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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Faculty Disclosure

	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			

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 lab 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)

- 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 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,*]

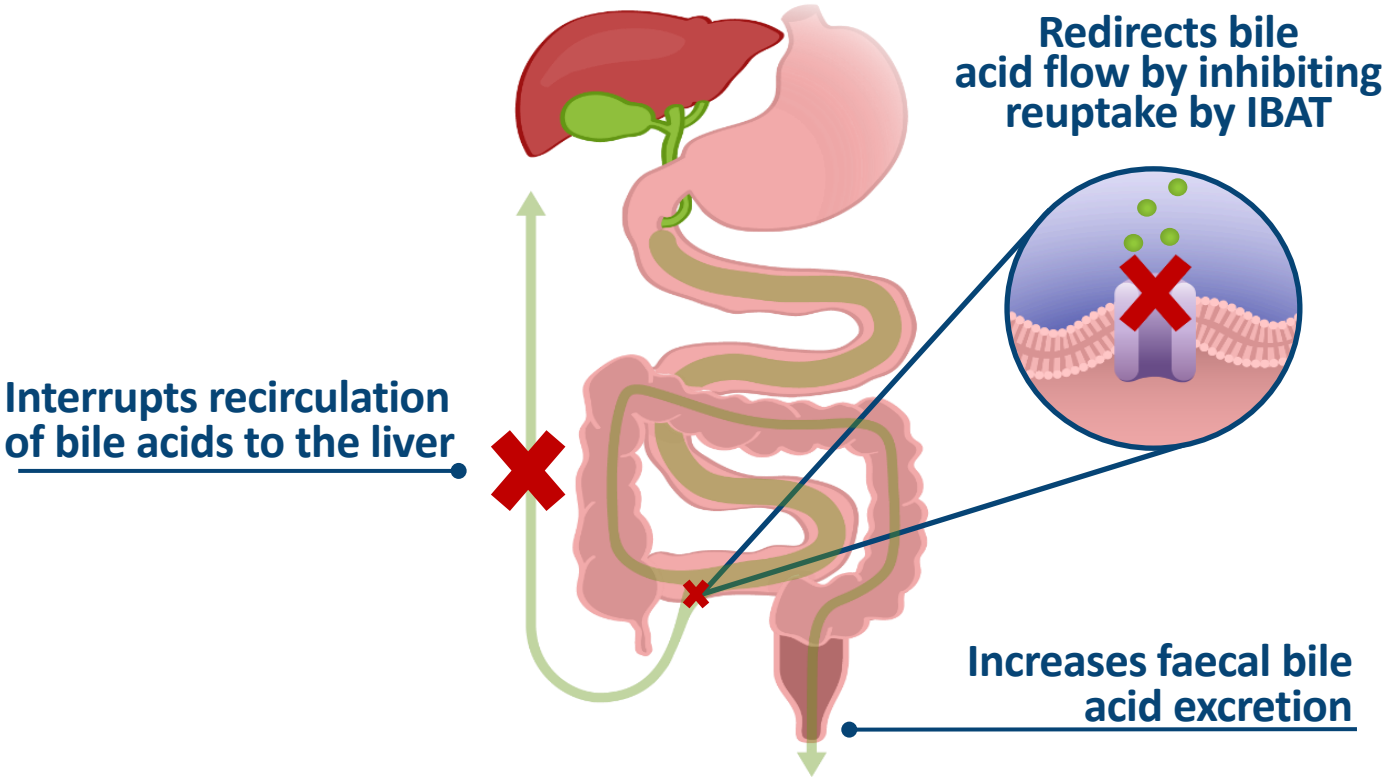
The efficacy of IBAT inhibitors has not been studied across every PFIC type

*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.[7,8]

EU, European Union; FDA, US Food and Drug Administration; 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. BYLVAY® (odevixibat) [prescribing information]. Boston, MA; Albireo Pharma, Inc. Jul 2021; 8. BYLVAY® (odevixibat) [summary of product characteristics]. Boston, MA; Albireo Pharma, Inc. Jul 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 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; FDA, US Food and Drug Administration; IBAT, ileal bile acid transporter; 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. 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.

MARCH-PFIC: Phase 3 Study Design

Key Entry Criteria

- Diagnosis of PFIC
- Age ≥ 12 months and < 18 years at time of Baseline
- Persistent, moderate to severe pruritus
- sBA ≥ 3 × ULN

*Maralixibat 570 µg/kg is equivalent to 600 µg/kg maralixibat chloride.
BID, twice daily; BL, Baseline; 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 March 23, 2023.

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), t-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* mutation.
BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis-associated protein type 1; MDR3, multidrug-resistance 3 protein; MYO5B, myosin VB; nt, non truncated mutations; sBA, serum bile acid; 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 analysed using a repeated measures model (MMRM) considering data from all study visits
- ItchRO(Obs) 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; BSEP, bile salt export pump; ItchRO(Obs), Itch-Reported Outcome (Observer); MMRM, mixed model repeated measures; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.
ClinicalTrials.gov ID: NCT03905330. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT03905330 on March 23, 2023.

Key Demographics and Baseline Characteristics

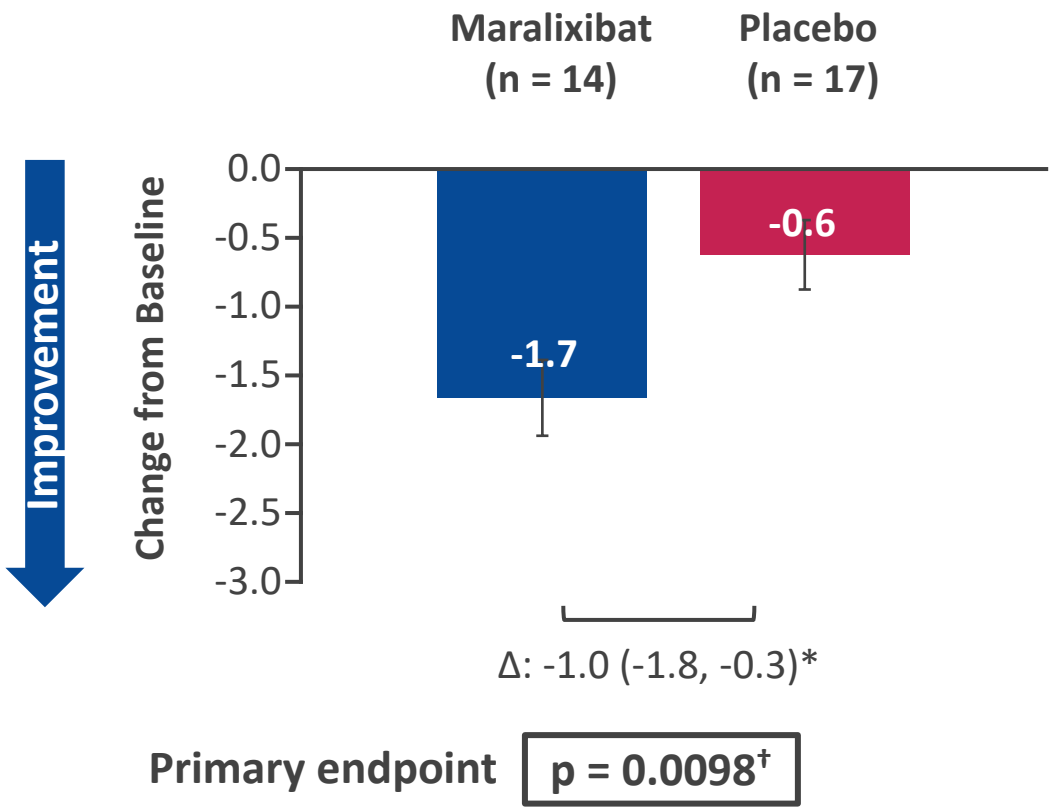
Variable	BSEP		All-PFIC		Full-Study	
	Maralixibat (n = 14)	Placebo (n = 17)	Maralixibat (n = 33)	Placebo (n = 31)	Maralixibat (n = 47)	Placebo (n = 46)
Age, years	6.3	4.2	4.9	4.4	4.8	4.7
Male (%)	50	35	52	42	43	48
Pruritus, ItchRO(Obs)	2.88	2.61	2.85	2.73	2.85	2.93
Total sBA, µmol/L	312	312	254	272	263	243
UDCA usage (%)	79	100	82	97	83	85
Rifampicin usage (%)	43	53	55	48	55	50
Alanine aminotransferase, U/L	98	155	88	127	108	121
Total bilirubin, mg/dL	3.48	2.71	4.12	4.04	4.10	3.80
Direct bilirubin, mg/dL	2.42	1.92	2.98	2.93	2.99	2.77
Height Z-score	-1.96	-2.19	-2.08	-2.06	-2.01	-1.91
Weight Z-score	-1.52	-1.24	-1.75	-1.28	-1.56	-1.22

Baseline characteristics and demographics were balanced between the cohorts

Note: All data are mean unless otherwise indicated. Percentages are 100 x n/N.
BSEP, bile salt export pump; ItchRO(Obs), Itch-Reported Outcome (Observer); PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid; UDCA, ursodeoxycholic acid.

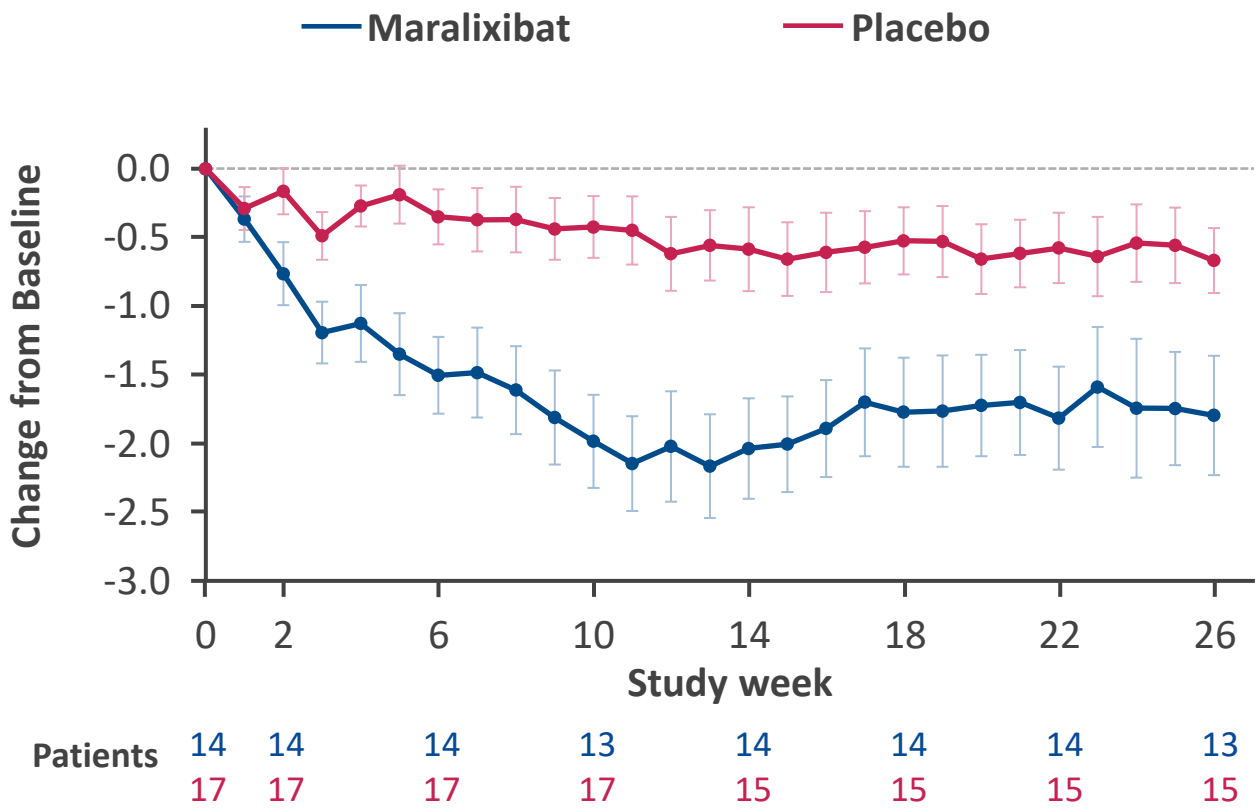
Primary Endpoint: Change in Weekly ItchRO(Obs) Score in BSEP Cohort

Pruritus Score (ItchRO[Obs]) MMRM Analysis



Primary endpoint **p = 0.0098†**

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

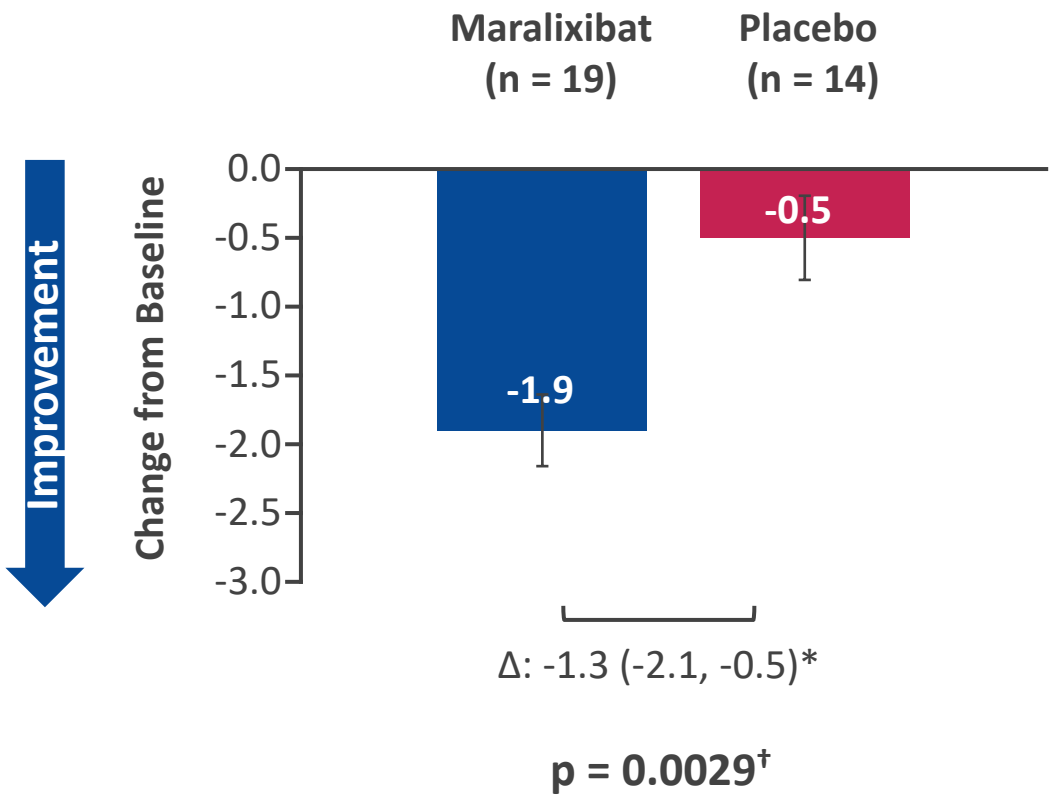


Maralixibat resulted in statistically significant and clinically meaningful improvements in pruritus in the BSEP cohort

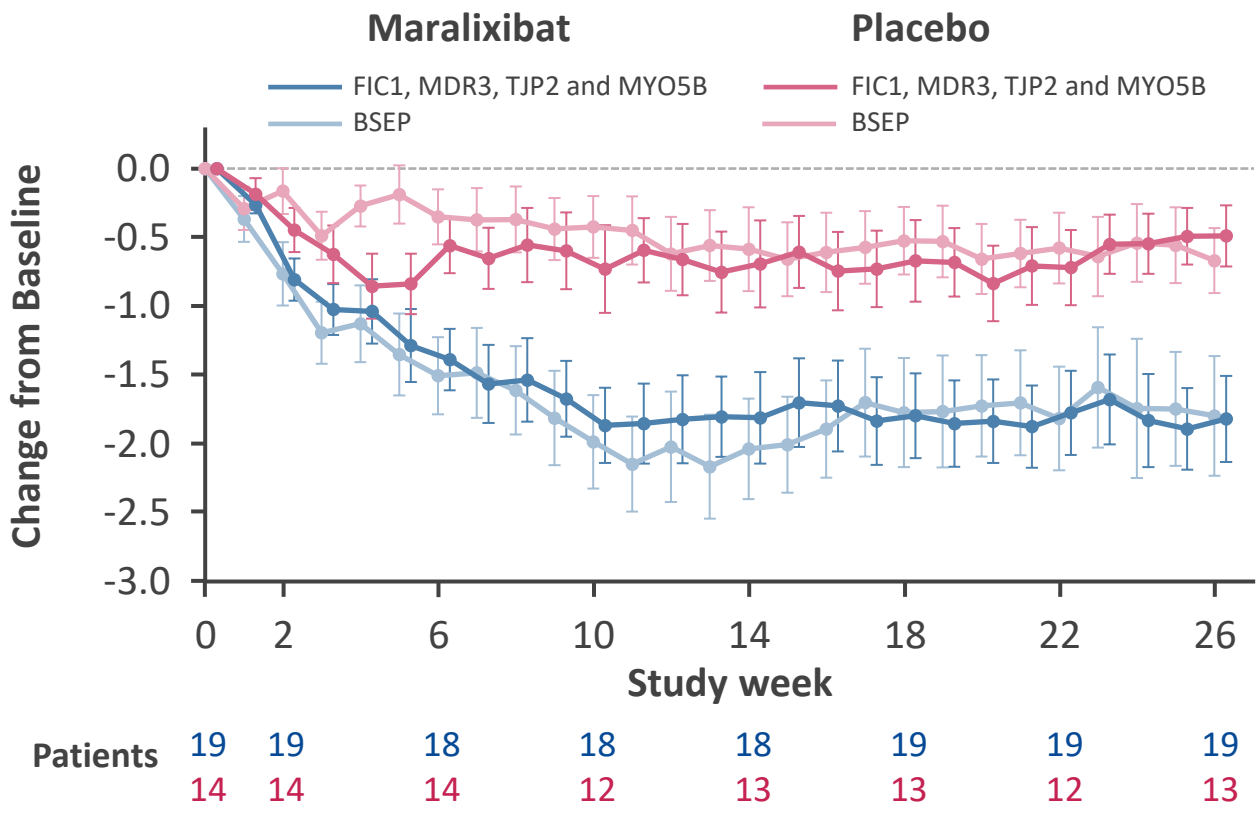
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals) using an MMRM. BSEP, bile salt export pump; CI, confidence interval; ItchRO(Obs), Itch-Reported 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

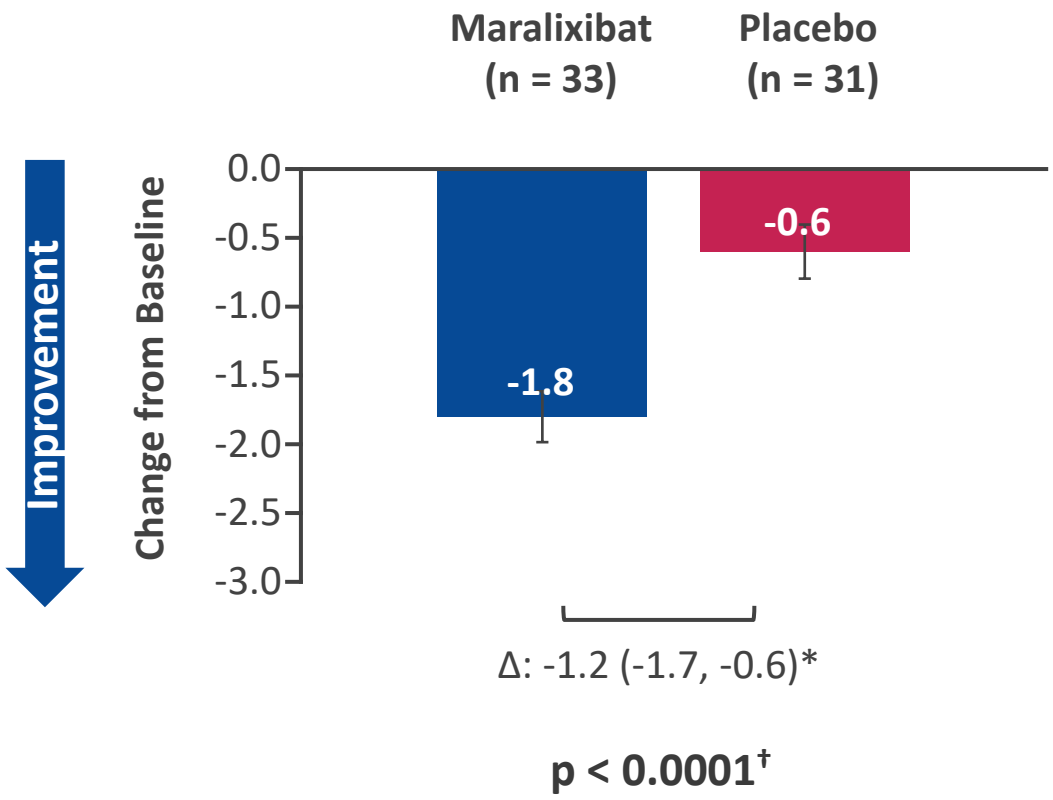


Maralixibat resulted in resulted in statistically significant and clinically meaningful improvements in pruritus in FIC1, MDR3, TJP2 and MYO5B

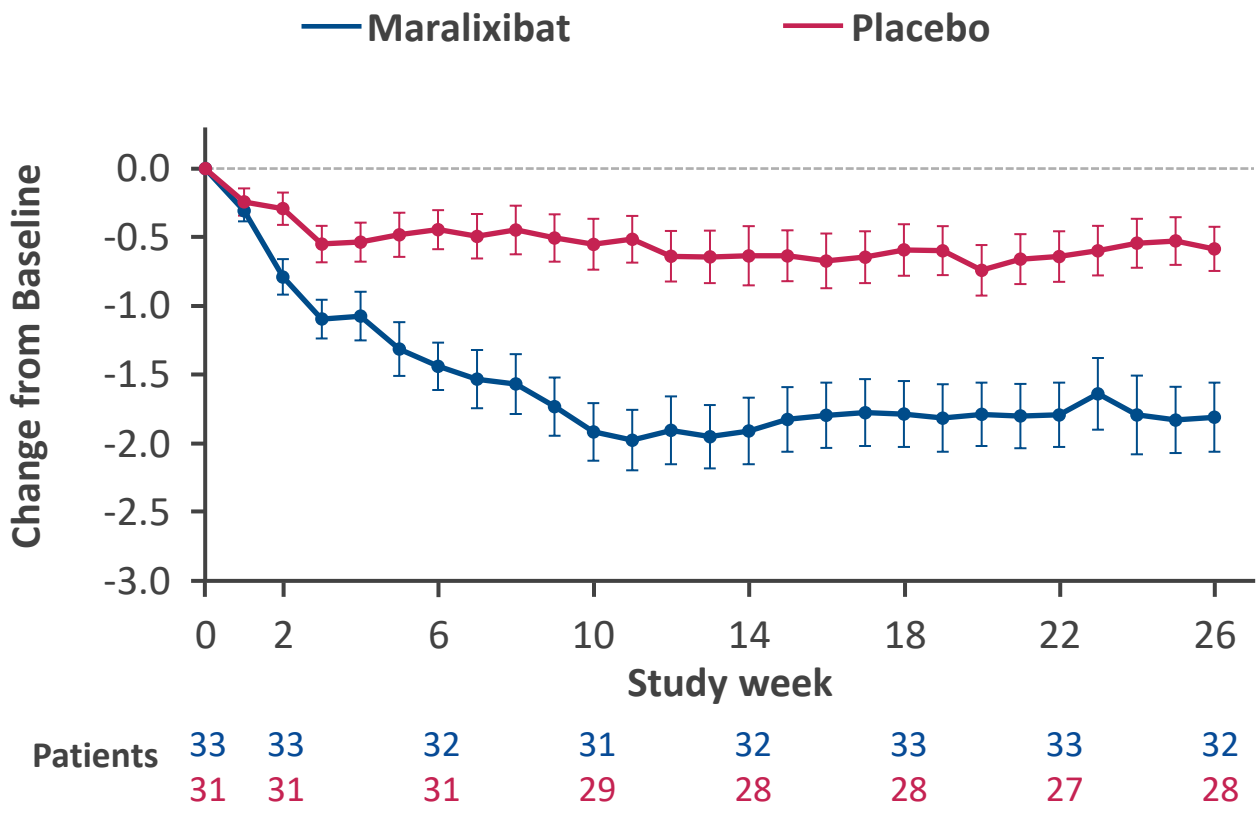
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals) using an MMRM. CI, confidence interval; FIC1, familial intrahepatic cholestasis-associated protein type 1; ItchRO(Obs), Itch-Reported Outcome (Observer); LS, least squares; MMRM, mixed model repeated measures; MDR3, multidrug-resistance 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

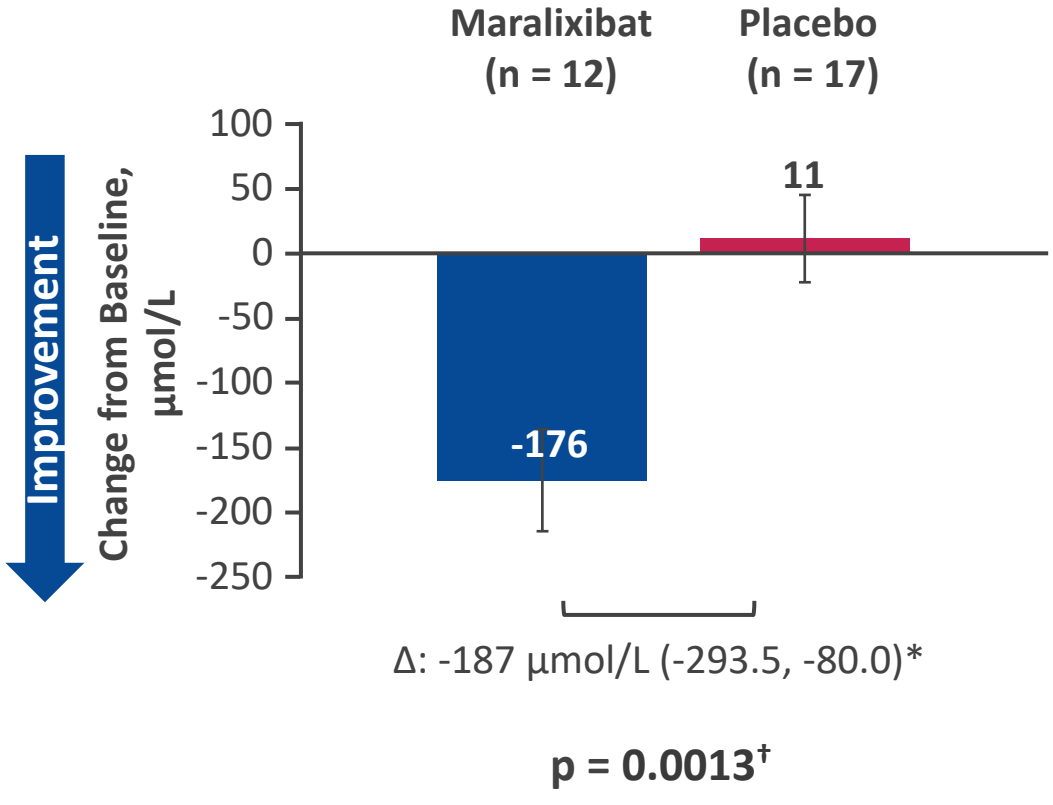


Maralixibat resulted in statistically significant and clinically meaningful improvements in pruritus in the All-PFIC cohort

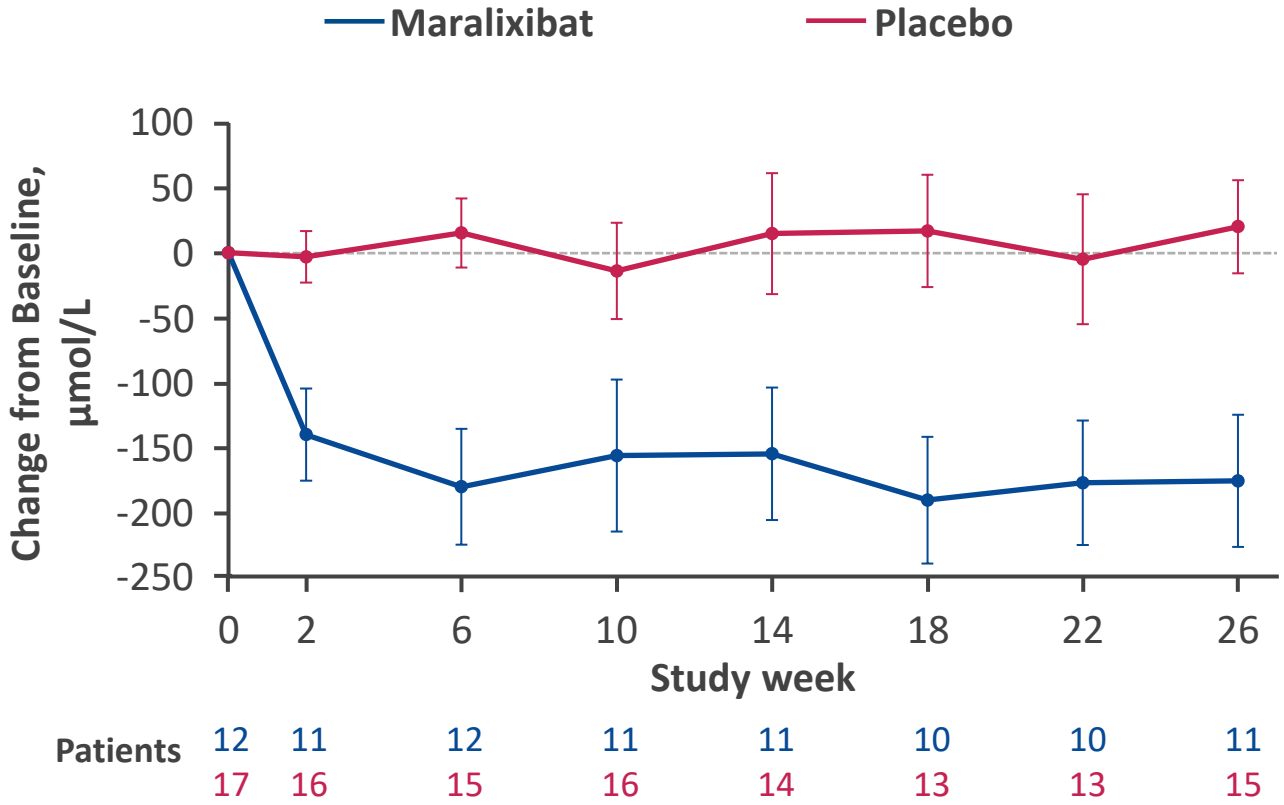
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals) using an MMRM. CI, confidence interval; ItchRO(Obs), Itch-Reported Outcome (Observer); LS, least 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 Acid in BSEP Cohort

sBA MMRM Analysis



Average sBA Over Time



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

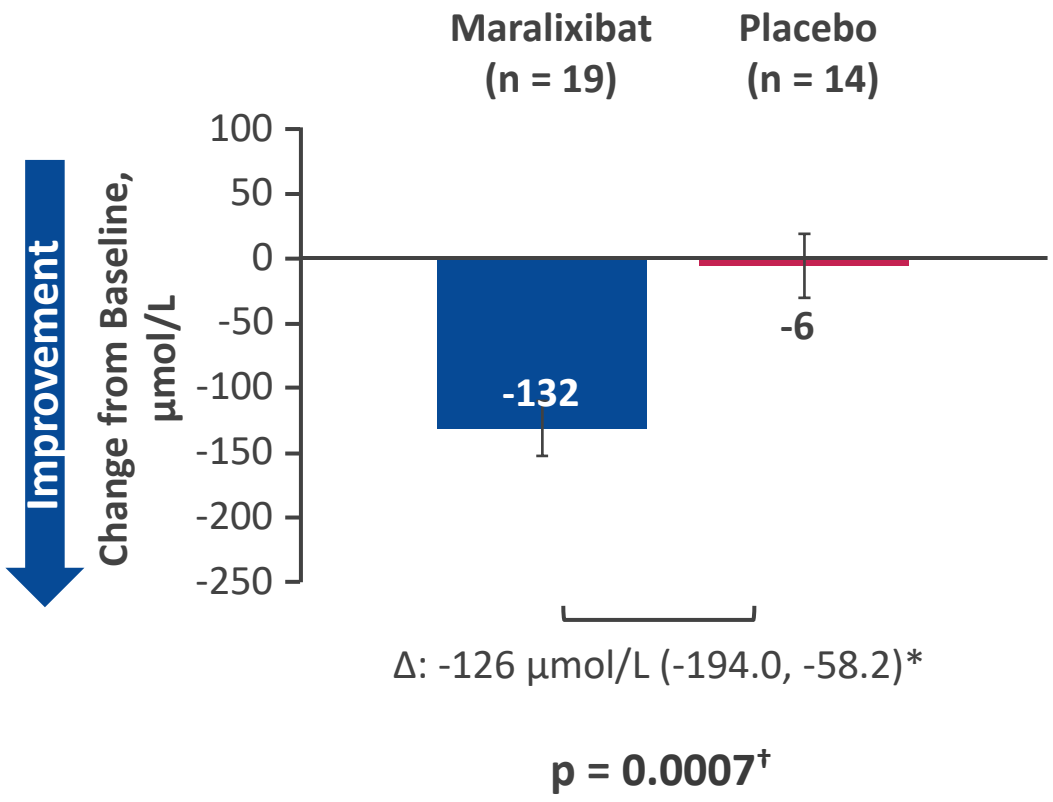
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (Weeks 18, 22 and 26) using an MMRM. Two participants in the maralixibat group did not have baseline sBAs.

CI, confidence interval; BSEP, bile salt export pump; LS, least squares; MMRM, mixed model repeated measures; sBA, serum bile acid.

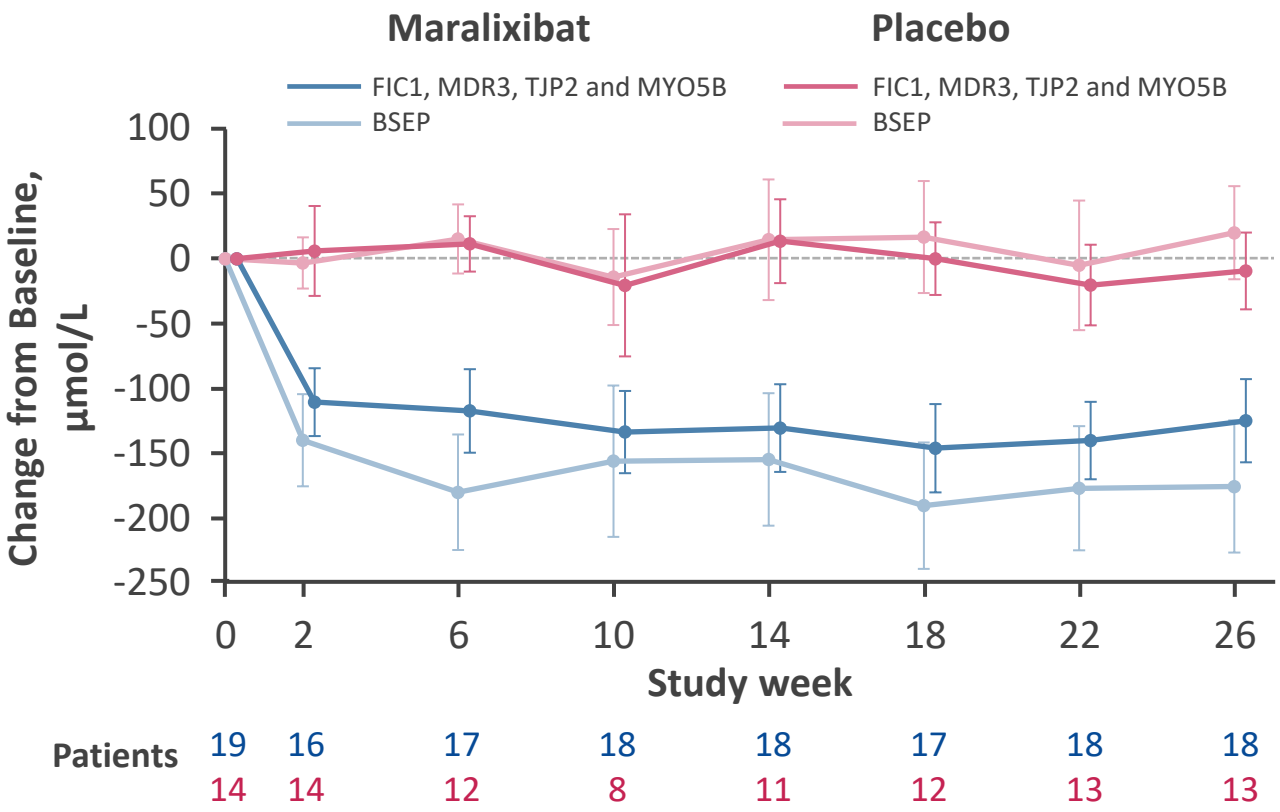
*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean.

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

sBA MMRM Analysis



Average sBA Over Time

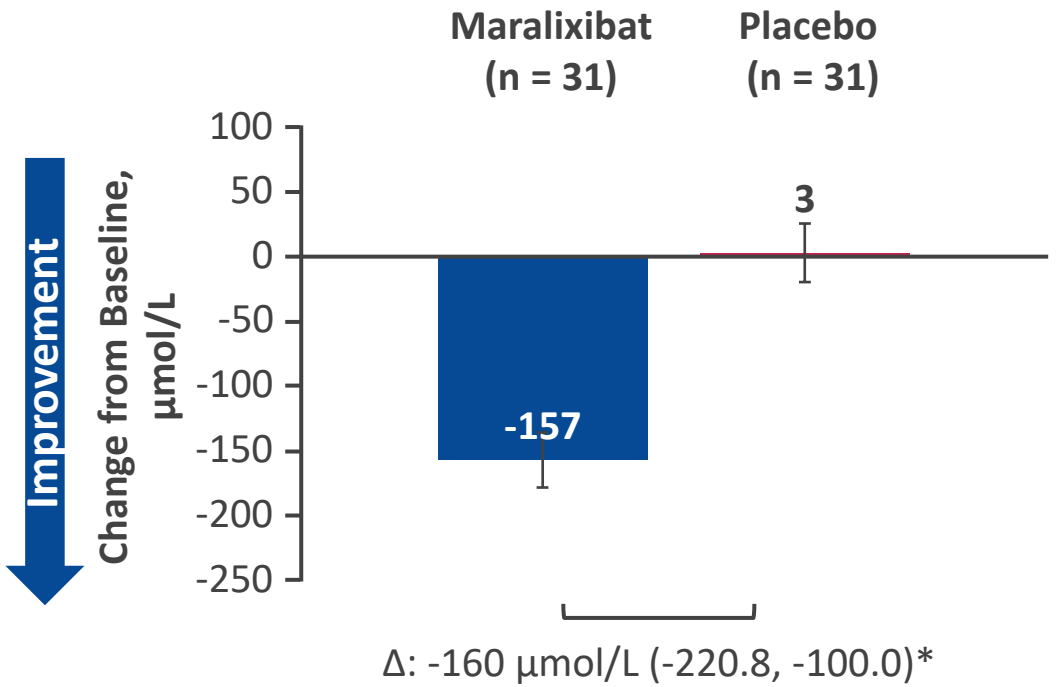


Maralixibat resulted in statistically significant improvements in serum bile acid levels in FIC1, MDR3, TJP2 and MYO5B

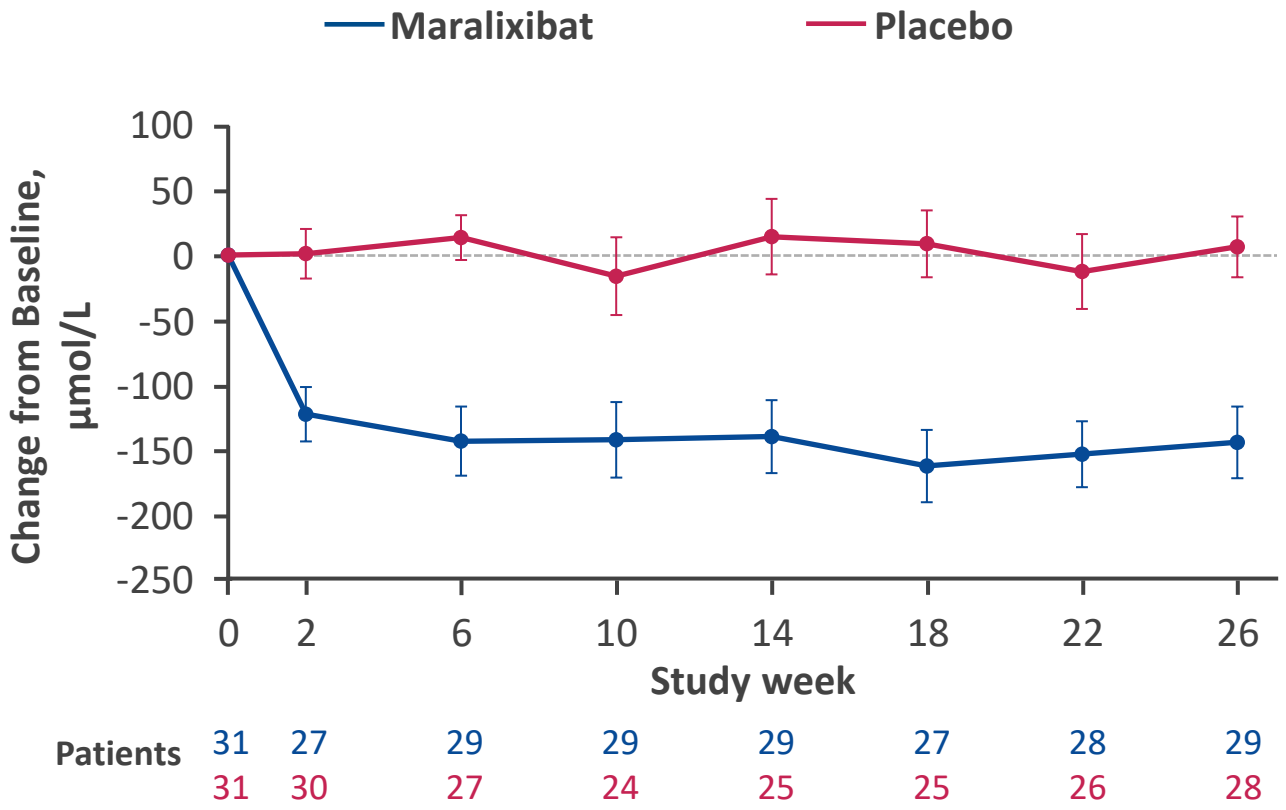
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (Weeks 18, 22 and 26) using an MMRM. CI, confidence interval; FIC1, familial intrahepatic cholestasis-associated protein type 1; LS, least squares; MMRM, mixed model repeated measures; MDR3, multidrug-resistance 3 protein; MYO5B, myosin VB; TJP2, tight junction protein 2; sBA, serum bile acid.
*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

sBA MMRM Analysis



Average sBA Over Time



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

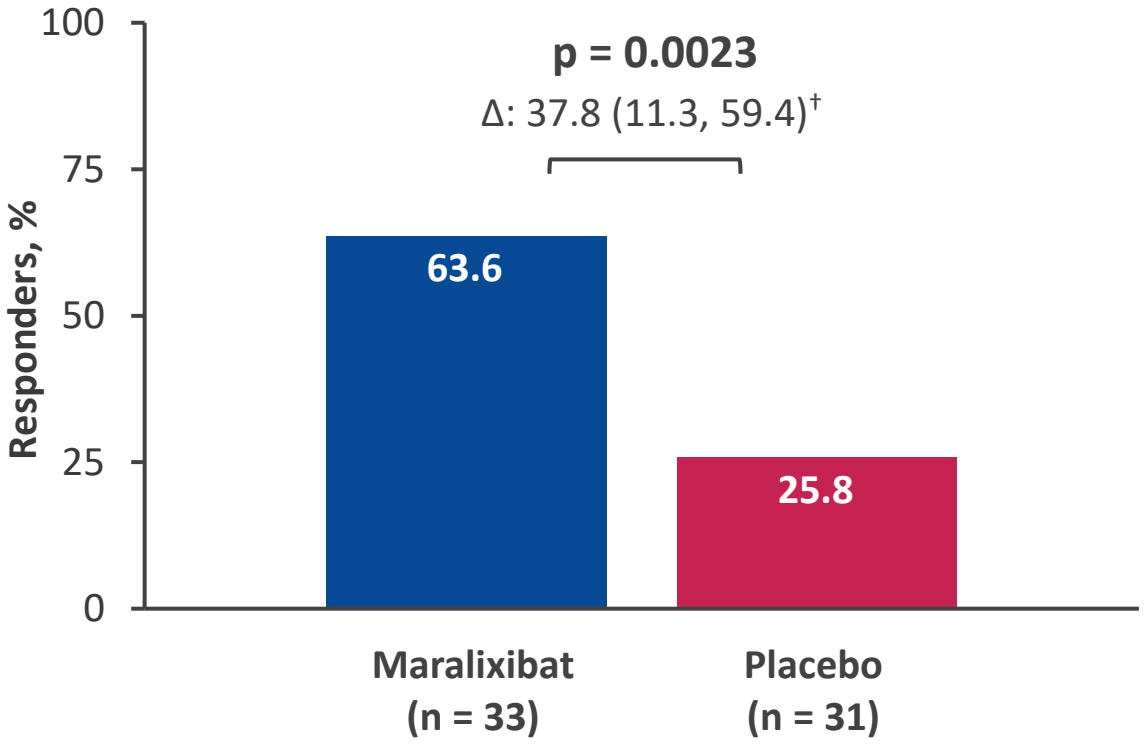
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (Weeks 18, 22 and 26) using an MMRM. Two participants in the maralixibat group did not have baseline sBAs.

CI, confidence interval; LS, least squares; MMRM, mixed model repeated measures; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.

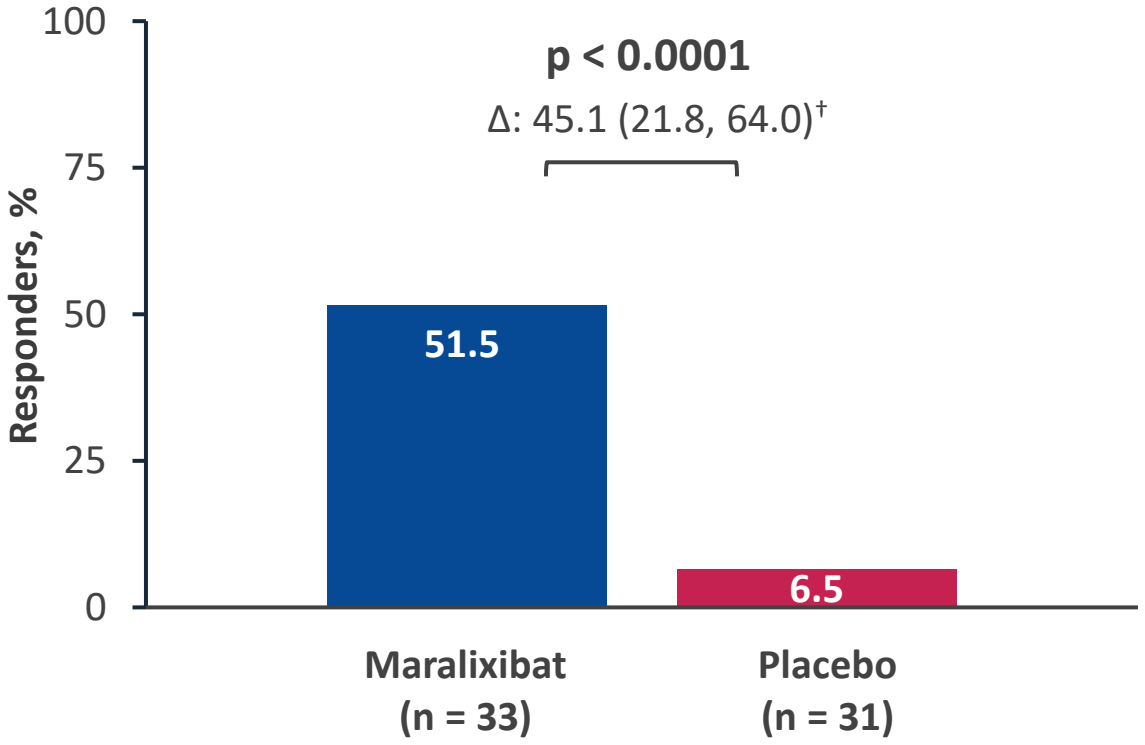
*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean.

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

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



sBA Responders*
≥75% reduction OR serum bile acid <102 µmol/L

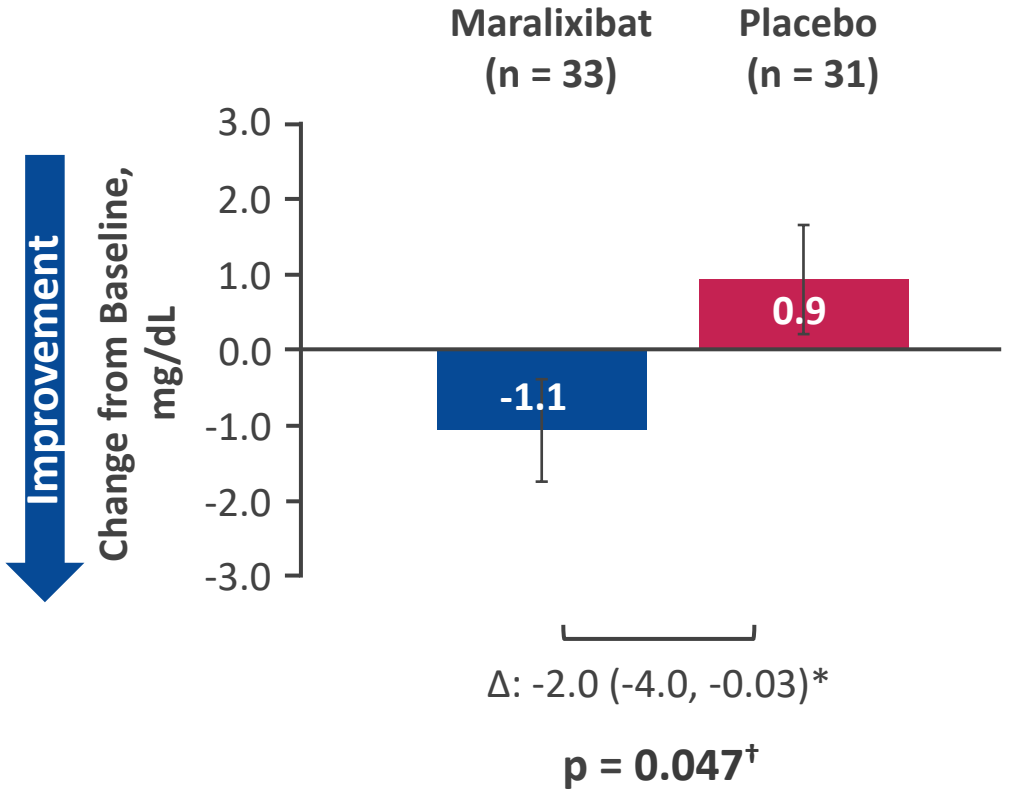


Significantly greater percentage of maralixibat-treated patients met the response thresholds for pruritus and serum bile acid in the All-PFIC cohort

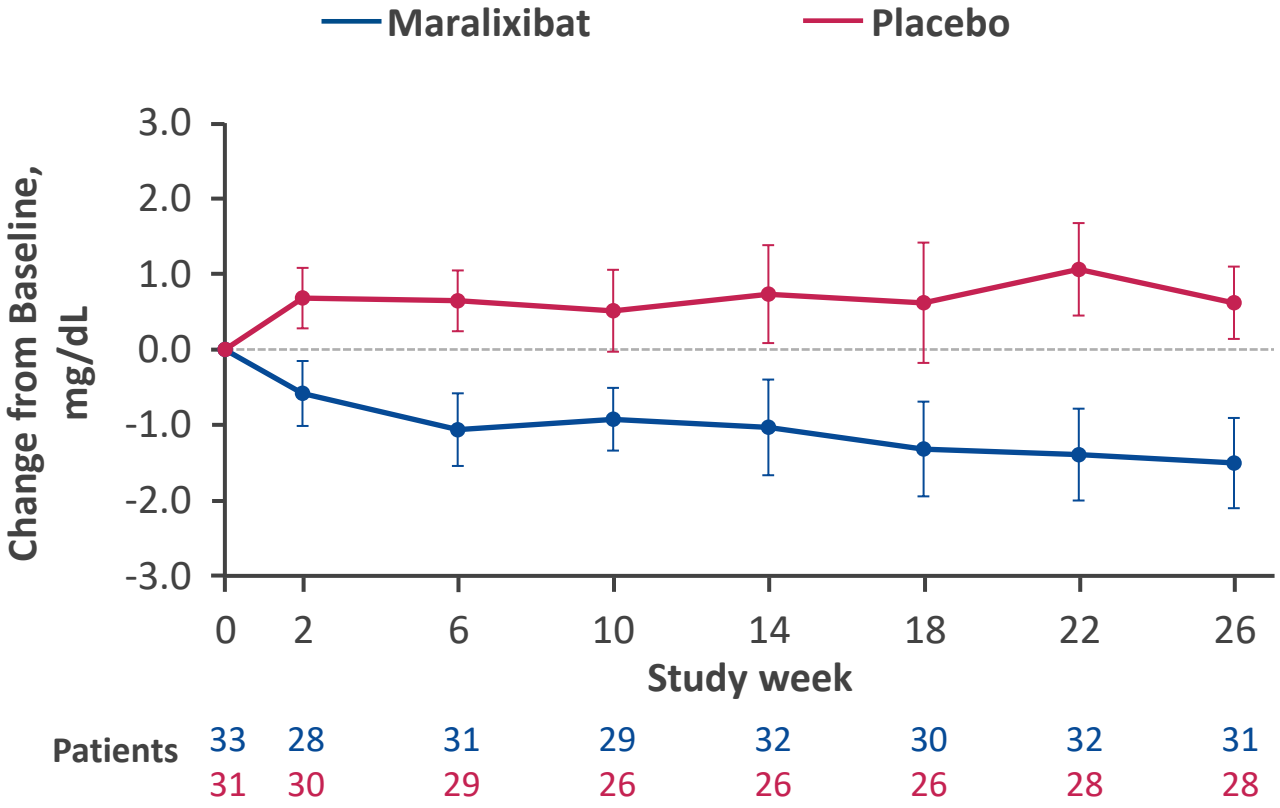
*To determine response: average pruritus severity score from the three 4-week periods (Weeks 15-18, 19-22 and 23-26), and the average sBA value from Weeks 18, 22 and 26 values are used;
†Difference with 95% exact CI. CI, confidence interval; PFIC, progressive familial intrahepatic cholestasis; sBA, serum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

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

Serum Total Bilirubin MMRM Analysis



Average Serum Total Bilirubin Over Time

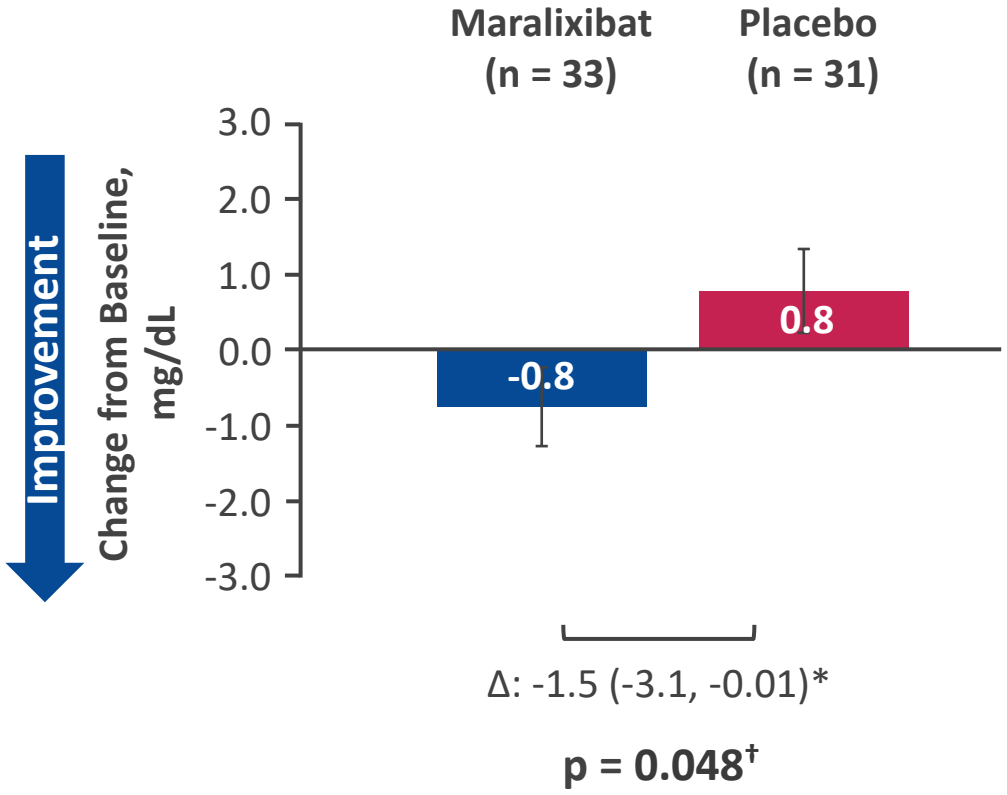


Maralixibat resulted in statistically significant improvements in total bilirubin in the All-PFIC cohort

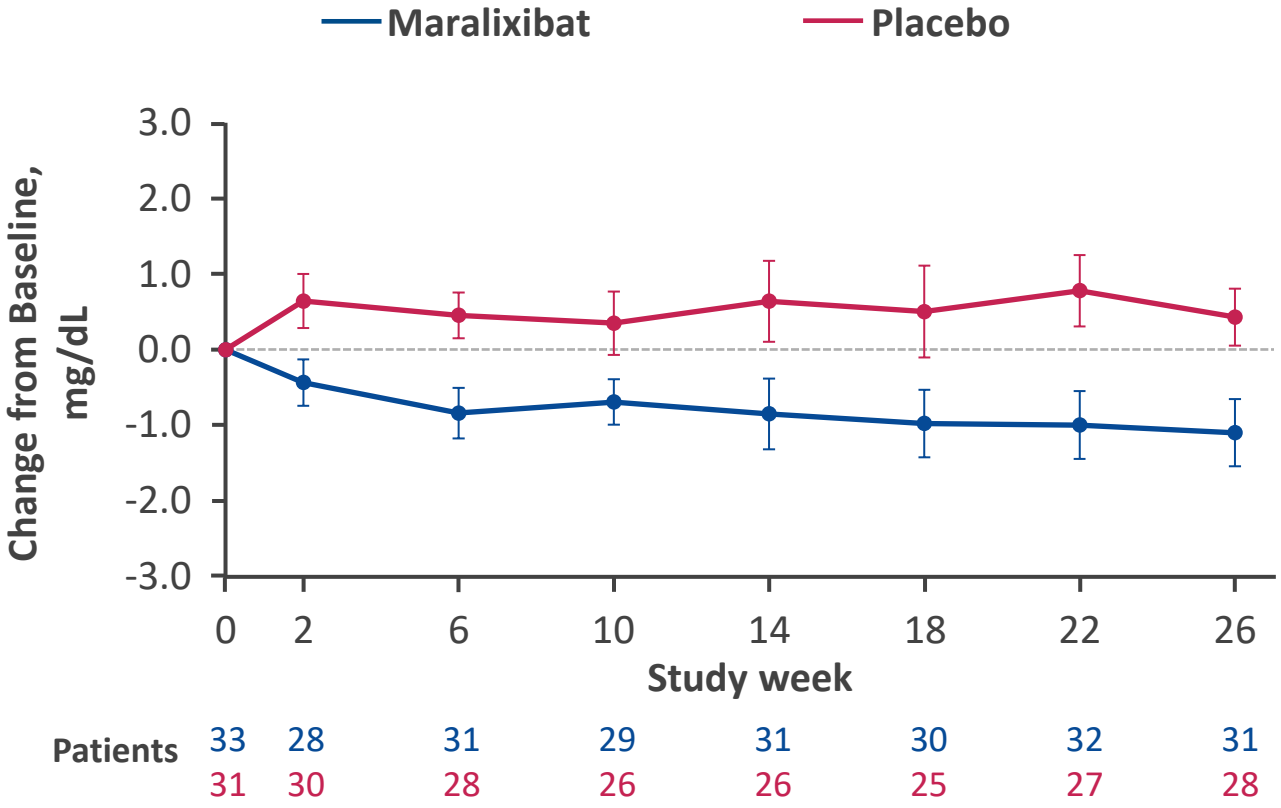
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (Weeks 18, 22 and 26) using an MMRM. CI, confidence interval; LS, least squares; MMRM, mixed model repeated measures; 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



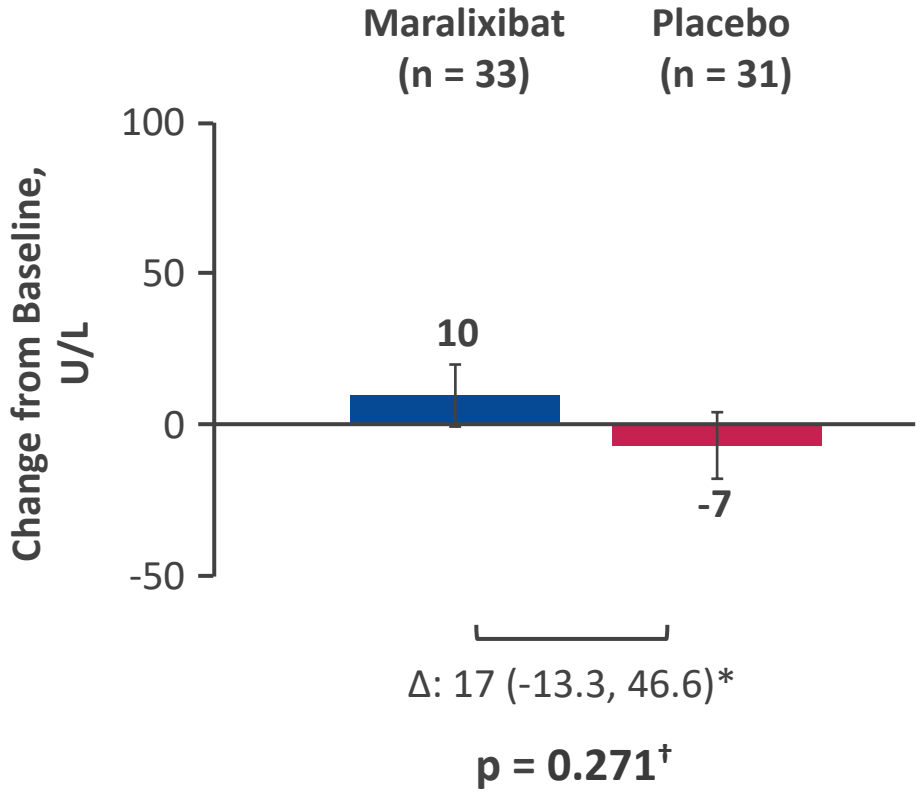
Patients								
	33	28	31	29	31	30	32	31
	31	30	28	26	26	25	27	28

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

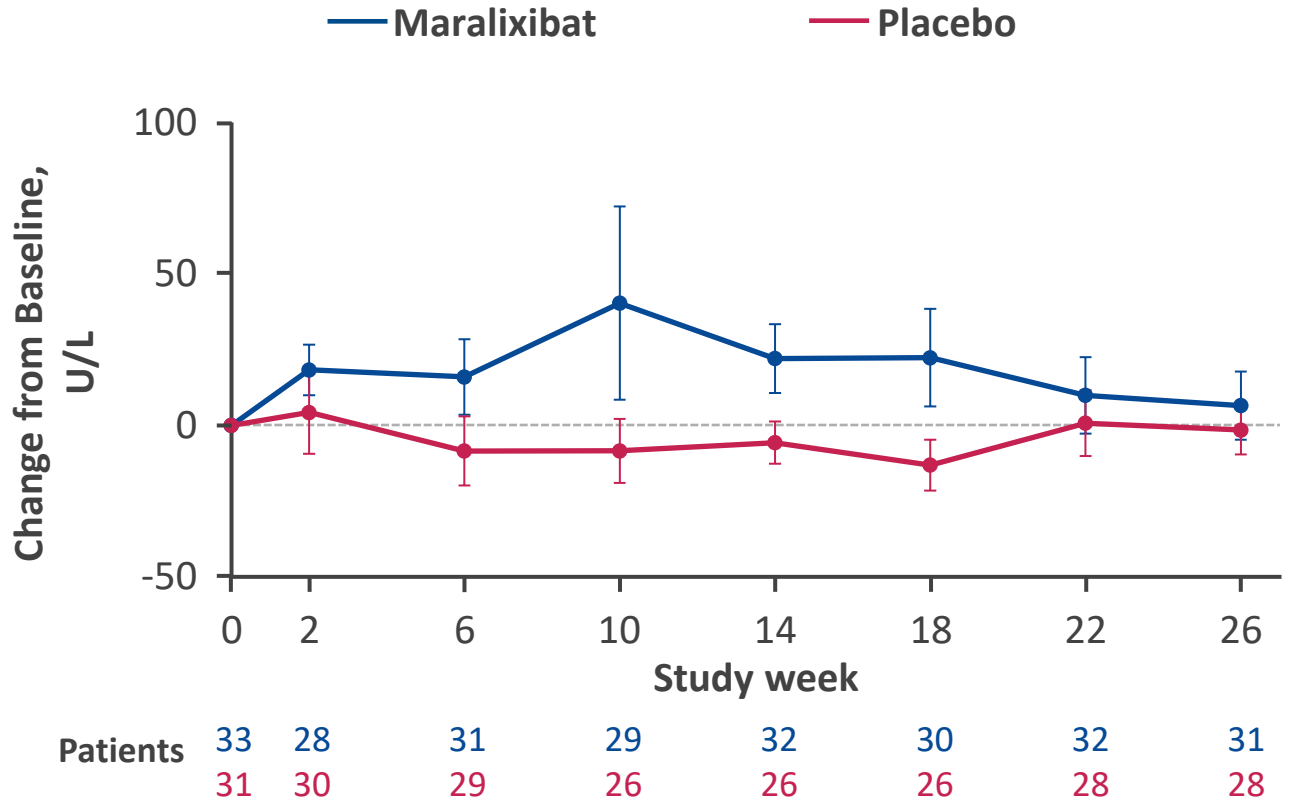
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (Weeks 18, 22 and 26) using an MMRM. CI, confidence interval; LS, least squares; MMRM, mixed model repeated measures; 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

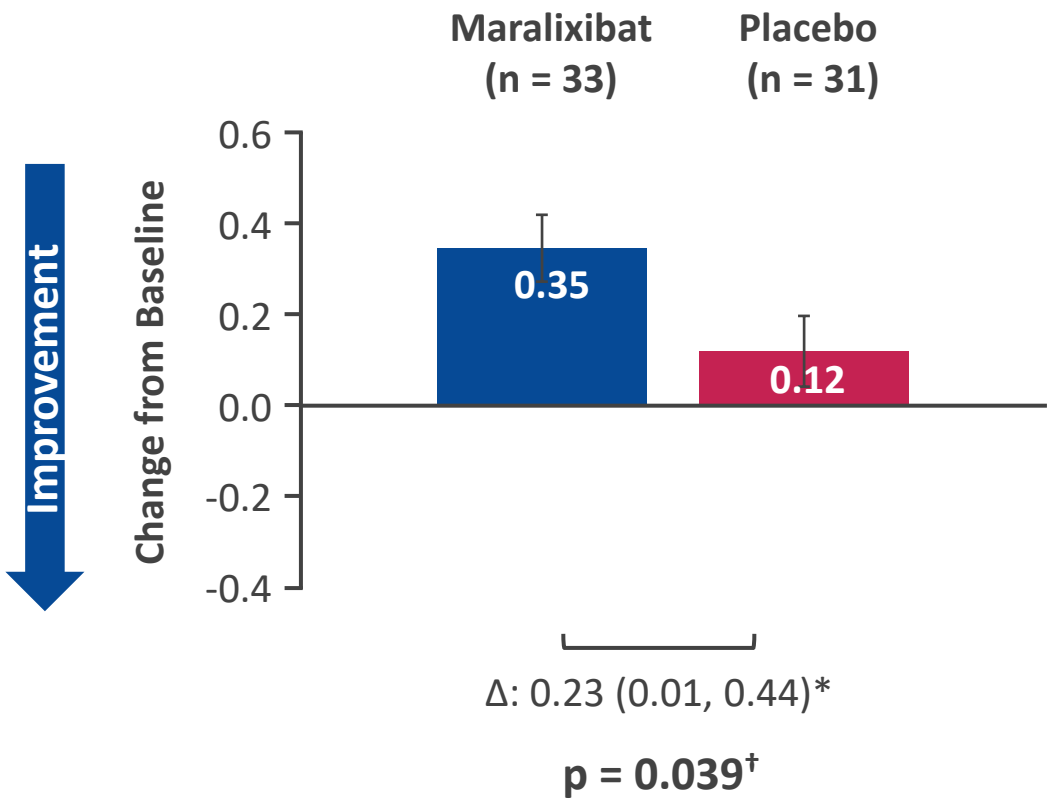


No significant changes in ALT levels were observed following maralixibat treatment in the All-PFIC cohort

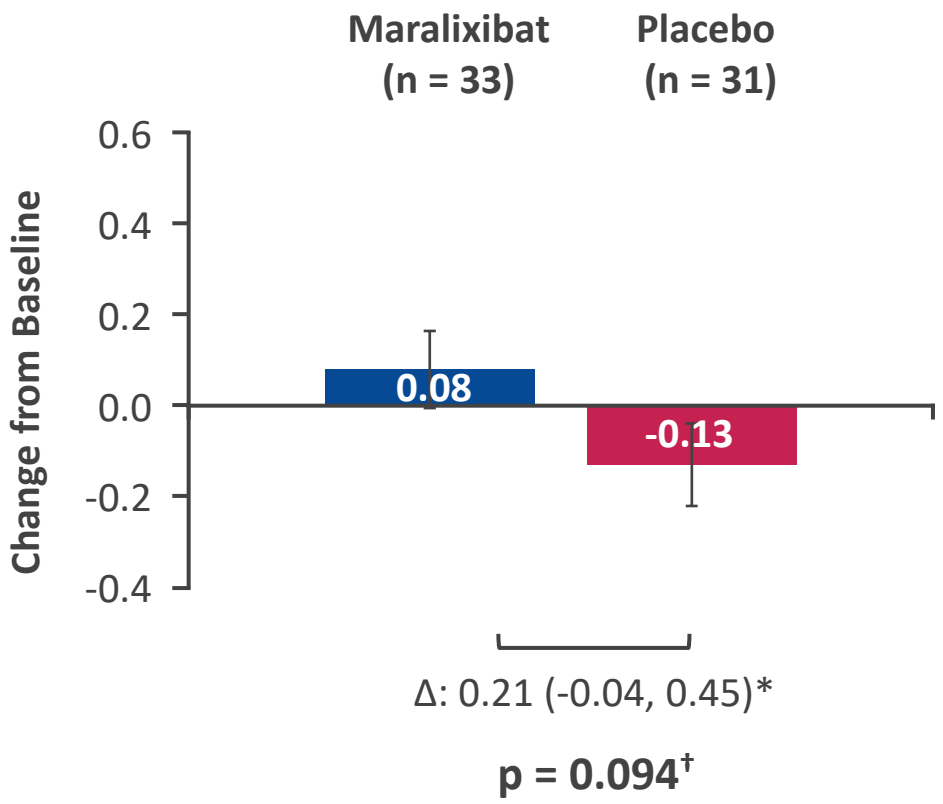
Data are LS mean (for bar plot) and mean (for line plot) with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (Weeks 18, 22 and 26) using an MMRM. ALT, alanine aminotransferase; CI, confidence interval; LS, least squares; 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 an MMRM. CI, confidence interval; 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: diarrhoea, n (%)	27 (57.4)	9 (19.6)

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

TEAE, treatment-emergent adverse event.

Conclusions

- MARCH-PFIC is the largest phase 3 trial conducted in children with PFIC that included PFIC types that had not been previously studied
- Primary and secondary endpoints were met
- Maralixibat demonstrated significant and rapid improvements in pruritus and sBA consistently 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 an sBA 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 acid.

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Author Disclosures

- A Miethke is a consultant and has a sponsored research agreement with Mirum Pharmaceuticals, Inc.
- F Ordóñez 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 Rønn, T Nunes, A Lascau, L Longpre, W Garner and 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 for Mirum Pharmaceuticals, Inc.
- N Ovchinsky is a consultant for Albireo and received research support to her institution from Mirum Pharmaceuticals, Inc., Albireo and Travere
- 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 have nothing to disclose

Back-up

MARCH-PFIC: Patient Disposition

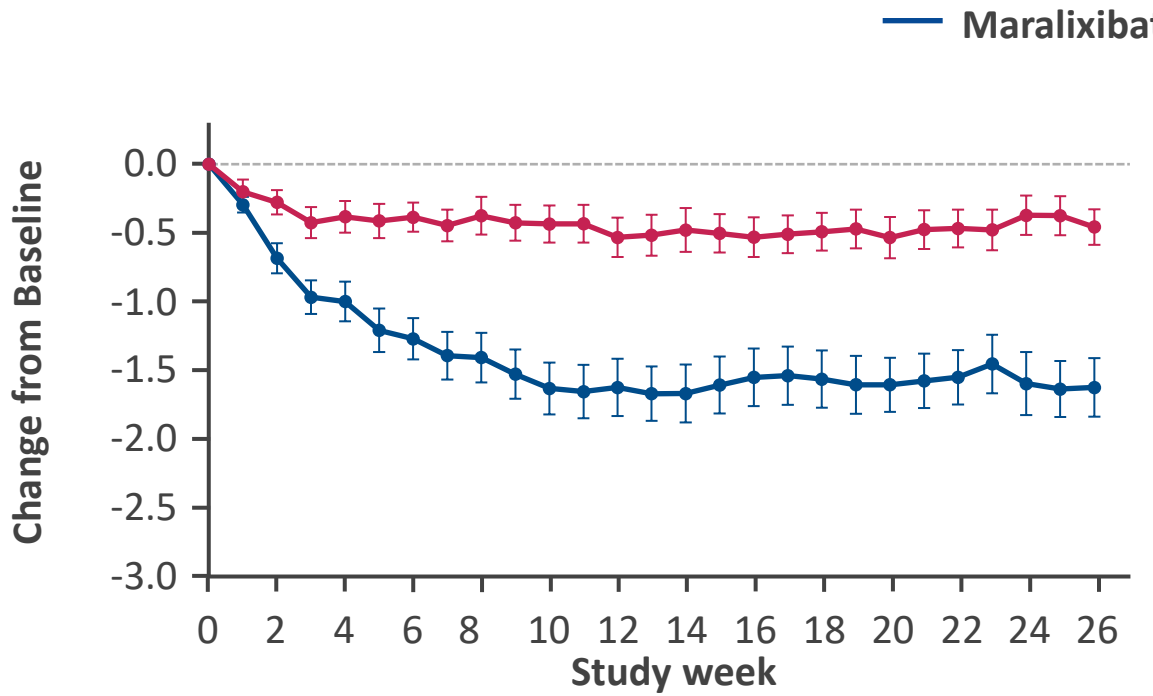
Status or Category	BSEP Deficiency		All-PFIC		Full-Study	
	Maralixibat (n = 14)	Placebo (n = 17)	Maralixibat (n = 33)	Placebo (n = 31)	Maralixibat (n = 47)	Placebo (n = 46)
Screened for eligibility, n					125	
Screen failure, n					32	
Randomised, n	14	17	33	31	47	46
Safety population, n	14	17	33	31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

The majority of randomised patients completed study treatment

BSEP, bile salt export pump; PFIC, progressive familial intrahepatic cholestasis.

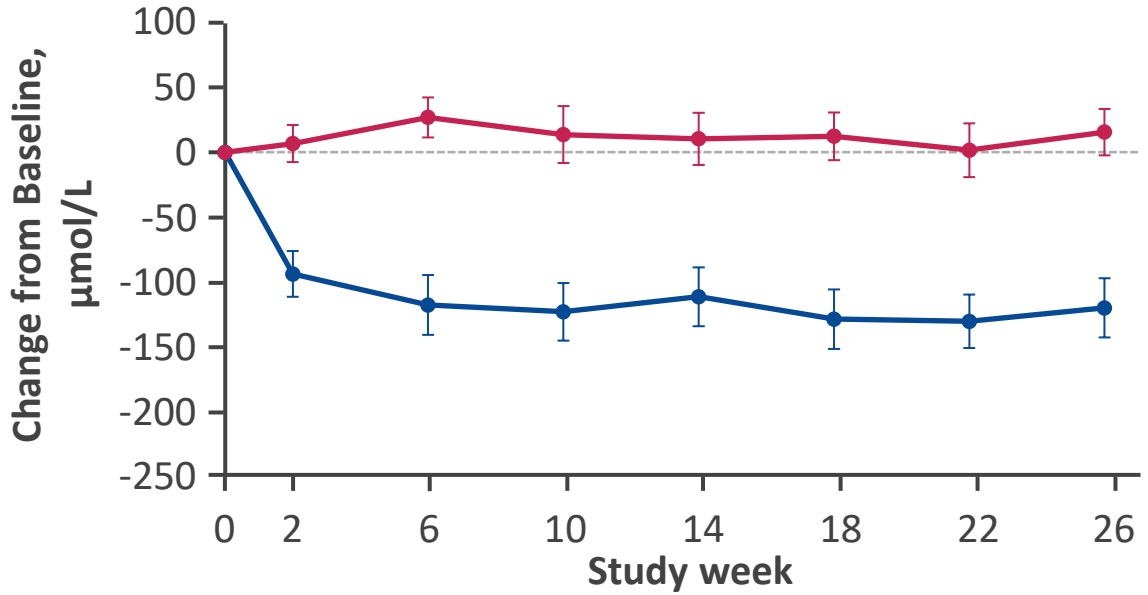
Change in Weekly ItchRO(Obs) Score and Serum Bile Acid in Full-Study Cohort (N = 93)

Average Pruritus Score (ItchRO[Obs]) Over Time



Patients														
Maralixibat	47	47	45	45	46	43	44	44	45	45	45	45	42	44
Placebo	46	46	46	45	44	44	44	42	42	42	42	41	40	41

Average sBA Over Time



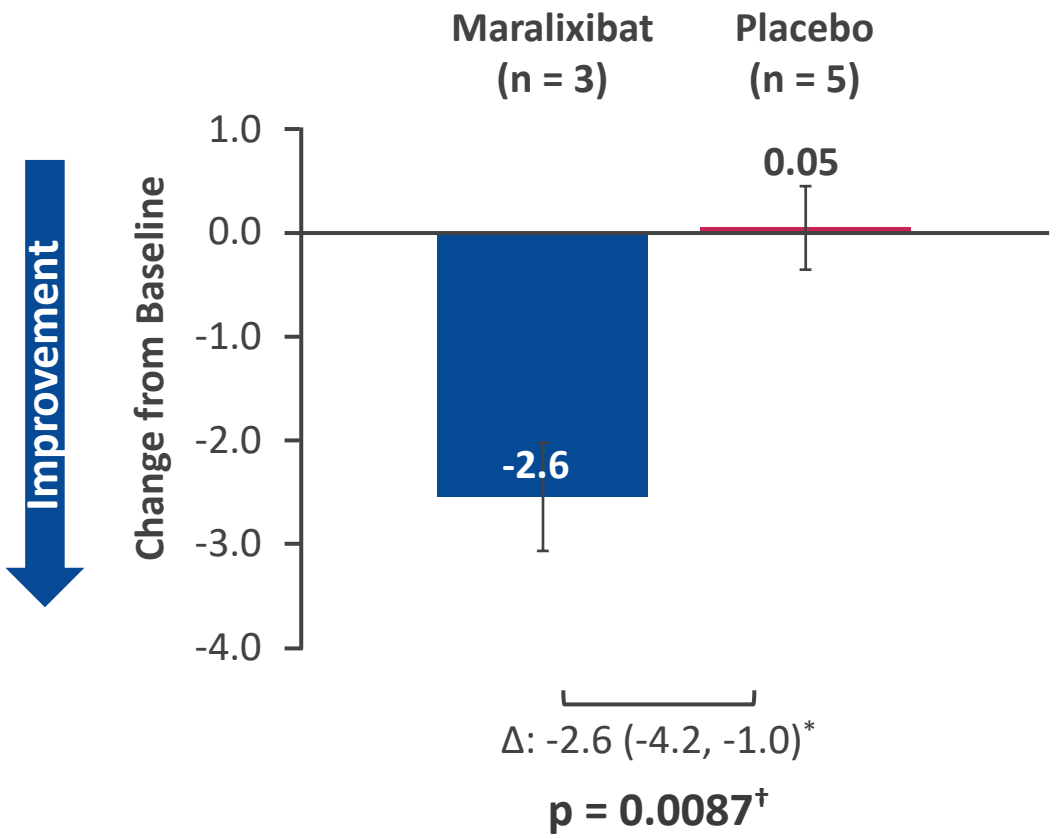
Maralixibat	45	39	37	41	41	38	39	40
Placebo	46	43	40	36	38	36	38	41

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

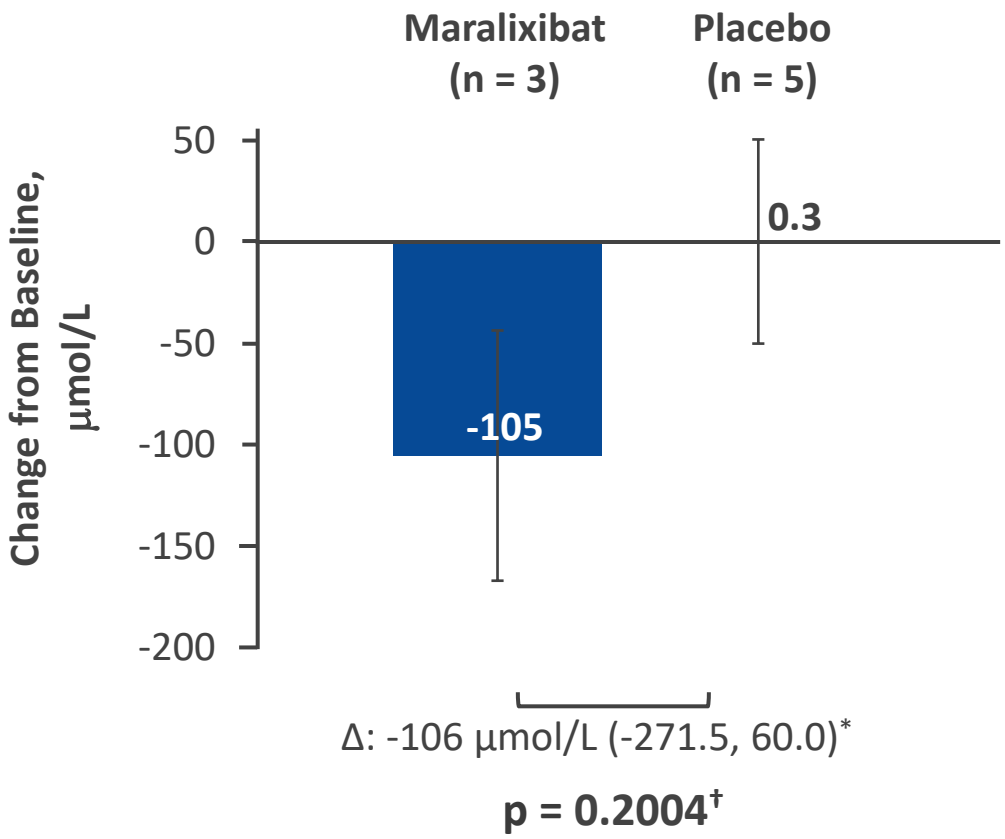
Data are means with standard error bars. Two participants in the maralixibat group did not have Baseline sBAs.
ItchRO(Obs), Itch-Reported Outcome (Observer); sBA, serum bile acid.

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

Pruritus Score (ItchRO[Obs]) MMRM Analysis



sBA MMRM Analysis

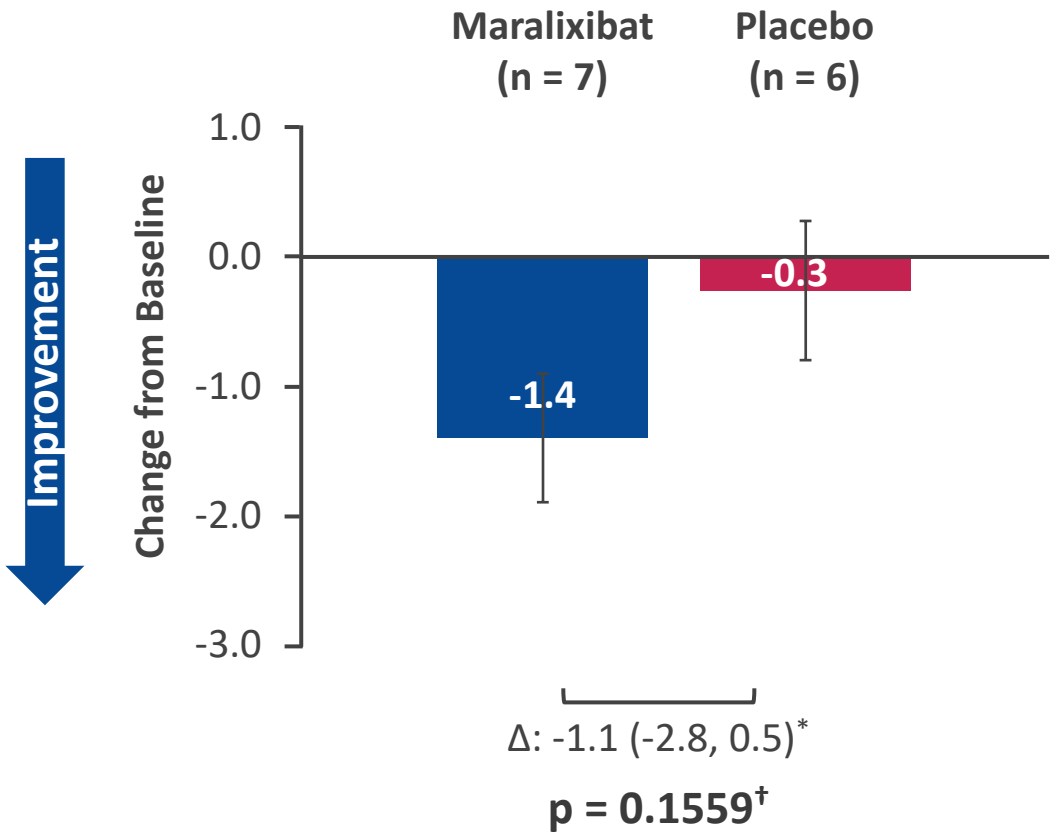


In patients with no-variant-found, maralixibat demonstrated improvements in pruritus and serum bile acid

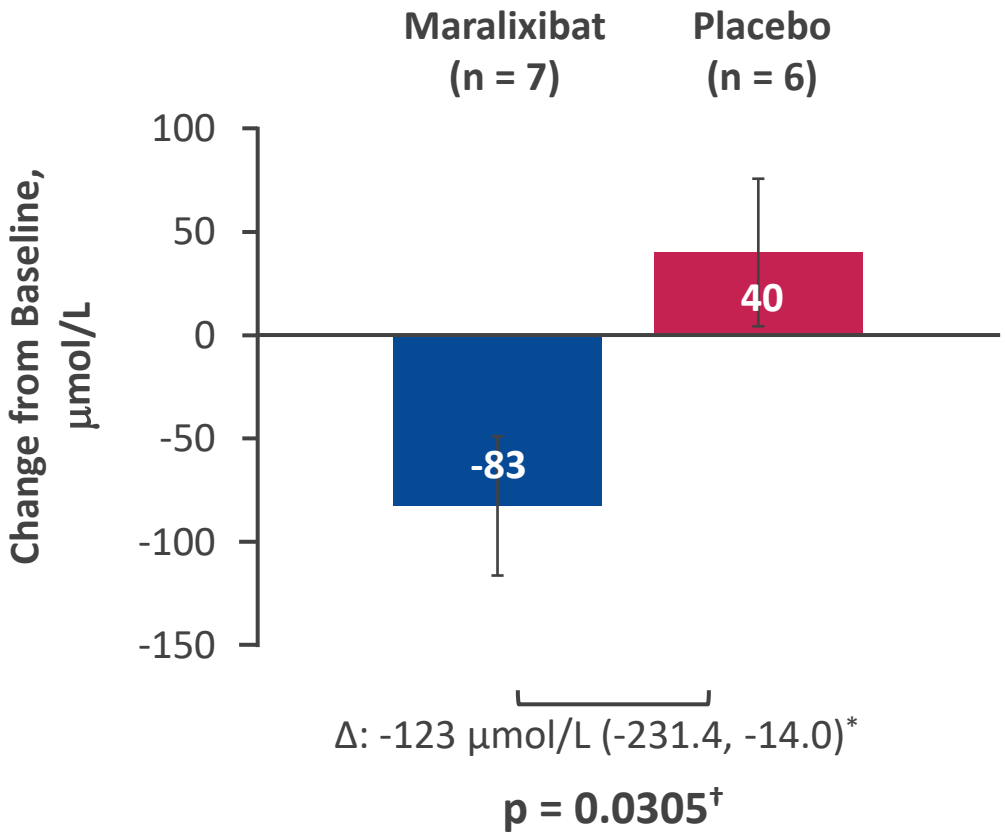
Data are LS mean with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals for ItchRO(Obs), Weeks 18, 22 and 26 for sBA) using a repeated measures mixed effect model. CI, confidence interval; ItchRO(Obs), Itch-Reported Outcome (Observer); LS, least squares; MMRM, mixed model repeated measures; sBA, serum bile acid.
*LS mean delta with 95% CI. †Maralixibat LS mean = placebo LS mean

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

Pruritus Score (ItchRO[Obs]) MMRM Analysis



sBA MMRM Analysis

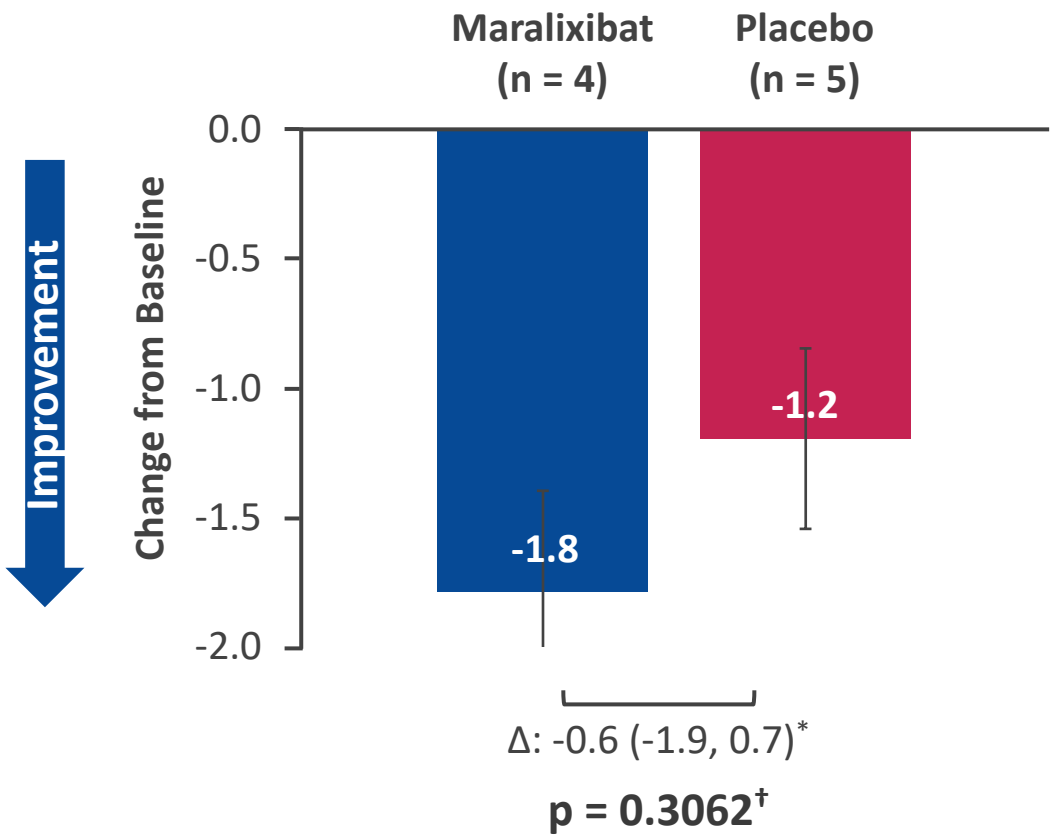


Data are LS mean with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last 3 time periods (4-week intervals for ItchRO(Obs), Weeks 18, 22 and 26 for sBA) using a repeated measures mixed effect model. CI, confidence interval; FIC1, familial intrahepatic cholestasis-associated protein type 1; ItchRO(Obs), Itch-Reported Outcome (Observer); LS, least squares; MMRM, mixed model repeated measures; sBA, serum bile acid.

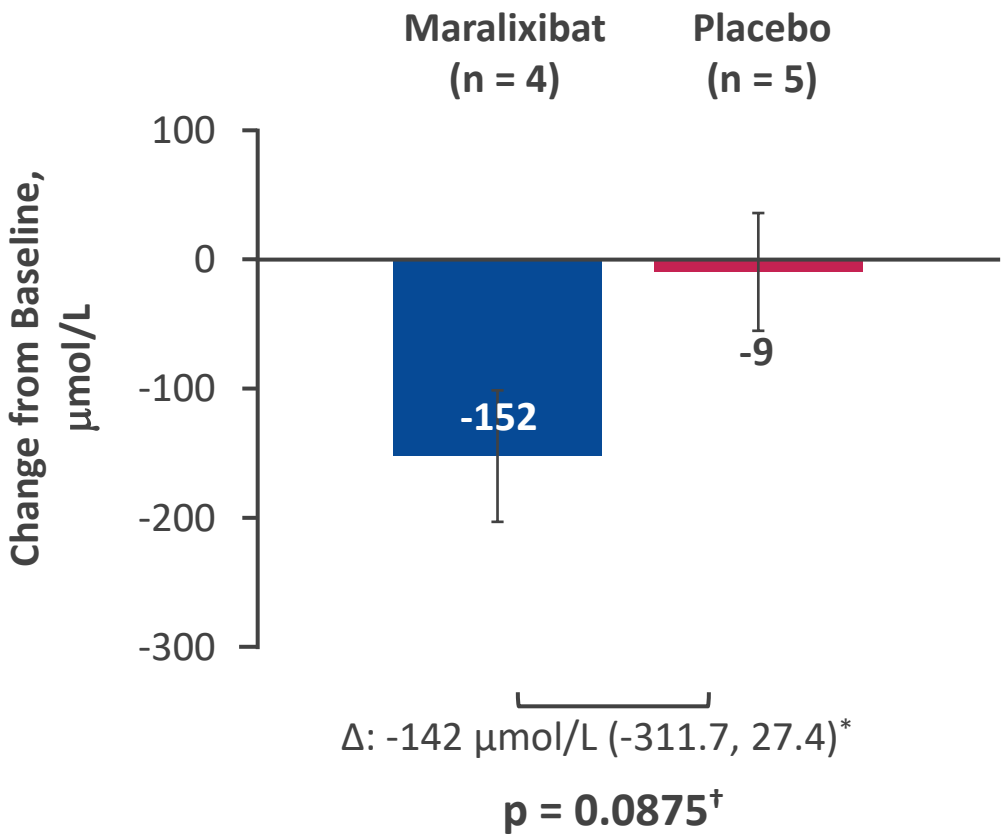
*LS mean delta with 95% CI. †Maralixibat LS mean = placebo LS mean.

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

Pruritus Score (ItchRO[Obs]) MMRM Analysis



sBA 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(Obs), Weeks 18, 22 and 26 for sBA) using a repeated measures mixed effect model. CI, confidence interval; ItchRO(Obs), Itch-Reported Outcome (Observer); LS, least squares; MDR3, multidrug-resistance 3 protein; MMRM, mixed model repeated measures; sBA, serum bile acid.

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