Maralixibat Leads to Significant Reductions in Bilirubin for Patients With Progressive Familial Intrahepatic Cholestasis: Data From MARCH-PFIC

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Progressive Familial Intrahepatic Cholestasis (PFIC)

- Genetic disorders resulting in disrupted bile composition and chronic cholestasis[1]
- PFIC causes debilitating pruritus, impaired growth, reduced quality of life and progressive liver disease, with most patients 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)
- Evidence suggests that elevated serum bilirubin levels may indicate poorer outcomes in patients with PFIC[6]
- MARCH-PFIC (MARCH), a clinical trial of maralixibat, achieved its primary and key secondary endpoints of pruritus and serum bile acid (sBA) improvement in patients treated with maralixibat compared with patients treated with placebo[7]

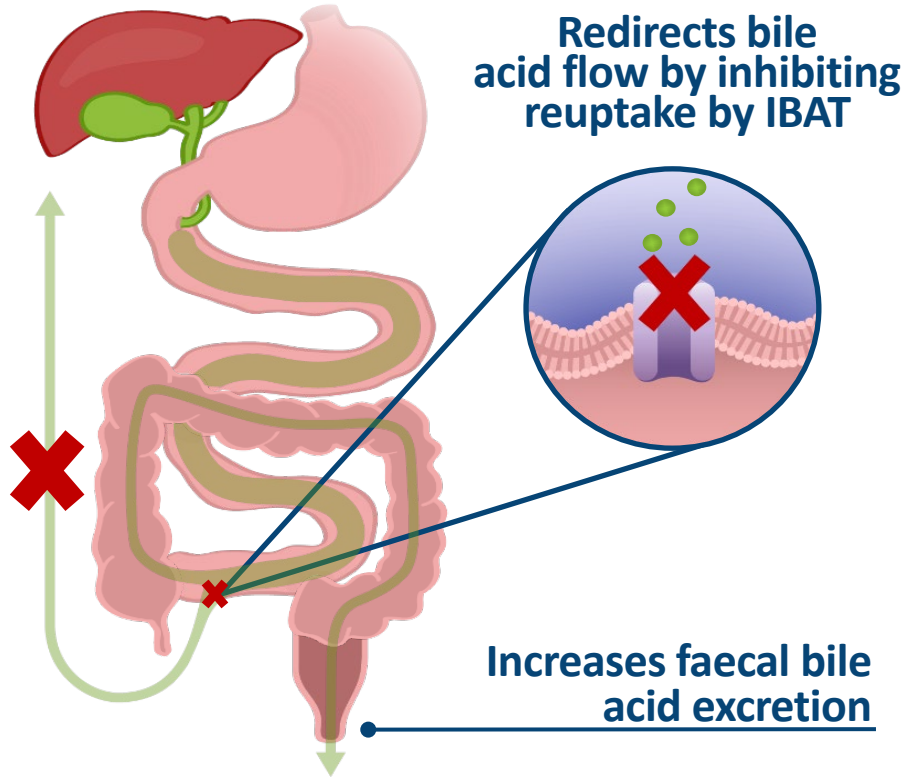
1. Jacquemin E, et al. *Clin Res Hepatol Gastroenterol*. 2012;36:S26-S35. 2. van Wessel D, et al. *J Hepatol*. 2020;73:84-93. 3. Kamath BM, et al. *Liver Int*. 2020;40:1812-1822.
4. Kamath BM, et al. *Patient*. 2018;11:69-82. 5. Loomes MK, et al. *Hepatol Commun*. 2022;6:2379-2390. 6. Kamath B, et al. *J Pediatr.* 2015;167:390-396. 7. ClinicalTrials.gov ID: NCT03905330. Accessed online at: https://www.clinicaltrials.gov/ct2/show/NCT03905330 on May 11, 2023.

Aim

To further characterise the impact of maralixibat on bilirubin in patients with PFIC as part of the MARCH trial

PFIC, progressive familial intrahepatic cholestasis.

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.

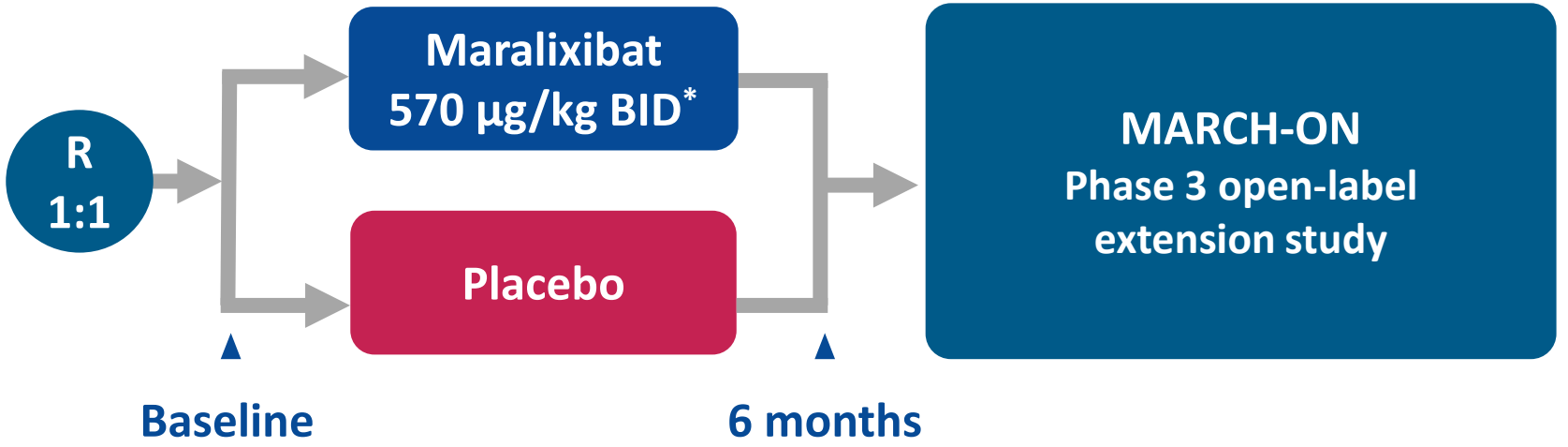
1. Thompson R, et al. Presented at EASL 2020. 2. Loomes MK, et al. *Hepatol Commun*. 2022;6:2379-2390. 3. Gonzales E, et al. *Lancet*. 2021;398:1581-1592.
4. LIVMARLI® (maralixibat) [prescribing information]. Foster City, CA; Mirum Pharmaceuticals, Inc. Mar 2023.
5. LIVMARLI® (maralixibat) [summary of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

MARCH: Phase 3 Study Design

MARCH STUDY

Key Entry Criteria

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



*Maralixibat 570 µg/kg is equivalent to 600 µg/kg maralixibat chloride.
BID, twice daily; 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: 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); total 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 patient 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, nontruncated; t, truncated; TJP2, tight junction protein 2.

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MARCH: 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 cohort):

- 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) approach 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 per 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.
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MARCH: Key Demographics and Baseline Characteristics

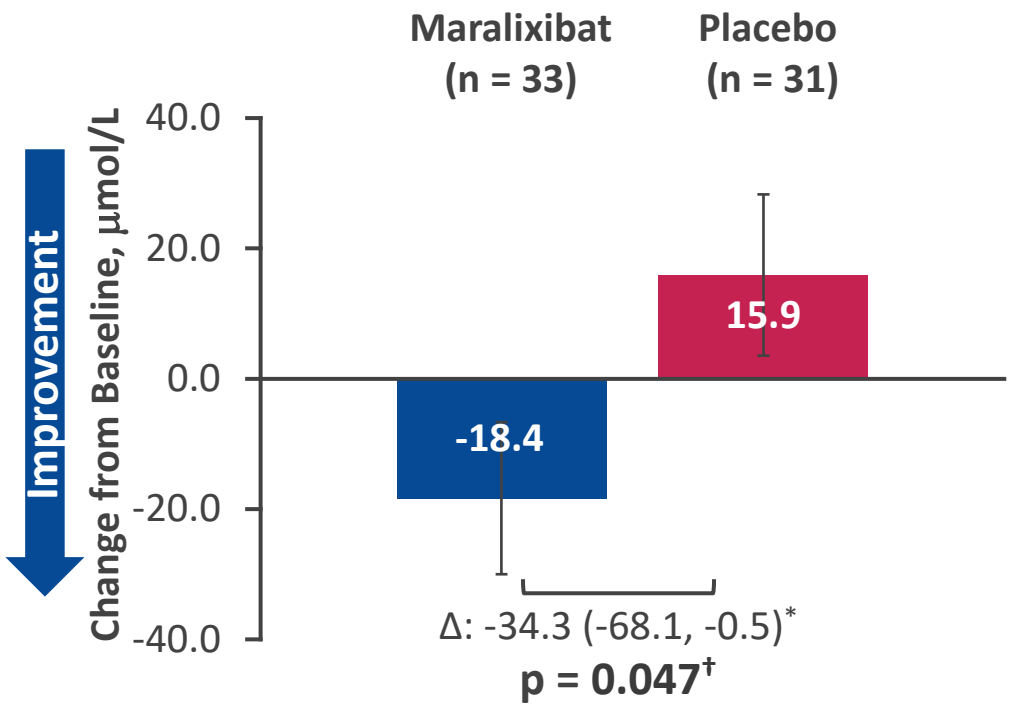
Variable	Maralixibat (n = 33)	Placebo (n = 31)
Age, years	4.9	4.4
Male, %	52	42
Pruritus, ItchRO(Obs)	2.85	2.73
Total sBA, µmol/L	254	272
UDCA usage, %	82	97
Rifampicin usage, %	55	48
Alanine aminotransferase, U/L	88	127
Total bilirubin, µmol/L	70	69
Direct bilirubin, µmol/L	51	50
Height Z-score	-2.08	-2.06
Weight Z-score	-1.75	-1.28

Baseline characteristics and demographics were balanced between groups

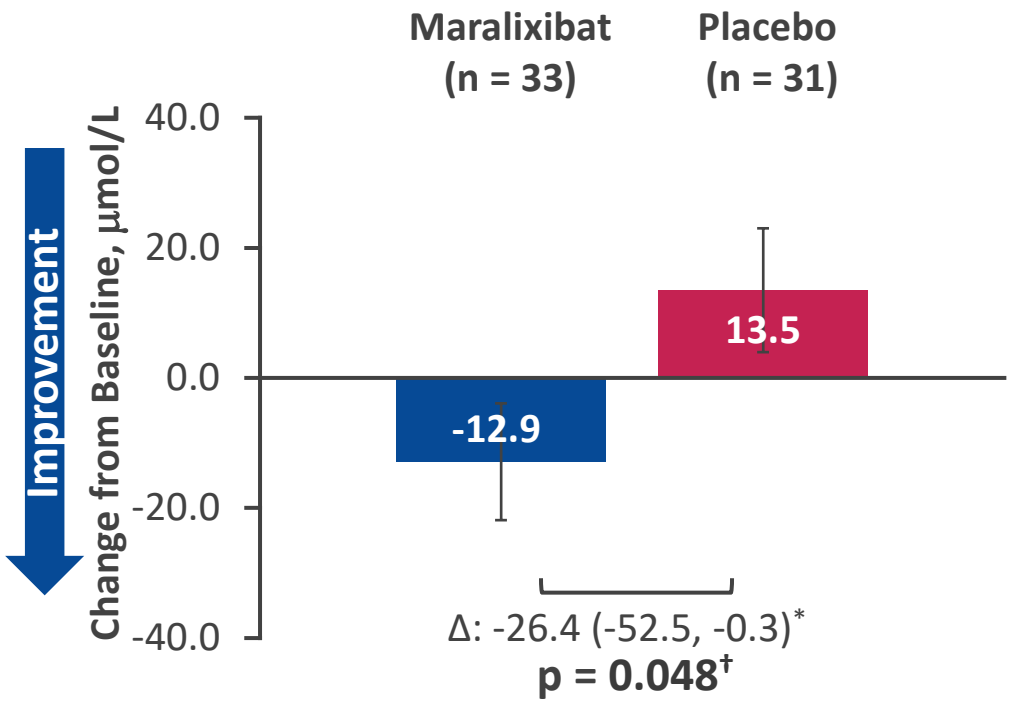
Note: All data are mean unless otherwise indicated. Percentages are 100 x n/N.
ItchRO(Obs), Itch-Reported Outcome (Observer); PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid; UDCA, ursodeoxycholic acid.

MARCH: Change From Baseline in Total and Direct Bilirubin

Serum Total Bilirubin MMRM Analysis



Serum Direct Bilirubin MMRM Analysis

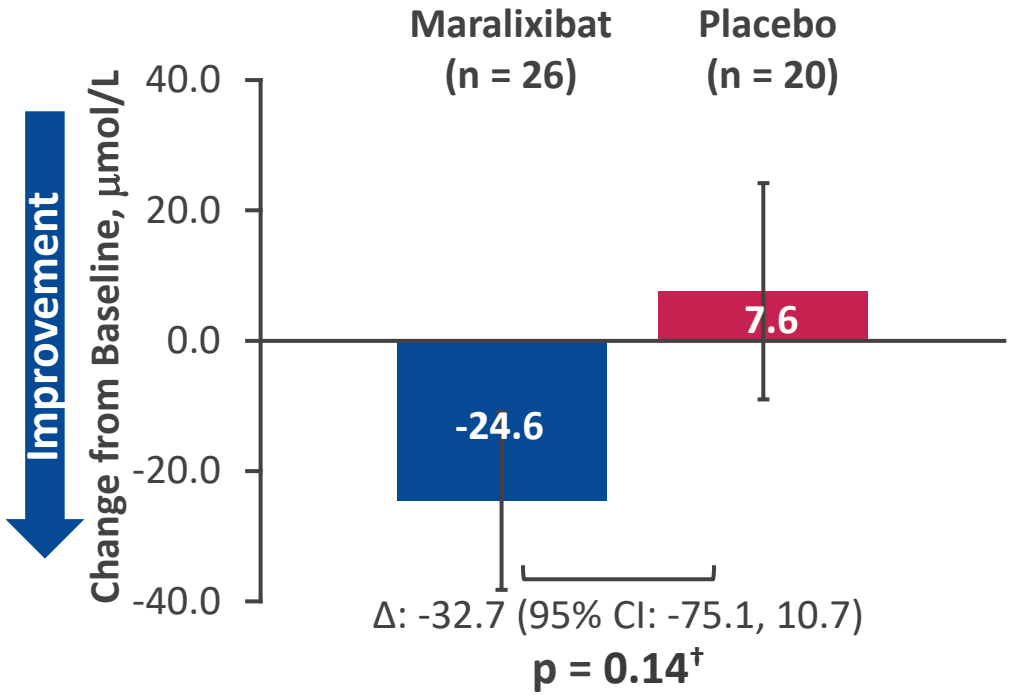


Maralixibat resulted in statistically significant improvements in total and direct bilirubin in the All-PFIC cohort

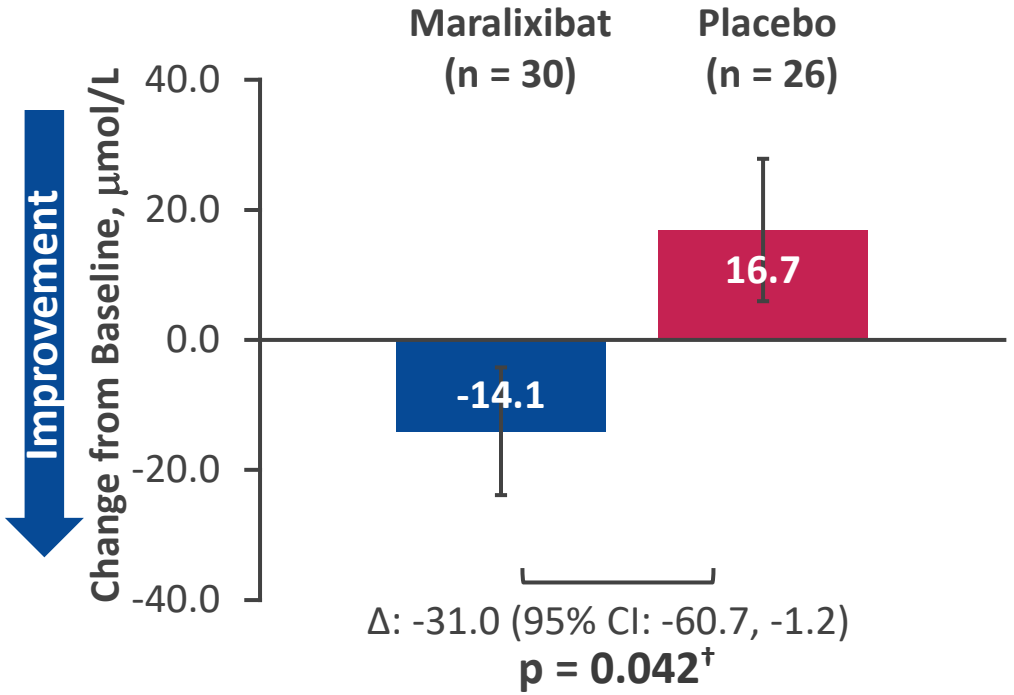
Data are LS mean with standard error bars. Effect size compared the difference between maralixibat and placebo, averaged over the last three time periods (Weeks 18, 22 and 26) using an MMRM approach.
*LS mean delta with 95% CI; †Maralixibat LS mean = placebo LS mean.
CI, confidence interval; LS, least squares; MMRM, mixed model repeated measures.

MARCH: Change From Baseline in Patients With Abnormal Total and Direct Bilirubin at Baseline

Abnormal Total Bilirubin at Baseline*
Abnormal is > 20.5 µmol/L



Abnormal Direct Bilirubin at Baseline*
Abnormal is > 5.1 µmol/L

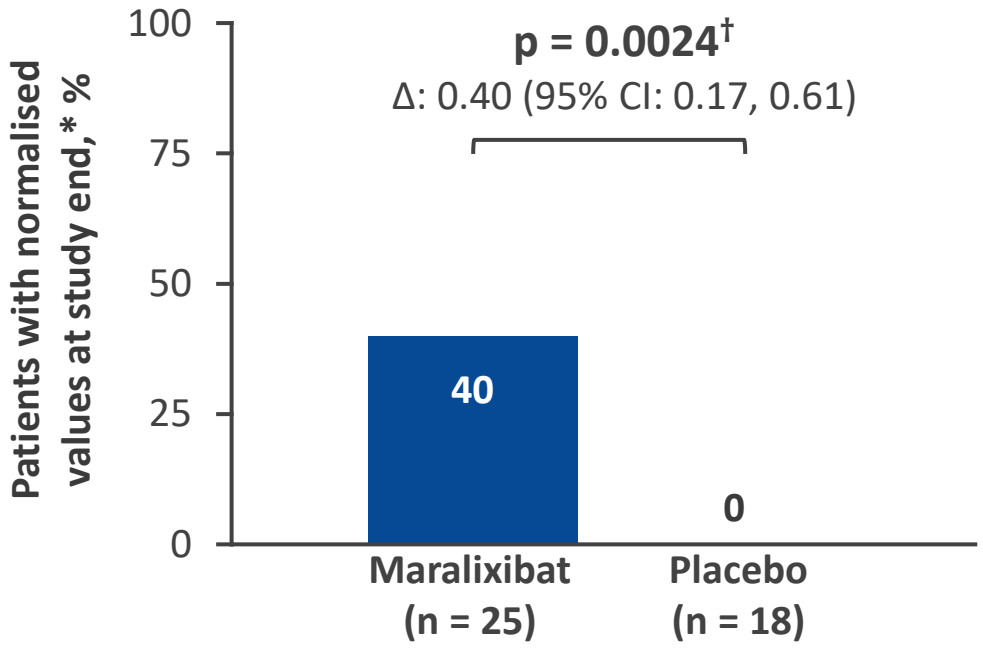


Maralixibat treatment resulted in improvements in bilirubin in patients who had abnormal bilirubin at Baseline

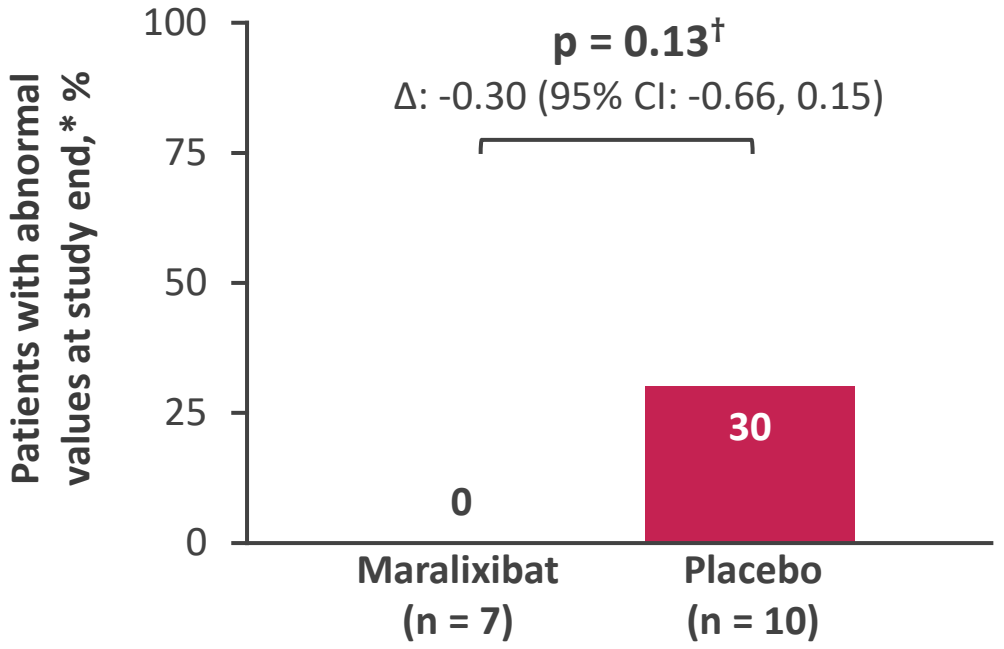
*Estimated change from an MMRM; numbers correspond to the average of Weeks 18-26 (18, 22 and 26); †Maralixibat LS mean = placebo LS mean.
CI, confidence interval; LS, least squares; MMRM, mixed model repeated measures.

MARCH: Total Bilirubin Normalisation

Improvement in Total Bilirubin Among Individuals With Abnormal Levels at Baseline
Abnormal is > 20.5 µmol/L



Worsening in Total Bilirubin Among Individuals With Normal Levels at Baseline
Normal is ≤ 20.5 µmol/L

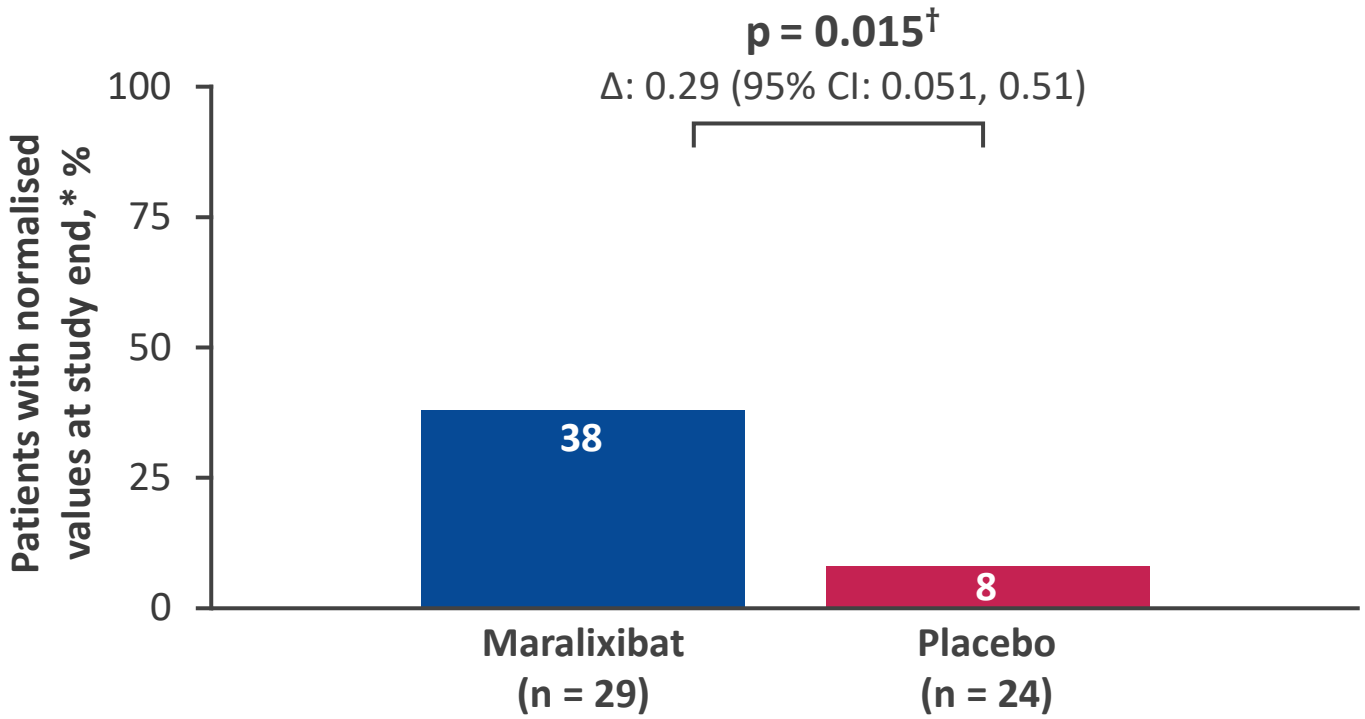


Significant percentage of patients experienced total bilirubin normalisation after maralixibat treatment, and no patients in the maralixibat group experienced a change from normal to abnormal values

*The average of Weeks 18, 22 and 26; †Barnard's exact test.
CI, confidence interval.

MARCH: Direct Bilirubin Normalisation

Improvement in Direct Bilirubin Among Individuals With Abnormal Levels at Baseline
Abnormal is > 5.1 µmol/L



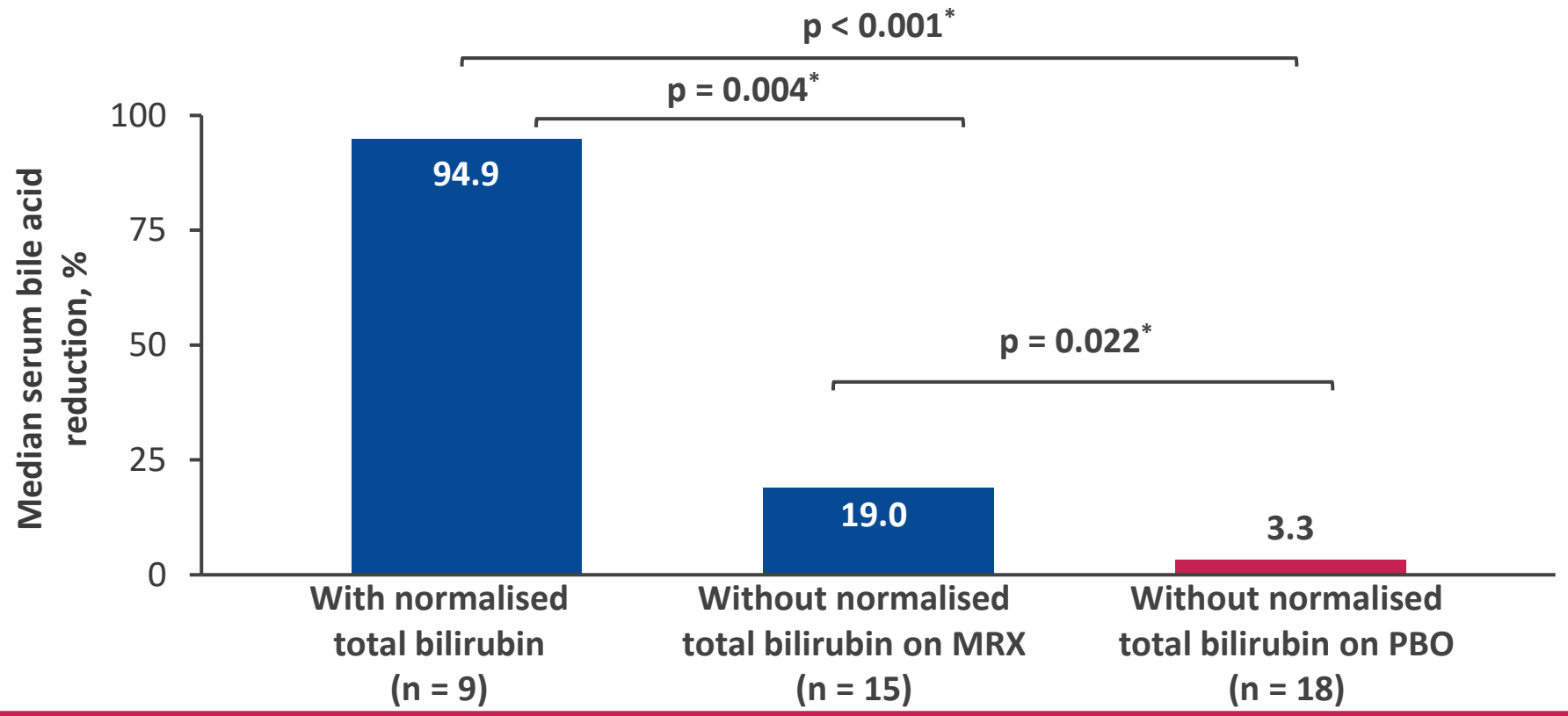
No participants in either the maralixibat or placebo group with normal direct bilirubin at Baseline experienced abnormal values at study end*

Significant percentage of patients experienced direct bilirubin normalisation after maralixibat treatment

*The average of Weeks 18, 22 and 26; †Barnard's exact test.
CI, confidence interval.

MARCH: Relationship Between Total Bilirubin Normalisation and Changes in Serum Bile Acids

Percent Change in Serum Bile Acids With and Without Normalised Total Bilirubin



Normalisation of total bilirubin was associated with a reduction in serum bile acid levels

*Wilcoxon rank-sum test. No multiplicity adjustment was performed.
MRX, maralixibat; PBO, placebo.

Conclusions

- MARCH is the largest Phase 3 trial conducted in children with PFIC that included PFIC types that had not previously been studied
- Maralixibat is the only IBAT inhibitor to demonstrate significant decreases in total and direct bilirubin compared with placebo in children across PFIC types
- Of patients with abnormal total bilirubin values at Baseline, 40% of maralixibat-treated patients achieved normalisation, versus none in the placebo group
- Reductions in bilirubin corresponded with reductions in serum bile acids
- These data suggest that maralixibat may yield clinically meaningful improvements in liver health in patients with PFIC

IBAT, ileal bile acid transporter; PFIC, progressive familial intrahepatic cholestasis.

Acknowledgements

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Author Disclosures

- A. Miethke is a consultant and has a sponsored research agreement with Mirum Pharmaceuticals, Inc.
- D. Mogul, T. Nunes, W. Garner and P. Vig are employees of and shareholders in Mirum Pharmaceuticals, Inc.
- R.J. Thompson is a consultant for Mirum Pharmaceuticals, Inc., Albireo, GenerationBio, Rectify Therapeutics and Alnylam, and is a shareholder in GenerationBio and Rectify Therapeutics.