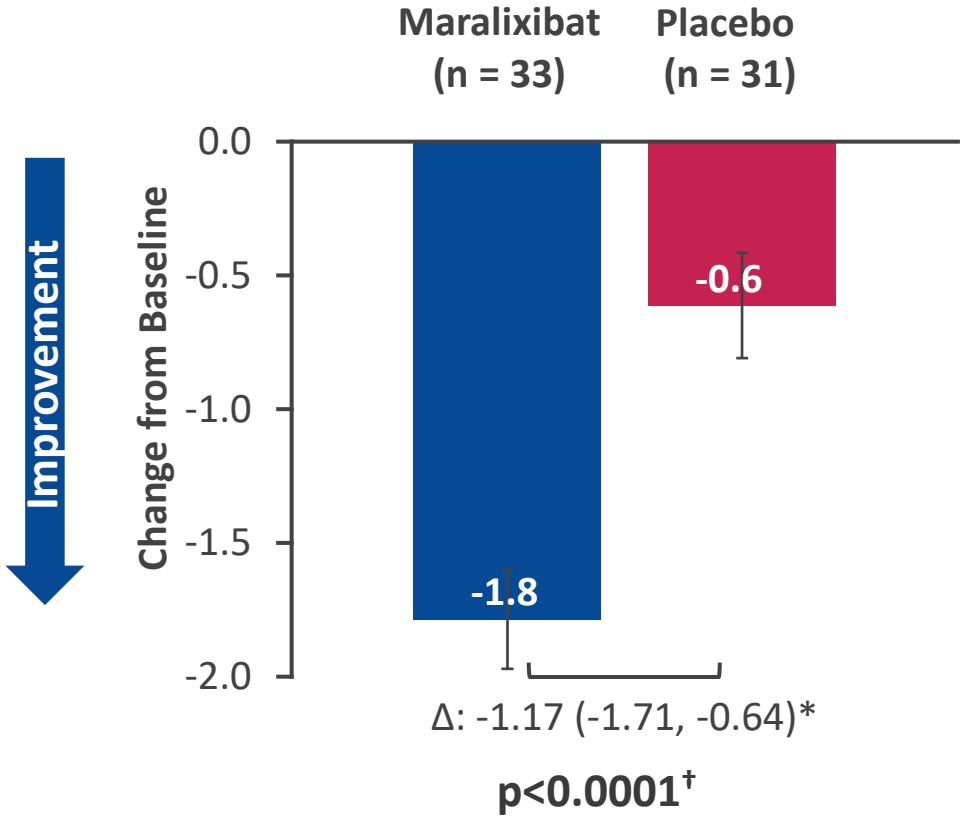


Maralixibat resulted in resulted in statistically significant and clinically meaningful improvements in pruritus in FIC1, MDR3, TJP2, and MYO5B

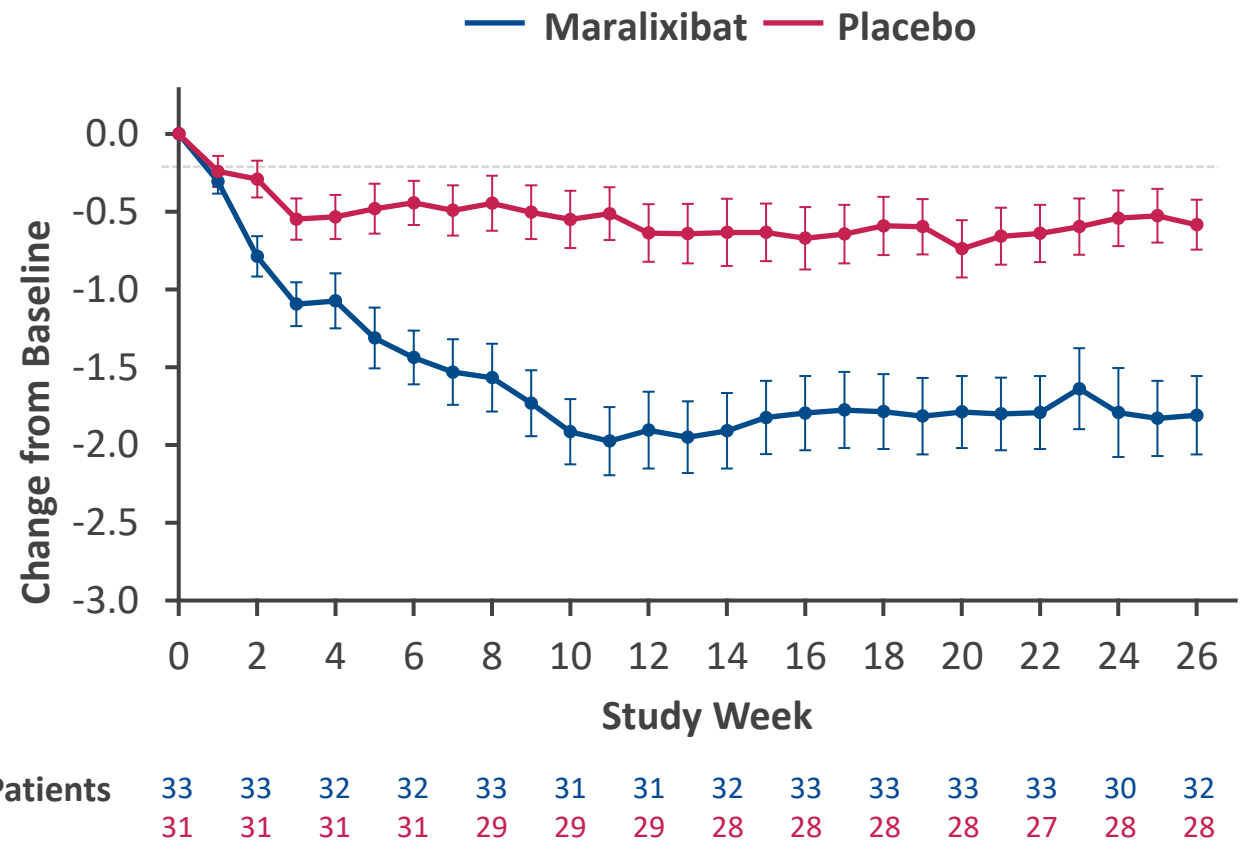
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals) using a MMRM. FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch Reported Outcome (Observer); LS, least squares; MMRM, mixed model repeated measures; MDR3, Multi-drug resistant 3 protein; MYO5B, myosin VB; TJP2, tight junction protein 2.
*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean.

Secondary Endpoint: Change in Weekly ItchRO(Obs) Score in All-PFIC Cohort

Pruritus Score (ItchRO[Obs]) MMRM Analysis



Weekly Average Pruritus Score (ItchRO[Obs]) Over Time

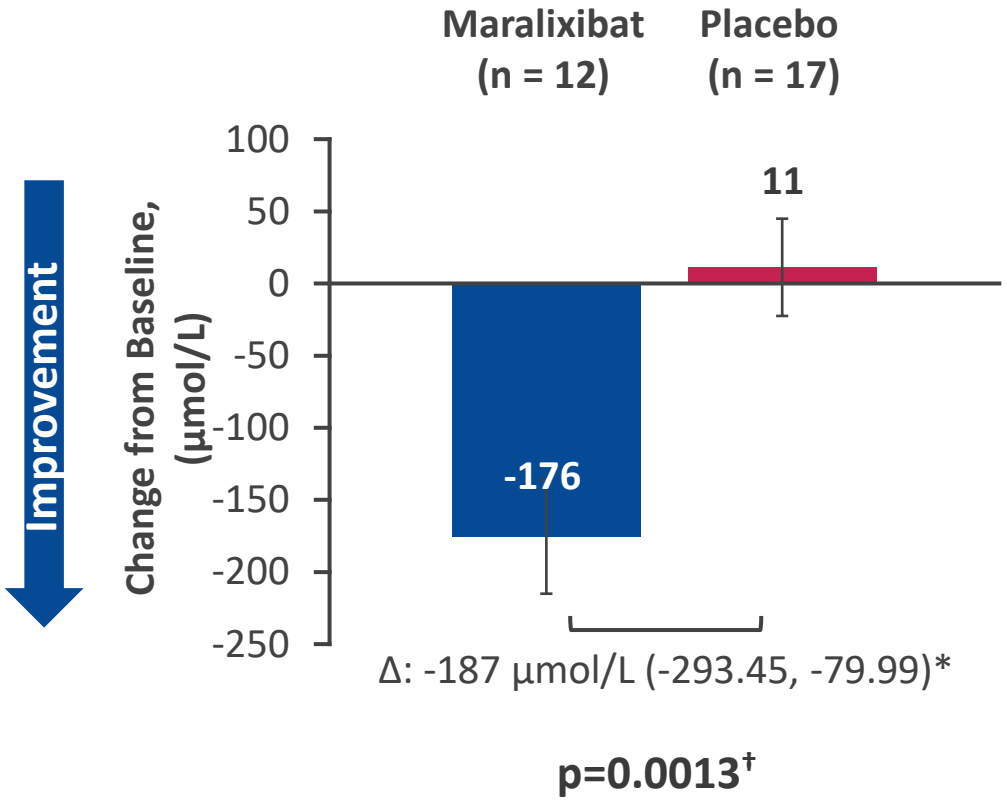


Maralixibat resulted in statistically significant and clinically meaningful improvements in pruritus in the All-PFIC cohort

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 (4-week intervals) using a MMRM. ItchRO(Obs), Itch Reported Outcome (Observer); LS, least squares; MMRM, mixed model repeated measures; PFIC, progressive familial intrahepatic cholestasis.
*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean.

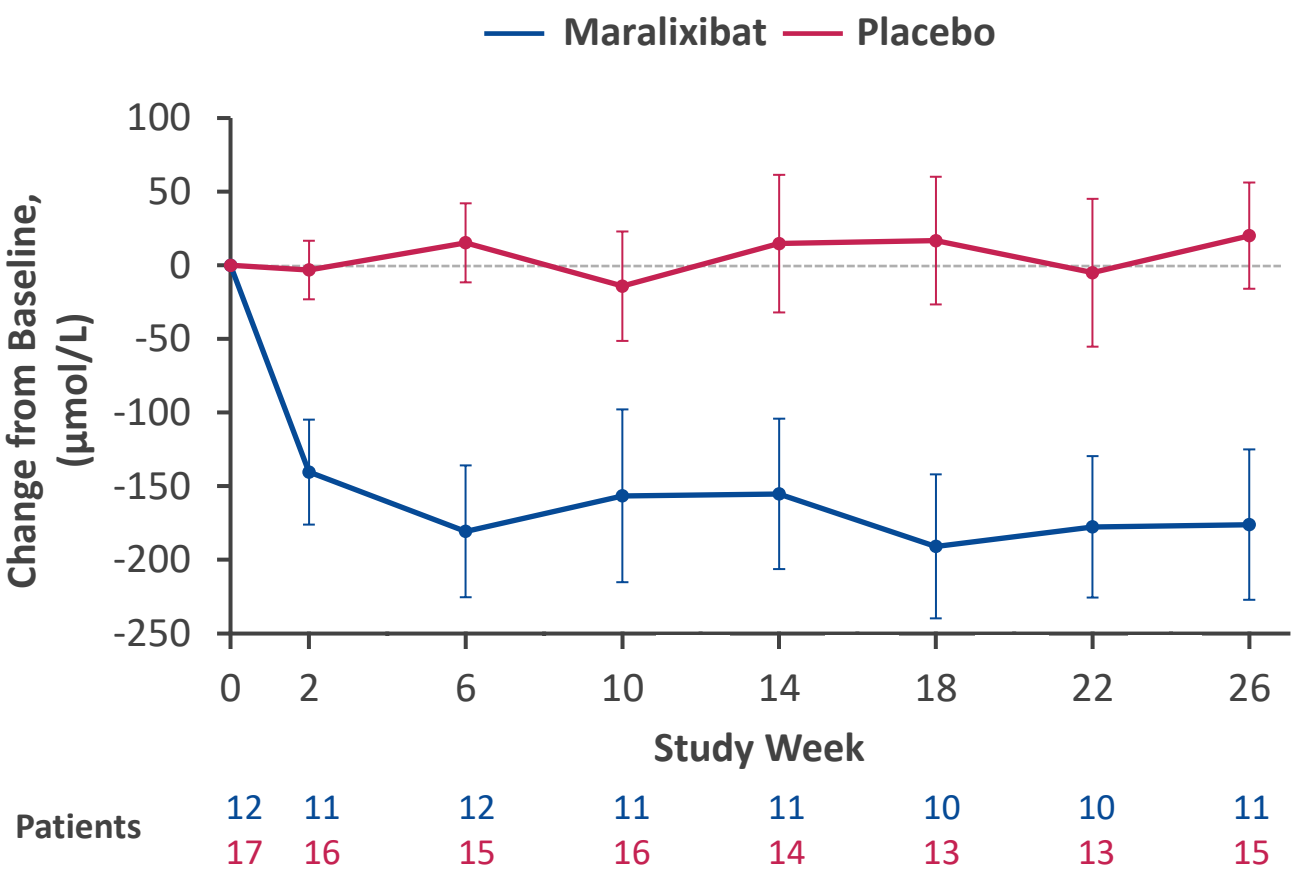
Secondary Endpoint: Change From Baseline in Serum Bile Acids in BSEP Cohort

Serum Bile Acid MMRM Analysis



p=0.0013†

Average Serum Bile Acids Over Time



Patients								
	12	11	12	11	11	10	10	11
	17	16	15	16	14	13	13	15

Maralixibat resulted in statistically significant improvements in serum bile acid levels in the BSEP cohort

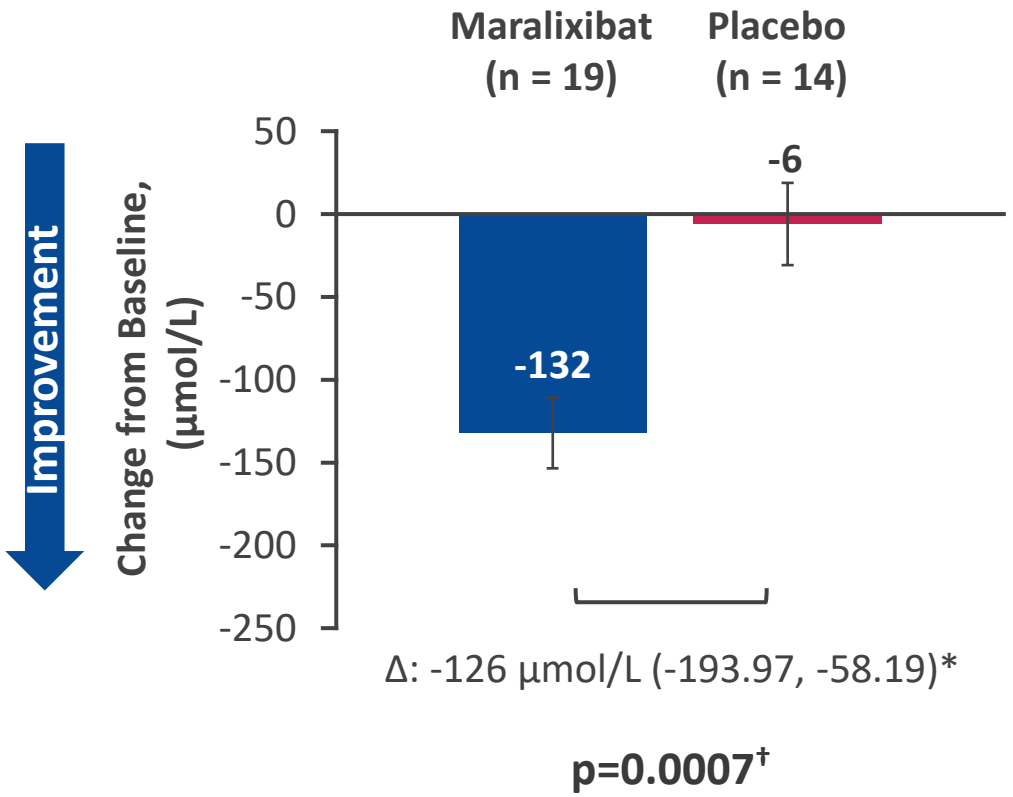
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (weeks 18, 22, and 26) using a MMRM. Two participants in the maralixibat group did not have baseline sBAs.

BSEP, bile salt export pump; LS, least squares; MMRM, mixed model repeated measures; sBA, serum bile acids.

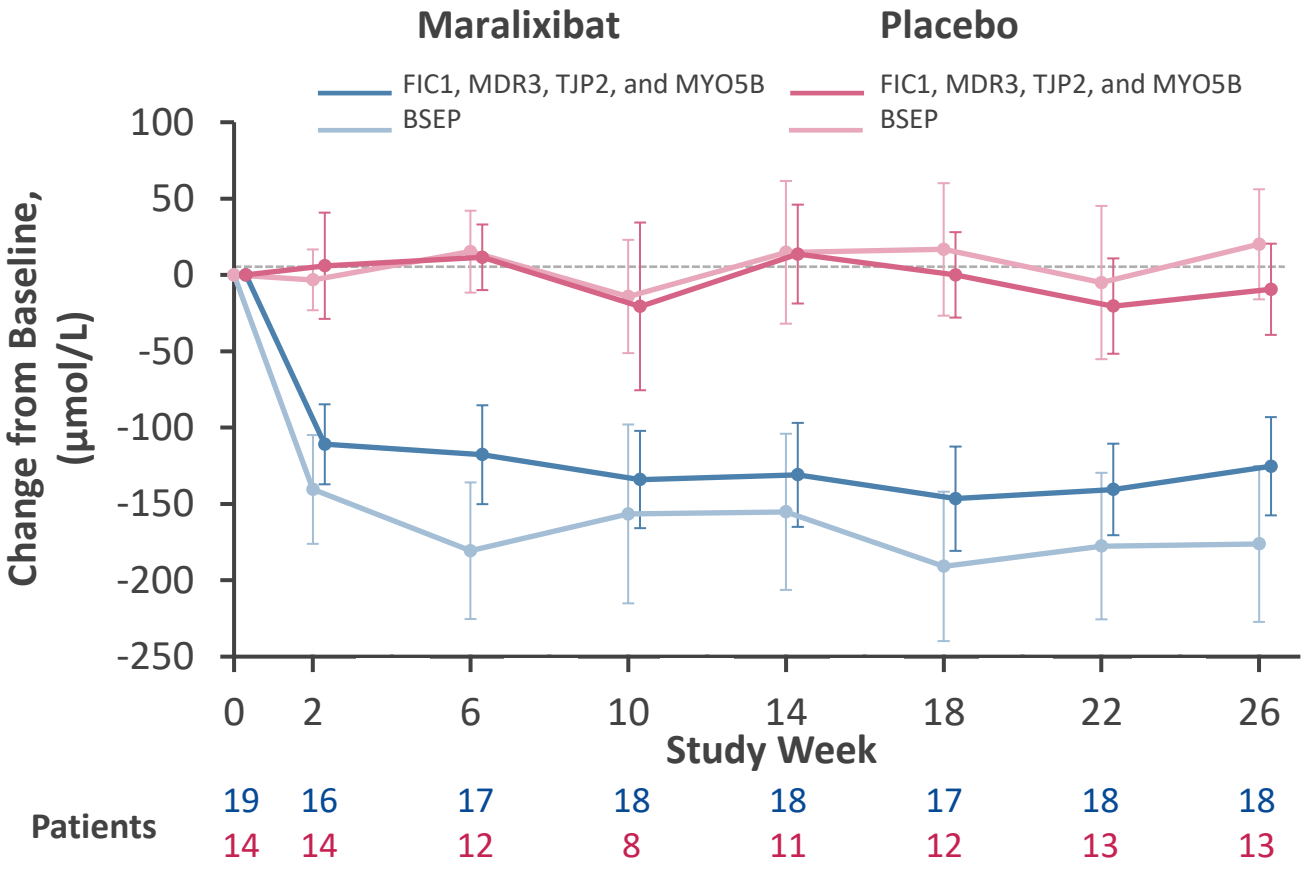
*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean.

Change From Baseline in Serum Bile Acid in FIC1, MDR3, TJP2, and MYO5B

Serum Bile Acid MMRM Analysis



Average Serum Bile Acids Over Time



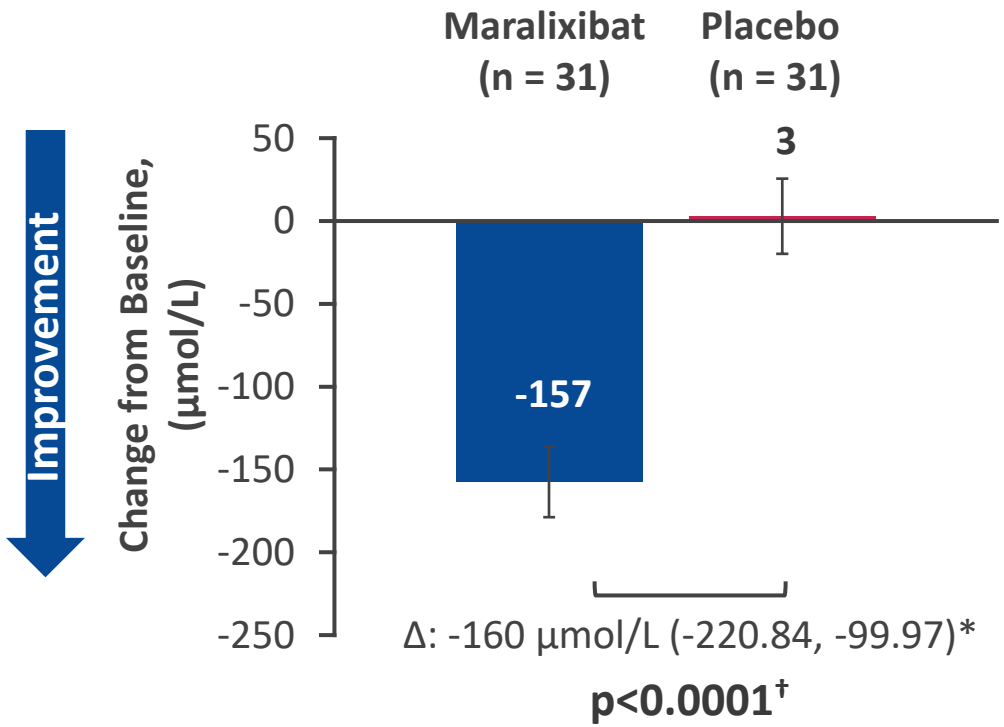
Maralixibat resulted in statistically significant improvements in serum bile acid levels in FIC1, MDR3, TJP2, and MYO5B

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 a MMRM. FIC1, familial intrahepatic cholestasis-associated protein 1; LS, least squares; MMRM, mixed model repeated measures; MDR3, Multi-drug resistant 3 protein; MYO5B, myosin VB; TJP2, tight junction protein 2.

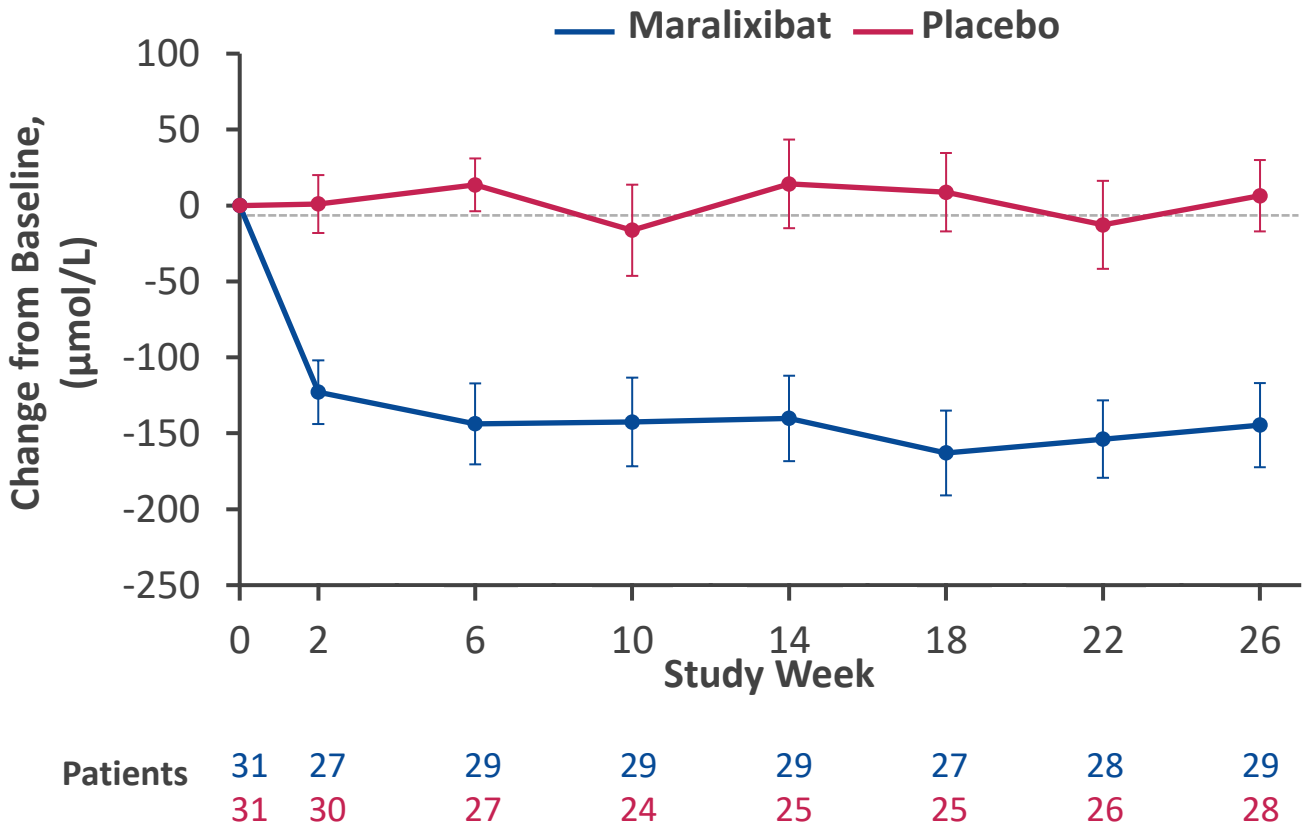
*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean.

Secondary Endpoint: Change From Baseline in Serum Bile Acid in All-PFIC Cohort

Serum Bile Acid MMRM Analysis



Average Serum Bile Acids Over Time



Patients								
	31	27	29	29	29	27	28	29
	31	30	27	24	25	25	26	28

Maralixibat resulted in statistically significant improvements in serum bile acid levels in the All-PFIC cohort

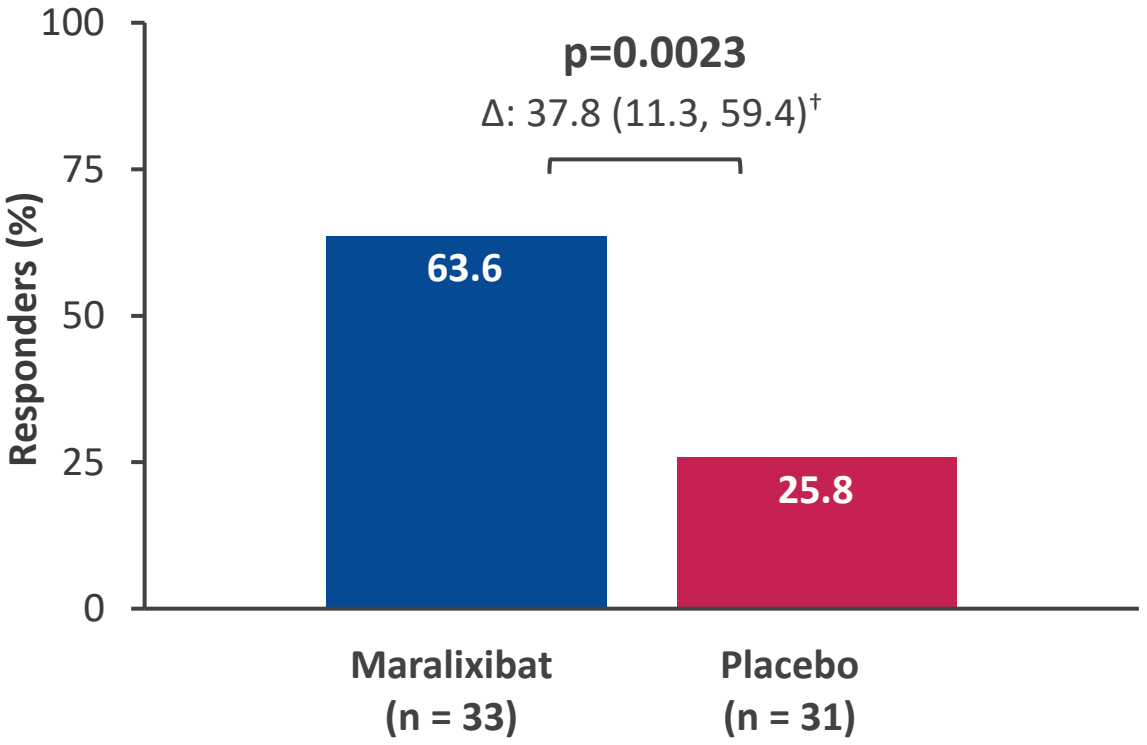
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (weeks 18, 22, and 26) using a MMRM. Two participants in the maralixibat group did not have baseline sBAs.

LS, least squares; MMRM, mixed model repeated measures; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acids.

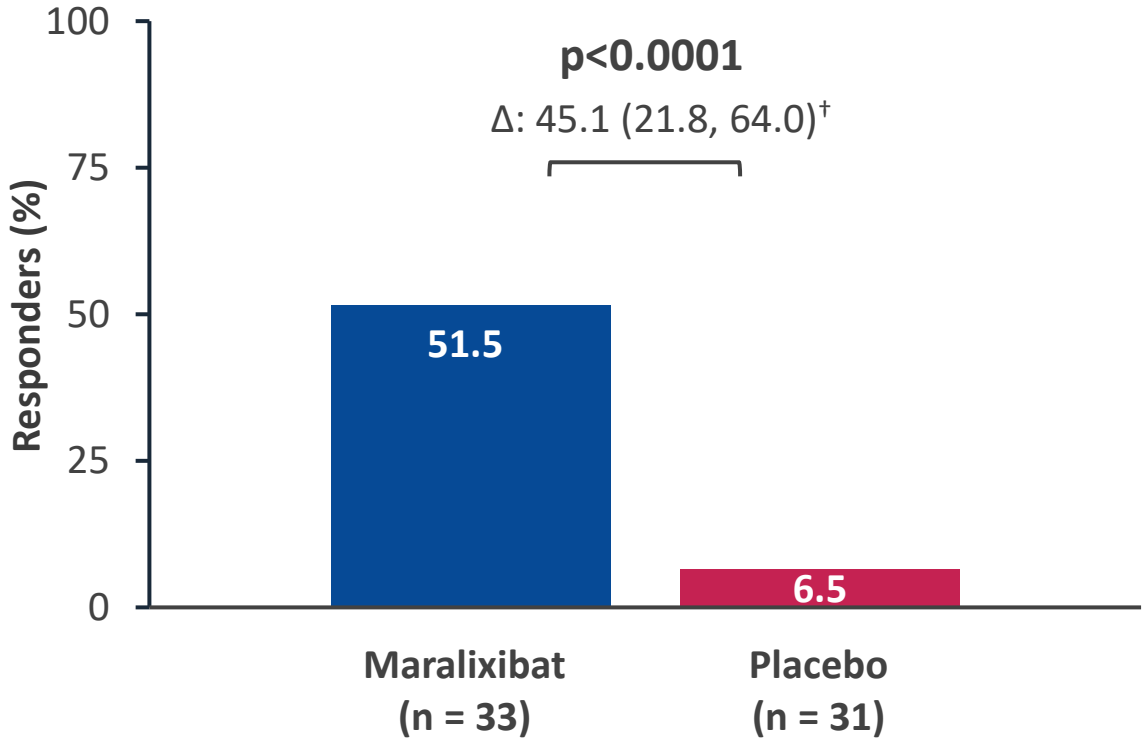
*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean.

Secondary Endpoint: Pruritus and sBA Responder Analyses in All-PFIC Cohort

Pruritus Responders*
≥1-point reduction OR score of ≤1.0



Serum Bile Acid Responders*
≥75% reduction OR serum bile acid <102 µmol/L

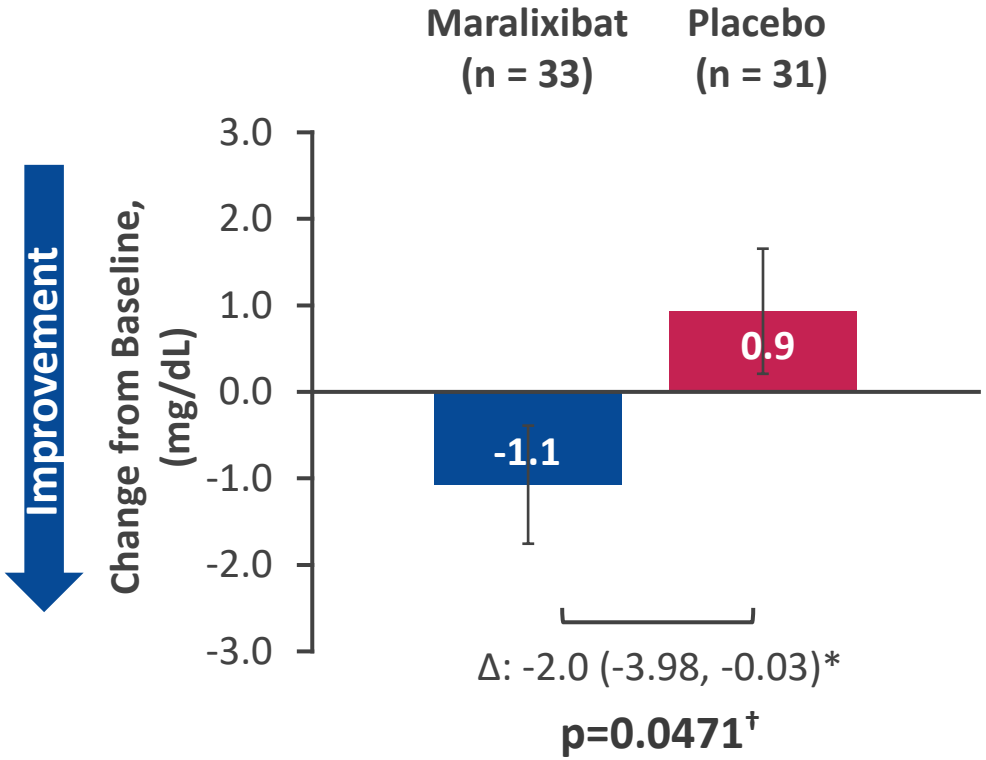


Significantly greater percentage of maralixibat-treated patients met the response thresholds for pruritus and serum bile acid in the All-PFIC cohort

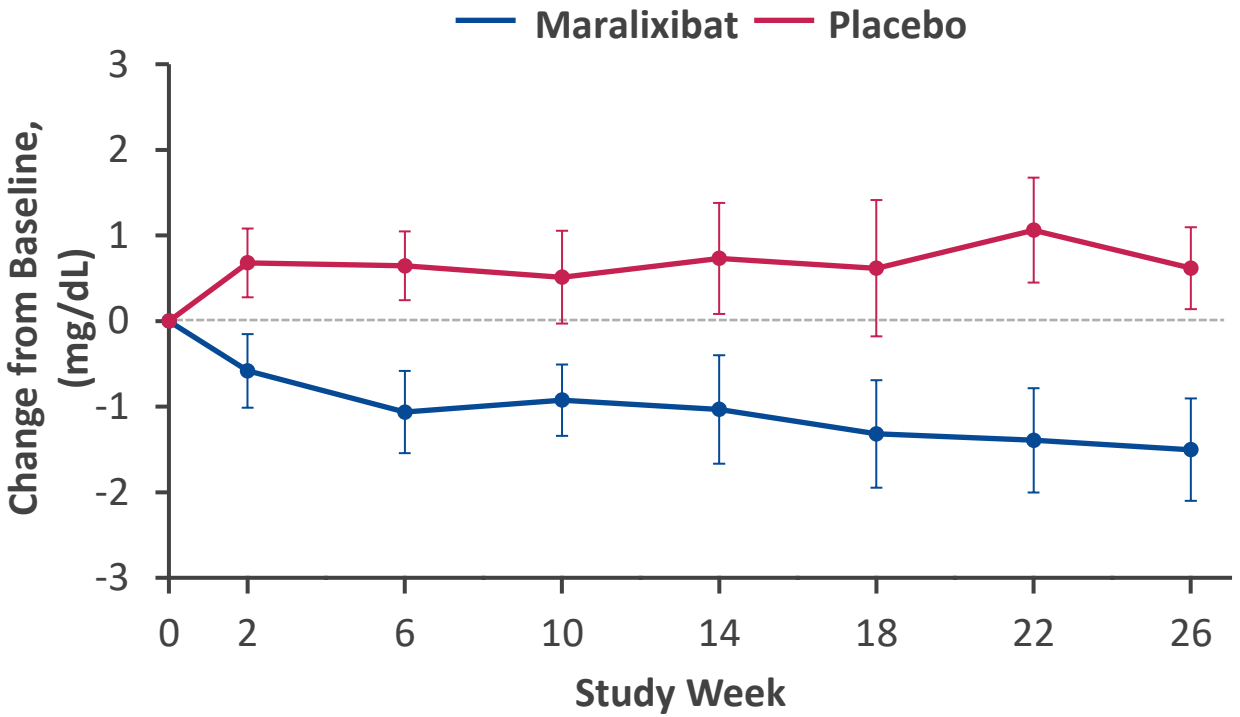
*To determine response: average pruritus severity score from the three 4-week periods (weeks 15–18, 19–22 and 23–26), and the average sBA value from Weeks 18, 22 and 26 values are used;
†Difference with 95% exact confidence interval. PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acids.

Exploratory Endpoint: Change From Baseline in Total Bilirubin in All-PFIC Cohort

Serum Total Bilirubin MMRM Analysis



Average Serum Total Bilirubin Over Time



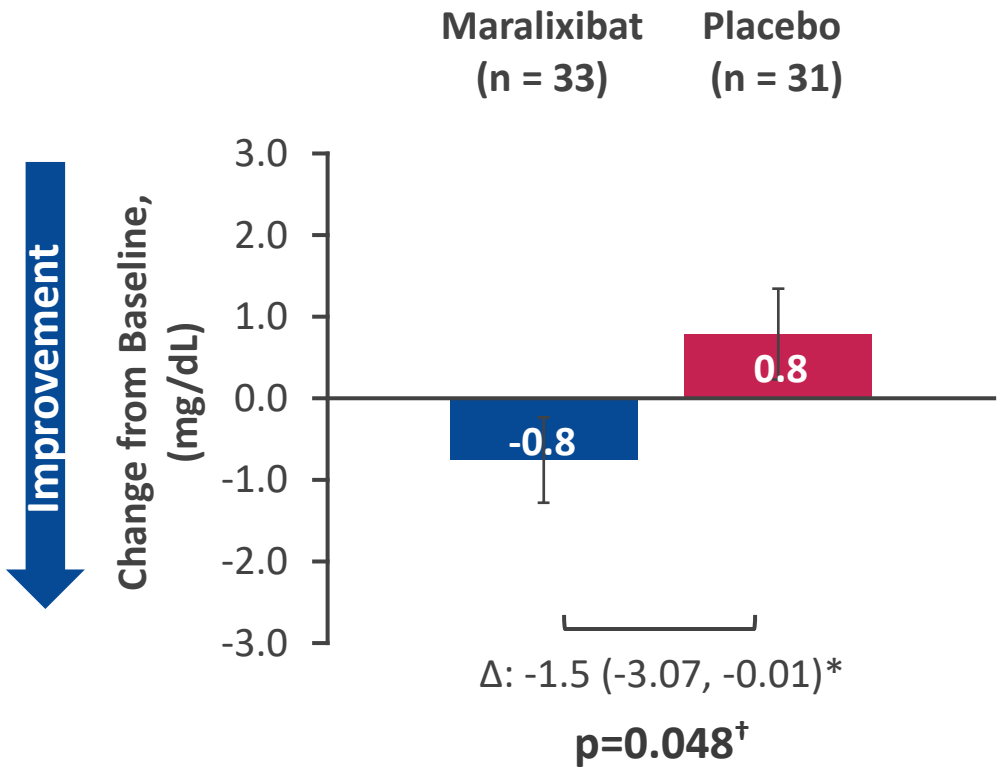
Patients								
	33	28	31	29	32	30	32	31
	31	30	29	26	26	26	28	28

Maralixibat resulted in statistically significant improvements in total bilirubin in the All-PFIC cohort

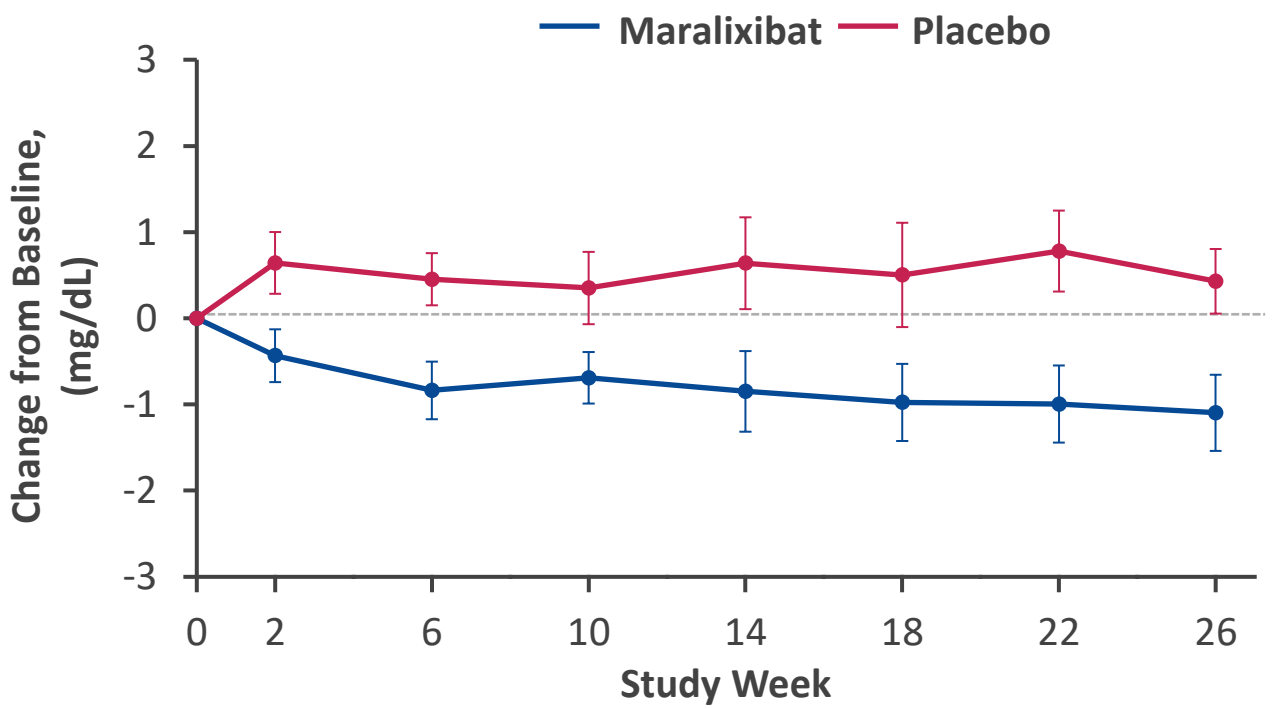
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (weeks 18, 22, and 26) using a MMRM. LS, least squares; MMRM, mixed model repeated measures; PFIC, progressive familial intrahepatic cholestasis.
*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean.

Exploratory Endpoint: Change From Baseline in Direct Bilirubin in All-PFIC Cohort

Serum Direct Bilirubin MMRM Analysis



Average Serum Direct Bilirubin Over Time



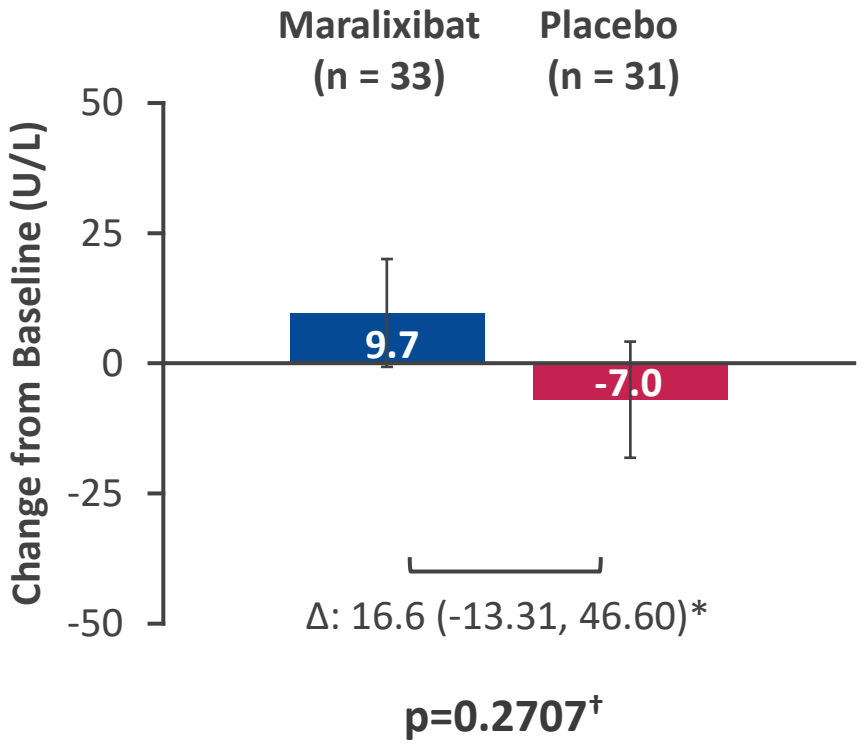
Patients	33	28	31	29	31	30	32	31
	31	30	28	26	26	25	27	28

Maralixibat resulted in statistically significant improvements in direct bilirubin in the All-PFIC cohort

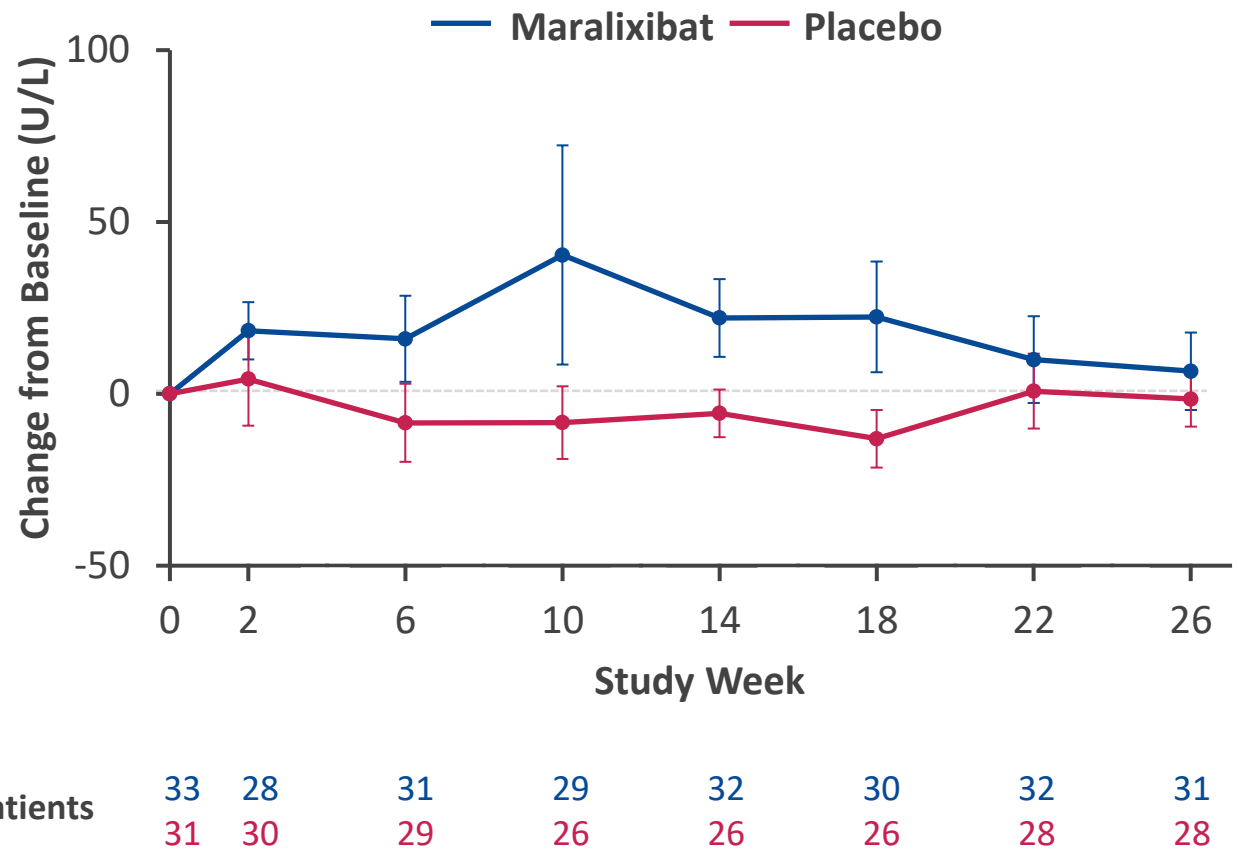
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (weeks 18, 22, and 26) using a MMRM. LS, least squares; MMRM, mixed model repeated measures; PFIC, progressive familial intrahepatic cholestasis.
*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean.

Change From Baseline in ALT in All-PFIC Cohort

Serum ALT MMRM Analysis



Average Serum ALT Over Time

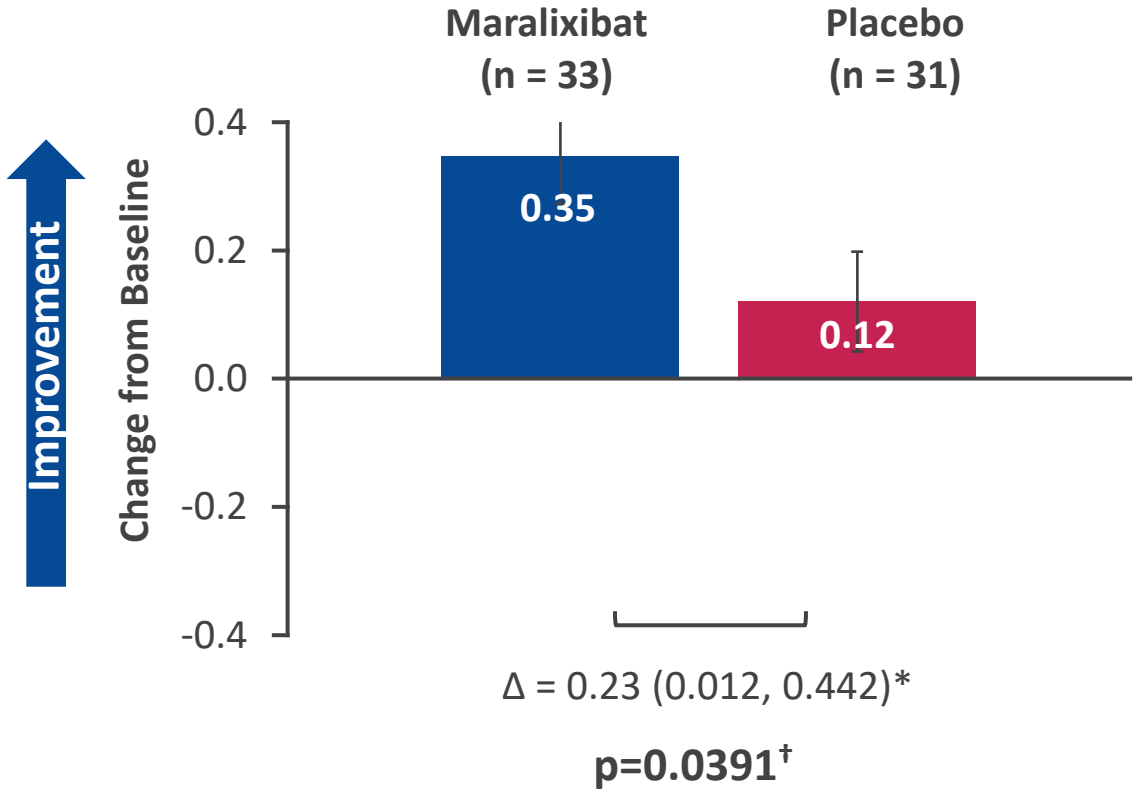


No significant changes in ALT levels were observed following maralixibat treatment in the All-PFIC cohort

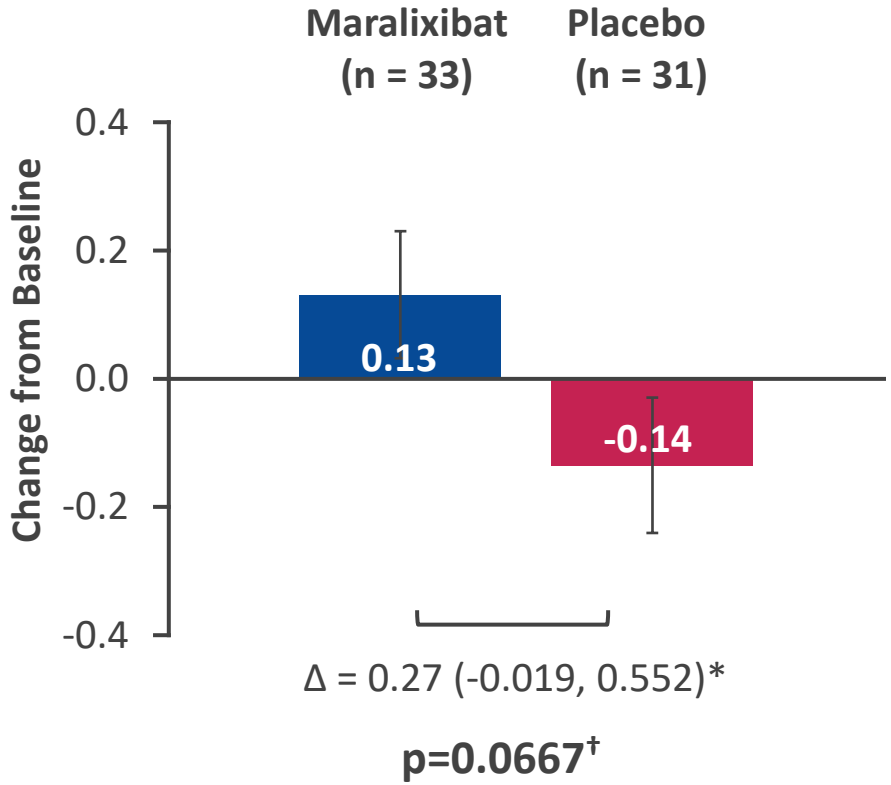
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (weeks 18, 22, and 26) using a MMRM. ALT, alanine aminotransferase; LS, least squares; MMRM, mixed model repeated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

Exploratory Endpoint: Change From Baseline in Weight and Height Z-Score in All-PFIC Cohort

Weight Z-score MMRM Analysis



Height Z-score MMRM Analysis



Maralixibat resulted in statistically significant improvements in weight Z-score and a trend in height Z-score in the All-PFIC cohort

Data are LS mean with standard error bars. Effect size compared the difference between maralixibat and placebo change from baseline at the average of Weeks 18, 22, and 26 (for weight z-score) and at Week 26 (for height z-score) using a MMRM. LS, least squares; MMRM, mixed model repeated measures; PFIC, progressive familial intrahepatic cholestasis.
*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean.

Summary of TEAEs in Full-Study Cohort (N = 93)

TEAE	Maralixibat (n = 47)	Placebo (n = 46)
Any TEAE, n (%)	47 (100%)	43 (93.5%)
Severe TEAE, n (%)	3 (6.4%)	3 (6.5%)
Serious TEAE, n (%)	5 (10.6%)	3 (6.5%)
TEAE leading to discontinuation, n (%)	1 (2.1%)	0
TEAE leading to death, n (%)	0	0
Most common TEAE: diarrhea, n (%)	27 (57.4%)	9 (19.6%)

- Diarrhea was predominantly mild and transient with a median duration of 5.5 days; no severe events reported
- One patient had a TEAE of mild diarrhea that led to discontinuation
- No deaths reported

TEAE, treatment emergent adverse event.

Key Takeaways

- MARCH is the largest Phase 3 trial conducted in children with PFIC that included PFIC types that had not previously been studied
- Primary and secondary endpoints were met
- Maralixibat demonstrated significant and rapid improvements in pruritus and serum bile acids, consistent across all PFIC types
- The magnitude of treatment effect observed with maralixibat is greater than previously documented
- Using the NAPPED threshold for BSEP deficiency associated with transplant-free survival, over half of the maralixibat-treated patients achieved a serum bile acid response across all PFIC types
- Significant improvements in bilirubin and weight Z-score were observed in the All-PFIC cohort, as well as a trend in height Z-score improvement
- Maralixibat was generally well tolerated, with no new safety signals observed

BSEP, bile salt export pump; NAPPED, NAtural Course and Prognosis of PFIC and Effect of Biliary Diversion; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acids.

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- The authors would like to thank the clinical trial participants, 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
- F Ordonez is a speaker for Alexion Pharmaceuticals and Valentech Pharma
- A Aqul is a consultant for Mirum Pharmaceuticals, Inc, Albireo, and Sarepta Therapeutics
- E Sokal is the founder and chairman of Cellaion, an investigator for Mirum Pharmaceuticals, Inc., Albireo and Intercept, and an advisor for Albireo
- U Baumann is a consultant for Mirum Pharmaceuticals, Inc., Albireo, and Vivet Pharmaceuticals
- L D'Antiga is a consultant and advisor for Mirum Pharmaceuticals, Inc., Albireo, Selecta, Vivet Pharmaceuticals, Tome, Spark, Genespire, and Alexion
- N Kasi is a consultant for Mirum Pharmaceuticals, Inc.
- N Mittal is an investigator for Mirum Pharmaceuticals, Inc.
- S Horslen is a hepatic safety adjudication committee (HSAC) member at Albireo and has received a research grant from Mirum Pharmaceuticals, Inc.
- A Van Leerberghe, S Weber Ronn, T Nunes, A Lascau, L Longpre, W Garner, P Vig are employees and stakeholders at Mirum Pharmaceuticals, Inc.
- R P Gonzalez-Peralta has received a research grant from Mirum Pharmaceuticals, Inc., and is an advisor, teacher, and educator for Mirum Pharmaceuticals, Inc., and Albireo
- U Ekong is a steering committee member and member at Mirum Pharmaceuticals, Inc.
- A Moukarzel, G Porta, J Covarrubias Esquer, P Czubkowski, M Candusso, R Squires, D D'Agostino, N Laborde, C Arikan, C H Lin, S Gilmour, F K Chiou, W D Huber, V Hupertz, J Hartley, N Laverdure, and N Ovchinsky have nothing to disclose

Back-Up

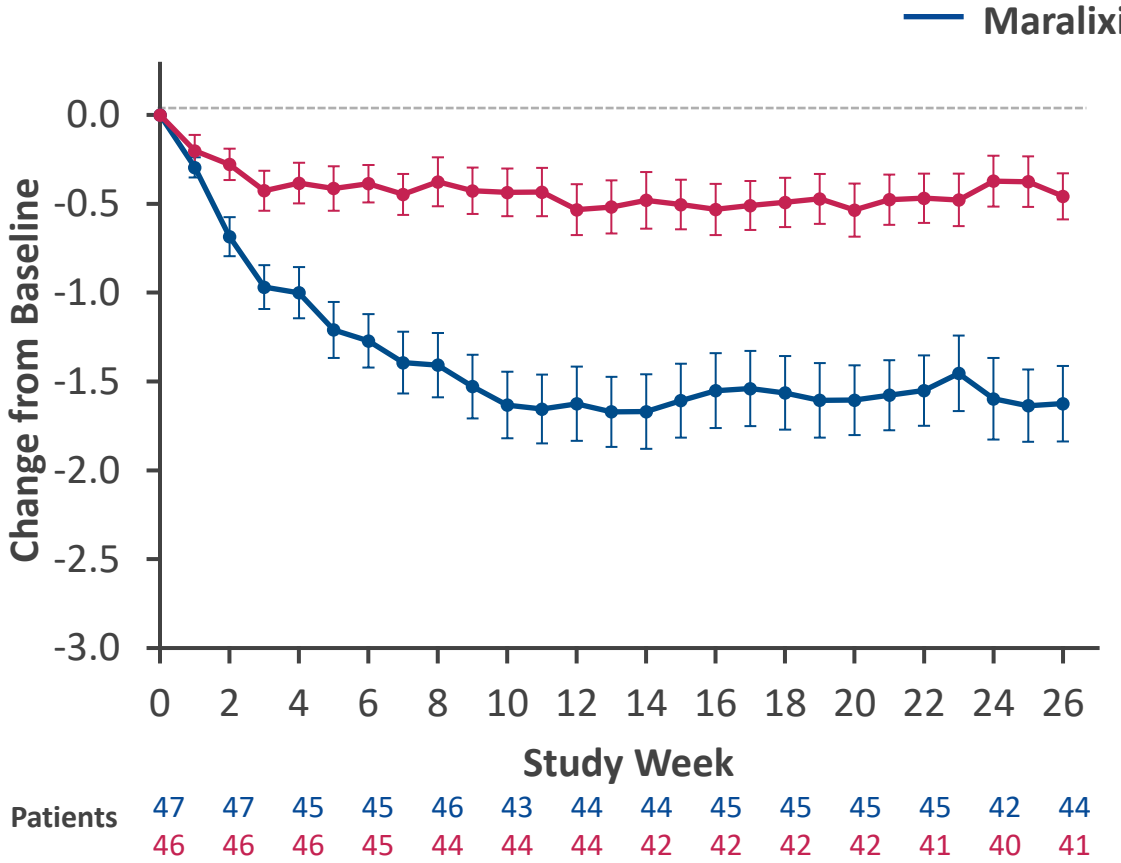
MARCH-PFIC: Patient Disposition

Status or Category	BSEP Deficiency		All-PFIC		Full-Study	
	Maralixibat (n = 14)	Placebo (n = 17)	Maralixibat (n = 33)	Placebo (n = 31)	Maralixibat (n = 47)	Placebo (n = 46)
Screened for eligibility					125	
Screen failure					32	
Randomized	14	17	33	31	47	46
Safety population	14	17	33	31	47	46
Completed study treatment	13 (92.9%)	15 (88.2%)	32 (97.0%)	28 (90.3%)	44 (93.6%)	42 (91.3%)
Reason for discontinuation						
Adverse event	0	0	0	0	1 (2.1%)	0
Liver transplant	0	0	0	0	1 (2.1%)	0
Withdrawal of consent	1 (7.1%)	1 (5.9%)	1 (3.0%)	2 (6.5%)	1 (2.1%)	3 (6.5%)
Disease progression	0	1 (5.9%)	0	1 (3.2%)	0	1 (2.2%)

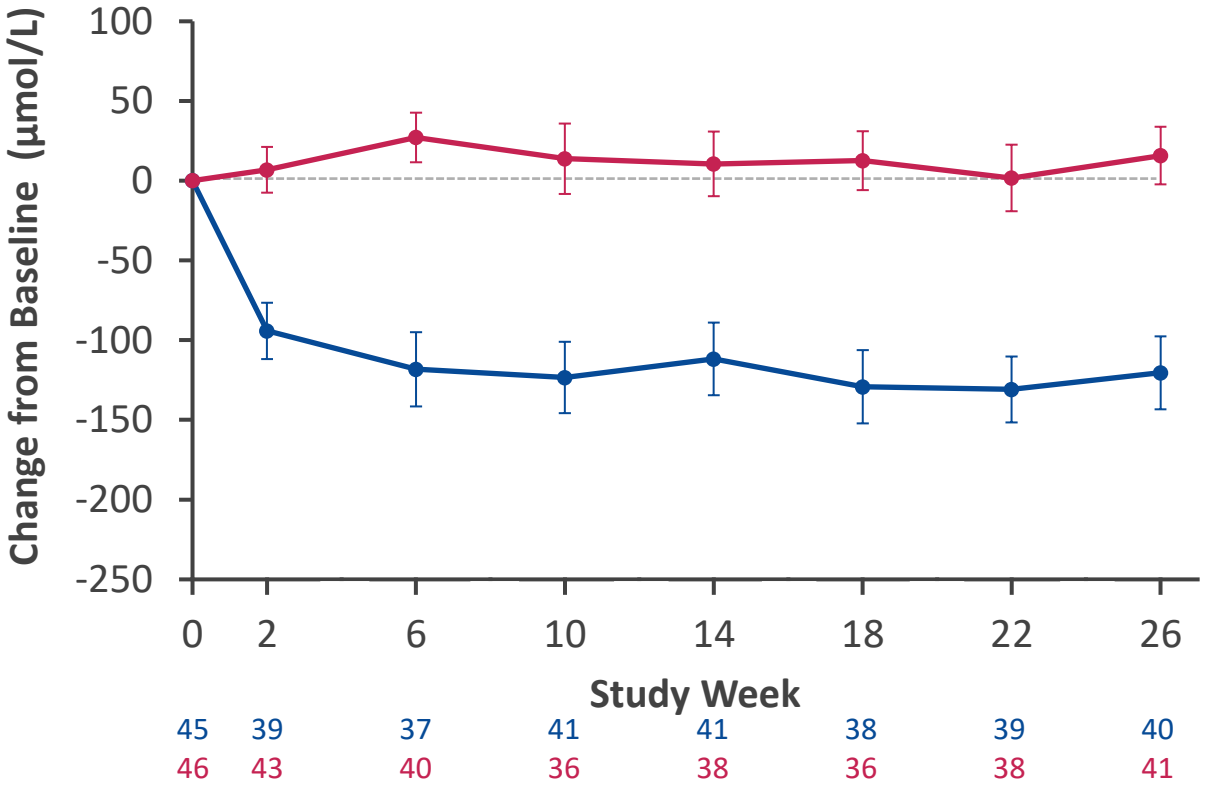
The majority of randomized patients completed study treatment

Change in Weekly ItchRO(Obs) Score and Serum Bile Acids in Full-Study Cohort (N=93)

Average Pruritus Score (ItchRO[Obs]) Over Time



Average Serum Bile Acid Over Time

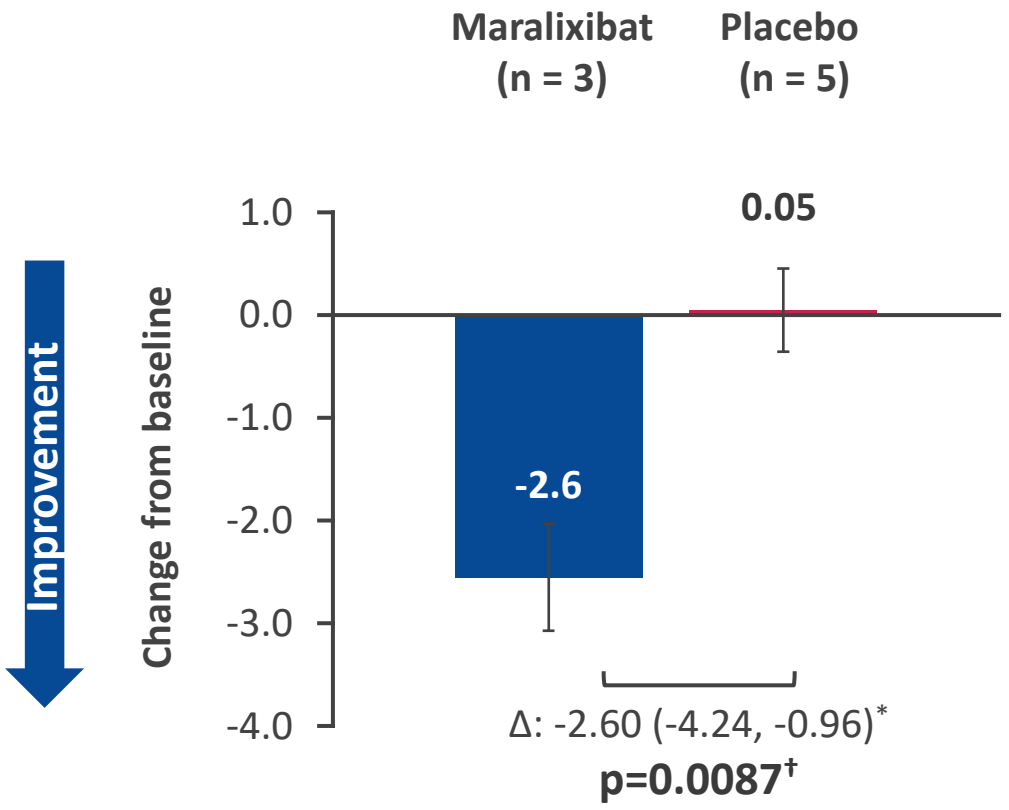


Maralixibat resulted in statistically significant and clinically meaningful improvements in pruritus severity and serum bile acid levels across the full-study population

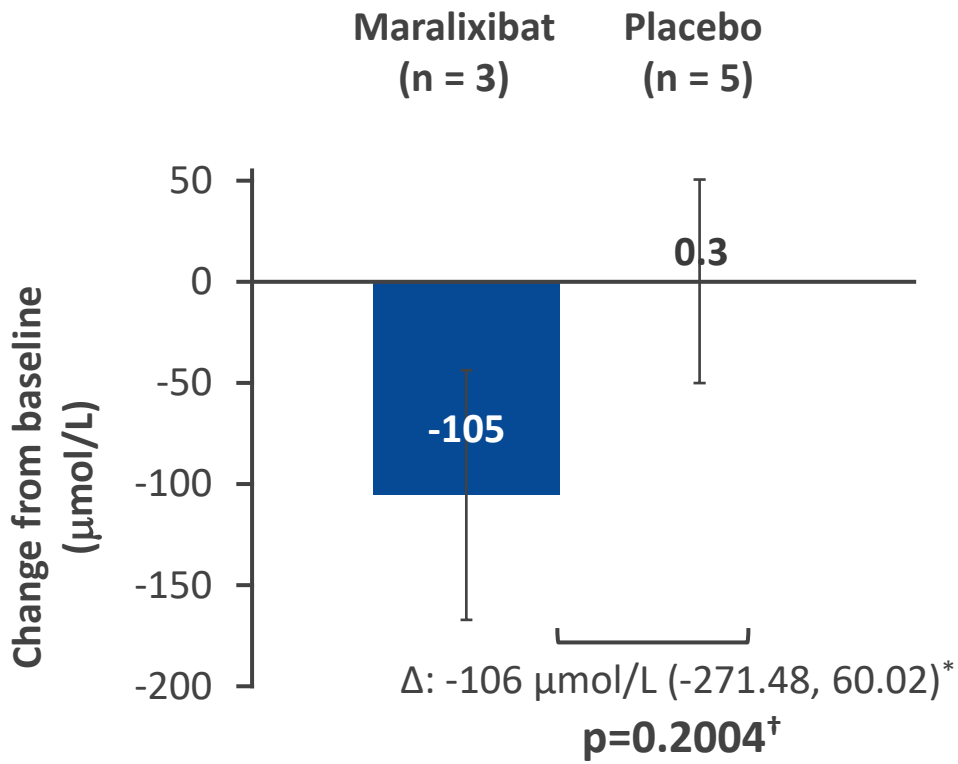
Data are means with standard error bars. Two participants in the maralixibat group did not have baseline serum bile acids.
ItchRO(Obs), Itch Reported Outcome (Observer)

Change in Weekly ItchRO(Obs) Score and Serum Bile Acids in No-Variant-Found

Pruritus Score (ItchRO[Obs]) MMRM Analysis



Serum Bile Acids MMRM Analysis

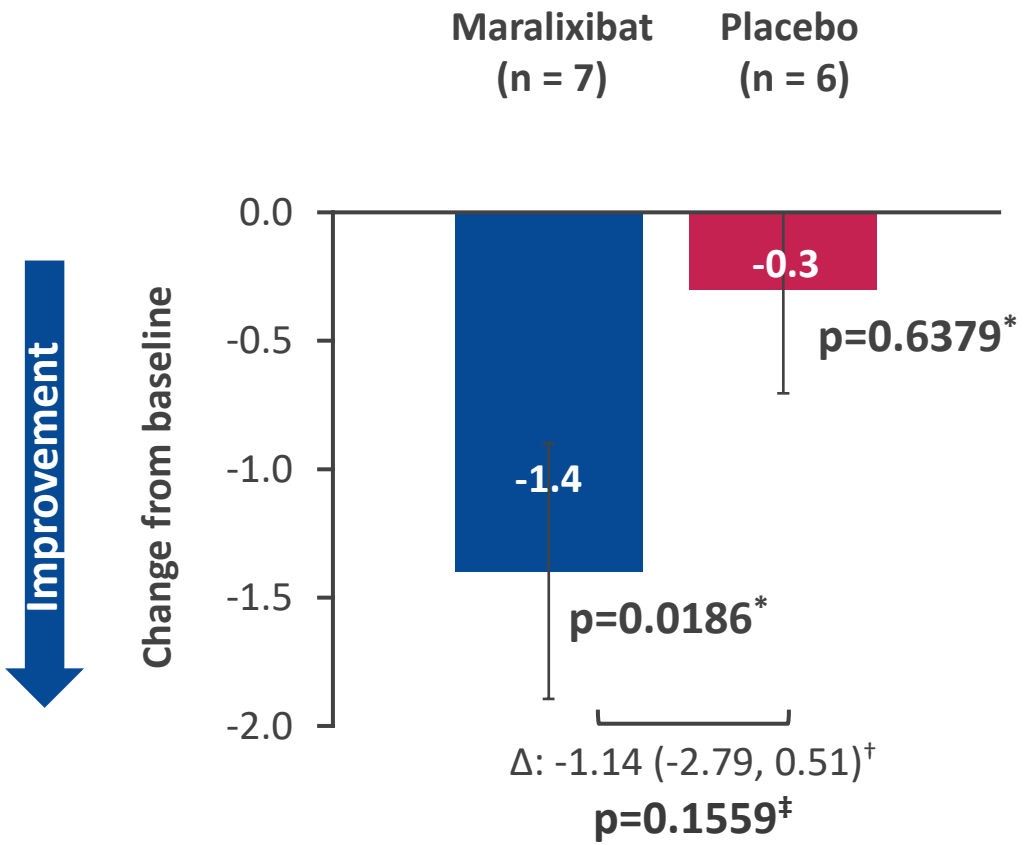


In patients with no-variant-found, maralixibat demonstrated improvements in pruritus and serum bile acids

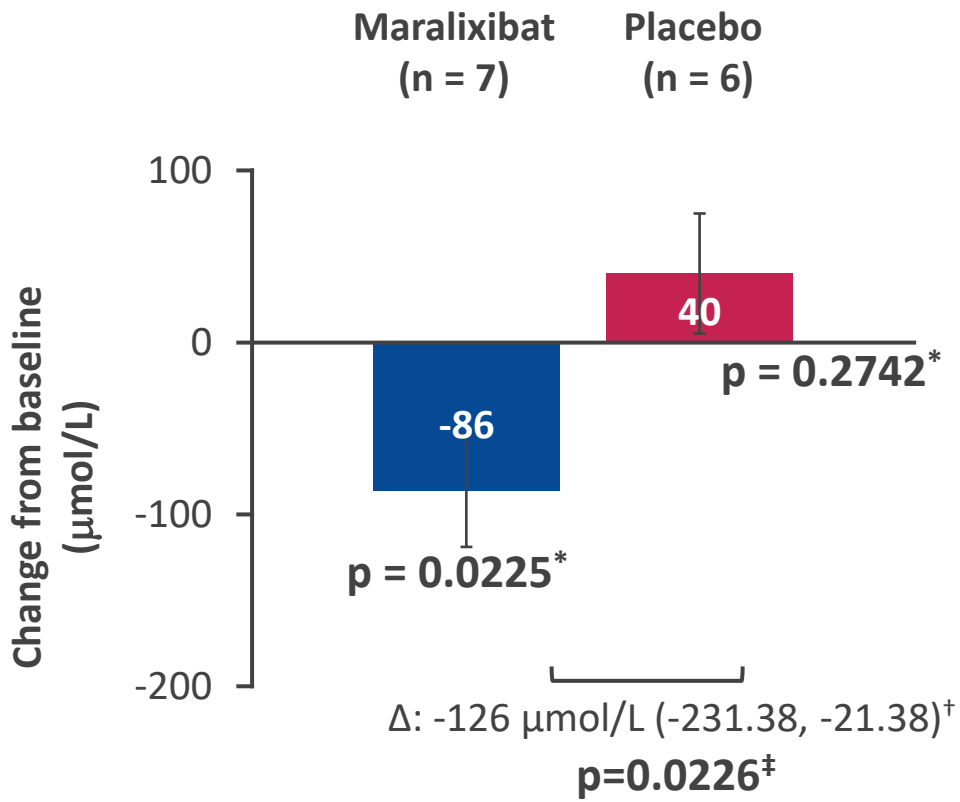
Data are LS Mean with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals for ItchRO, Weeks 18, 22, and 26 for sBA) using a repeated measures mixed effect model. LS, least squares; MMRM, mixed model repeated measures.
*LS Mean Delta with 95% CI. †Maralixibat LS Mean = Placebo LS Mean

Change in Weekly ItchRO(Obs) Score and Serum Bile Acids in FIC1

Pruritus Score (ItchRO[Obs]) MMRM Analysis



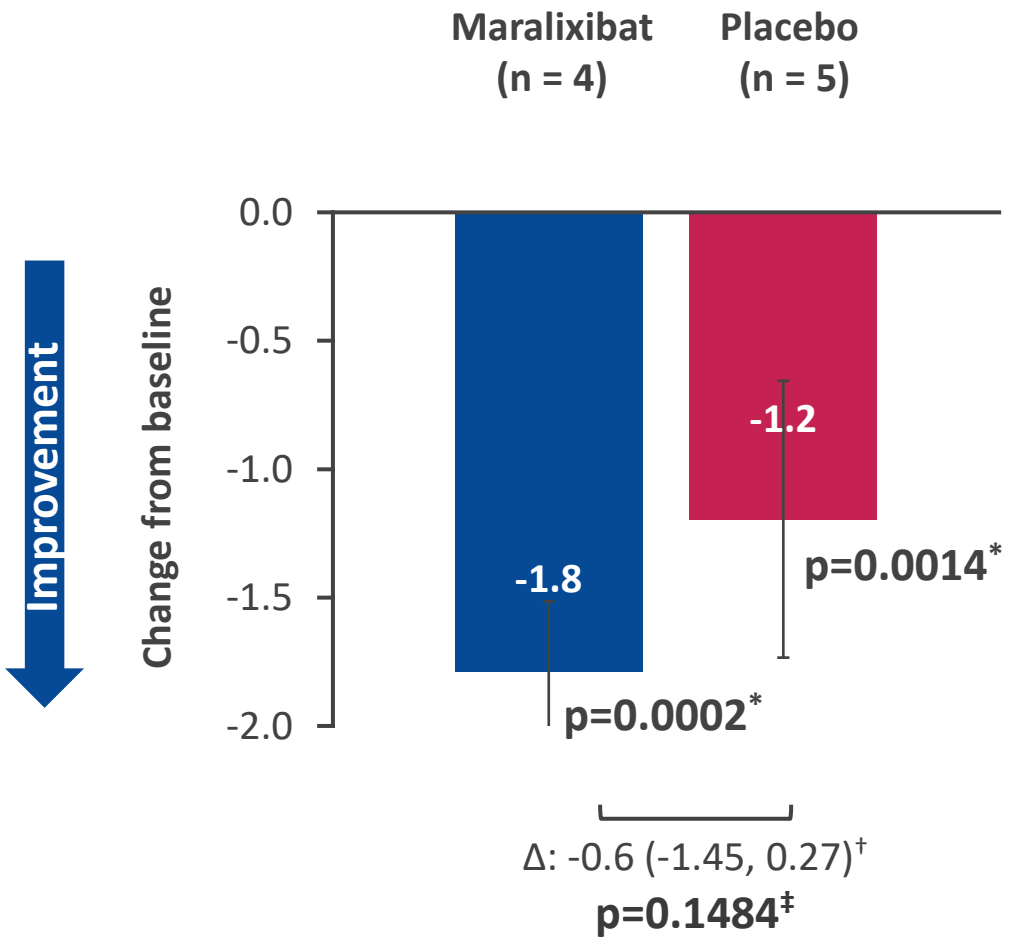
Serum Bile Acids MMRM Analysis



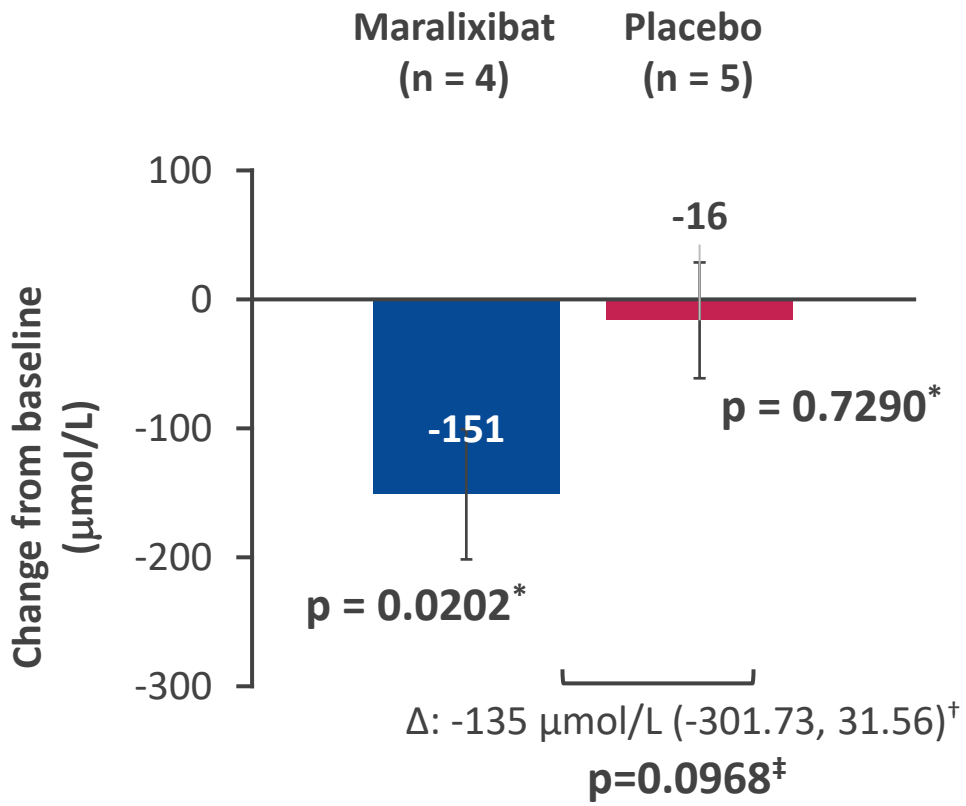
Data are LS Mean with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals for ItchRO, Weeks 18, 22, and 26 for sBA) using a repeated measures mixed effect model. FIC1, familial intrahepatic cholestasis-associated protein 1; LS, least squares; MMRM, mixed model repeated measures.
*Versus baseline. †LS Mean Delta with 95% CI. ‡Maralixibat LS Mean = Placebo LS Mean.

Change in Weekly ItchRO(Obs) Score and Serum Bile Acids in MDR3

Pruritus Score (ItchRO[Obs]) MMRM Analysis



Serum Bile Acids MMRM Analysis



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 for ItchRO, Weeks 18, 22, and 26 for sBA) using a repeated measures mixed effect model. LS, least squares; MDR3, Multi-drug resistant 3 protein; MMRM, mixed model repeated measures.
*Versus baseline. †LS Mean Delta with 95% CI. ‡Maralixibat LS Mean = Placebo LS Mean.