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


1Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio; 2Hotel-Dieu de France, Saint Joseph University Hospital, Beirut, Lebanon; 3Hospital Sirio Libanés, Sao Paulo, Brazil; 4Nois de Mexico SA CV, Jalisco, Mexico; 5Department of Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics, The Children’s Memorial Health Institute, Warsaw, Poland; 6Cardioinfantil Foundation - LaCardio, Bogota, Colombia; 7Ospedale Pediatrico Bambino Gesù IRCCS, Lazio, Italy; 8University of Texas Southwestern Medical Center, Dallas, Texas; 9Pediatrics, UPMC Children’s Hospital of Pittsburgh, Pittsburgh, Pennsylvania; 10Pediatric Hepatology, UCLouvain, Cliniques Universitaires Saint-Luc, Brussels, Belgium; 11Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; 12Pediatric Gastroenterology and Hepatology, Hannover Medical School, Hannover, Germany; 13Department of Paediatric Hepatology, Gastroenterology and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy; 14Medical University of South Carolina, Charleston, South Carolina; 15Hôpital des Enfants – CHU Toulouse, Toulouse, France; 16Koc University School of Medicine, Istanbul, Turkey; 17Children’s Hospital Los Angeles, Los Angeles, California; 18Pediatrics, University of Alberta, Alberta, Canada; 19University of Texas Health Science Center at San Antonio, San Antonio, Texas; 20KK Women’s and Children’s Hospital, Singapore; 21Medical University of Vienna, Vienna, Austria; 22Mirum Pharmaceuticals, Inc., Foster City, California; 23Cleveland Clinic Children’s, Cleveland, Ohio; 24Pediatric Gastroenterology, Hepatology, and Liver Transplant, AdventHealth for Children and AdventHealth Transplant Institute, Orlando, Florida; 25MedStar Georgetown Transplant Institute, MedStar Georgetown University Hospital, Washington, DC; 26Birmingham Women and Children’s Hospital, Birmingham, United Kingdom; 27Pediatric Hepato-Gastroenterology and Nutrition Unit, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Lyon, France; 28New York University Grossman School of Medicine, New York, New York; 29Institute of Liver Studies, King’s College London, London, United Kingdom
<table>
<thead>
<tr>
<th>Company Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/Patent</th>
<th>Stock Options</th>
<th>Ownership/Equity Position</th>
<th>Employee</th>
<th>Other (please specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirum Pharmaceuticals, Inc.(^a)</td>
<td>X</td>
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</tbody>
</table>

\(^a\)Products or services produced by this company are relevant to my presentation.
Alexander G. Miethke

- Medical School at Humboldt University (Charite), Berlin, Germany
- Pediatric Residency, GI and Transplant Hepatology Fellowship at Cincinnati Children’s Hospital
- Faculty at Cincinnati Children’s since 2009
- NIH-, industry-, and foundation-funded research on cholestatic liver diseases including PFIC, biliary atresia, and PSC
- FC Cincinnati and Union Berlin soccer fan

PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis.
Progressive Familial Intrahepatic Cholestasis

• Genetic disorders resulting in disrupted bile composition and chronic cholestasis

• Debilitating pruritus, impaired growth, reduced QoL and progressive liver disease, with many children undergoing liver transplantation

• PFIC types include deficiencies of:
  – 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,
  – sBA control (relative decrease in sBA of <102 µmol/L or ≥75% reduction) after surgical biliary diversion is associated with native liver survival ≤15 years (NAPPED)

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

EU, European Union; 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.

*aOdevixibat 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.

Maralixibat: IBAT Inhibitor That Interrupts Enterohepatic Circulation

Redirects bile acid flow by inhibiting reuptake by IBAT

Interrupts recirculation of bile acids to the liver

Increases fecal bile acid excretion

Clinical effects of maralixibat in ALGS:

- Improvements in pruritus¹-³
- Reduction in peripheral sBA¹-³
- Improved transplant-free survival¹,²

Maralixibat is approved for the treatment of cholestatic pruritus in patients with ALGS ≥3 months of age in the US and ≥2 months of age in the EU³,⁴

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


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, Copyright (2021), with permission from Elsevier.
Key Entry Criteria

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

MARCH-PFIC: Phase 3 Study Design

Maralixibat 570 µg/kg BID
Placebo

R 1:1

6 mo

MARCH-ON
Phase 3 open-label extension study

**Key Entry Criteria**

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

**Maralixibat**

570 µg/kg BID

**Placebo**

BL

6 mo

MARCH-ON
Phase 3 open-label extension study


BID, twice daily; BL, Baseline; BSEP, bile salt export pump; PFIC, progressive familial intrahepatic cholestasis; R, randomized; sBA, serum bile acid; ULN, upper limit of normal.

*Criteria for primary BSEP cohort only. Maralixibat 570 µg/kg is equivalent to 600 µg/kg maralixibat chloride.

**MARCH-PFIC: Study Populations**

<table>
<thead>
<tr>
<th>Full-study population (N=93)</th>
<th>All-PFIC cohort (n=64)</th>
<th>BSEP cohort: nt-BSEP (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FIC1 (n=13), MDR3 (n=9), TJP2 (n=7) and MYO5B (n=4) (n=33)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterozygosis(^a) (n=2), t-BSEP (n=9), variants not found (n=8), fluctuating sBA (n=2) and surgery (n=8)</td>
<td></td>
</tr>
</tbody>
</table>

**Exploratory cohort (n=29)**

BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis-associated protein type 1; MDR3, multidrug-resistance 3 protein; MYO5B, myosin VB; PFIC, progressive familial intrahepatic cholestasis; nt, nontruncated; sBA, serum bile acid; t, truncated; TJP2, tight junction protein 2.

\(^a\)One subject had a heterozygous ABCB11 mutation, and another had a heterozygous ATP8B1 variant.
Primary Endpoint (BSEP cohort):
Mean change in morning ItchRO(Obs) severity score between Baseline and average of the last 12 weeks

Endpoints were analyzed 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

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)
### Key Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>BSEP</th>
<th>All-PFIC</th>
<th>Full-Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maralixibat (n=14)</td>
<td>Maralixibat (n=33)</td>
<td>Maralixibat (n=47)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=17)</td>
<td>Placebo (n=31)</td>
<td>Placebo (n=46)</td>
</tr>
<tr>
<td>Age, y</td>
<td>6.3</td>
<td>6.9</td>
<td>4.8</td>
</tr>
<tr>
<td>Male, %</td>
<td>50</td>
<td>52</td>
<td>43</td>
</tr>
<tr>
<td>Pruritus, ItchRO(Obs)</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Sleep disturbance, EDQ(Obs)</td>
<td>3.7</td>
<td>3.7</td>
<td>3.6</td>
</tr>
<tr>
<td>Total sBA, µmol/L</td>
<td>312</td>
<td>254</td>
<td>263</td>
</tr>
<tr>
<td>UDCA usage, %</td>
<td>79</td>
<td>82</td>
<td>83</td>
</tr>
<tr>
<td>Rifampicin usage, %</td>
<td>43</td>
<td>55</td>
<td>55</td>
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<tr>
<td>ALT, U/L</td>
<td>98</td>
<td>88</td>
<td>108</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>3.5</td>
<td>4.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Direct bilirubin, mg/dL</td>
<td>2.4</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Height z score</td>
<td>-2.0</td>
<td>-2.1</td>
<td>-2.0</td>
</tr>
<tr>
<td>Weight z score</td>
<td>-1.5</td>
<td>-1.8</td>
<td>-1.6</td>
</tr>
</tbody>
</table>

Note: All data are mean unless otherwise indicated. Percentages are 100 x n/N.

ALT, alanine aminotransferase; BSEP, bile salt export pump; EDQ(Obs), Exploratory Diary Questionnaire (Observer); ItchRO(Obs), Itch-Reported Outcome (Observer); PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid; UDCA, ursodeoxycholic acid.

Baseline characteristics and demographics were balanced between the cohorts.
Primary Endpoint: Change in Weekly ItchRO(Obs) Score in BSEP Cohort

Pruritus Score (ItchRO(Obs)) MMRM Analysis

Maralixibat (n=14)  
Placebo (n=17)

Change from Baseline

Maralixibat: -1.7  
Placebo: -0.6

Δ: -1.0 (-1.8, -0.3)\textsuperscript{a}

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

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

Primary endpoint \( P=0.0098 \textsuperscript{b} \)

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; ItchRO(Obs), Itch-Reported Outcome (Observer); LS, least squares; MMRM, mixed model repeated measures.

\textsuperscript{a}LS mean delta with 95% CI. \textsuperscript{b}Maralixibat LS mean = placebo LS mean.
Maralixibat 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. BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis-associated protein type 1; ItchRO(Obs), Itch-Reported Outcome (Observer); LS, least squares; MDR3, multidrug-resistance 3 protein; MMRM, mixed model repeated measures; 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 sBA in All-PFIC Cohort

Maralixibat resulted in statistically significant improvements in sBA 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.

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])

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo (n=28)</th>
<th>Maralixibat (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders, %</td>
<td>28.6</td>
<td>63.6</td>
</tr>
</tbody>
</table>

*P* = 0.006

Δ: 35.1 (7.4, 57.0)\(^b\)

**sBA Responders**

- ≥75% reduction OR sBA <102 µmol/L

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo (n=28)</th>
<th>Maralixibat (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders, %</td>
<td>7.1</td>
<td>50</td>
</tr>
</tbody>
</table>

*P* < 0.001

Δ: 42.9 (18.3, 62.8)\(^b\)

**Significantly greater percentage of maralixibat-treated patients met the response thresholds for pruritus and sBA in the All-PFIC cohort**

ItchRO(Obs), Itch-Reported Outcome (Observer); PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.

\(^a\)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.

\(^b\)Difference with 95% exact CI.
Exploratory Endpoint: Change From Baseline in Sleep and Relationship to Pruritus in All-PFIC Cohort

Sleep Disturbance Score (EDQ[Obs])

Maralixibat (n=33) Placebo (n=31)

Δ: -1.2 (-1.8, -0.6)b

P=0.0002

Correlation between Sleep Disturbance (EDQ[Obs])a and Pruritus Scores (ItchRO[Obs])c

Significant improvement in sleep was observed in maralixibat-treated patients and was strongly correlated with improvements in pruritus.
MARCH: Change From Baseline and Normalization of Total Bilirubin

Serum Total Bilirubin MMRM Analysis

Maralixibat resulted in statistically significant improvements in total bilirubin and percent of patients normalized 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, least squares; MMRM, mixed model repeated measures; PFIC, progressive familial intrahepatic cholestasis.

*a LS mean delta with 95% CI. bMaralixibat LS mean = placebo LS mean. cThe average of Weeks 18, 22, and 26. dBarnard exact test.
Exploratory Endpoint: Change From Baseline in Weight and Height z Scores in All-PFIC Cohort

Weight z Score MMRM Analysis

Maralixibat (n=33)  Placebo (n=31)

Δ: 0.23 (0.01, 0.44)\(^a\)

\(P=0.039\)\(^b\)

Height z Score MMRM Analysis

Maralixibat (n=33)  Placebo (n=31)

Δ: 0.21 (-0.04, 0.45)\(^a\)

\(P=0.094\)\(^b\)

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

\(^a\)LS mean delta with 95% CI. \(^b\)Maralixibat LS mean = placebo LS mean.
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 were reported.

### TEAEs of Clinical Interest Occurring in ≥ 5% of Participants in Either Arm (by FMQ and Preferred Term)

<table>
<thead>
<tr>
<th>TEAE, n (%)</th>
<th>Maralixibat (n=47)</th>
<th>Placebo (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27 (57.4)</td>
<td>9 (19.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (25.5)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (8.5)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3 (6.4)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>3 (6.4)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (6.4)</td>
<td>5 (10.9)</td>
</tr>
<tr>
<td><strong>Liver function tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transaminase AEs</td>
<td>8 (17)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>6 (12.8)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>7 (14.9)</td>
<td>9 (19.6)</td>
</tr>
<tr>
<td><strong>FSV deficiency</strong></td>
<td>13 (27.7)</td>
<td>16 (34.8)</td>
</tr>
<tr>
<td>Fractures</td>
<td>3 (6.4)</td>
<td>0</td>
</tr>
</tbody>
</table>
Conclusions

- MARCH-PFIC is the largest phase 3 trial conducted in children with PFIC
- Maralixibat demonstrated significant and rapid improvements in pruritus and sBA consistently across all PFIC types
  - Changes in pruritus were strongly correlated with improvements in sleep, suggesting that the use of maralixibat may yield meaningful improvements in this domain of QoL
- 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
- Maralixibat demonstrated significant decreases in bilirubin compared with placebo
  - Almost half of maralixibat-treated patients with abnormal bilirubin at Baseline achieved normalization vs none in the placebo group
- Significant improvements in 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
- These data suggest that maralixibat may yield clinically meaningful improvements in liver health in patients with PFIC

BSEP, bile salt export pump; 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.
• 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

- AGM is a consultant and has a sponsored research agreement with Mirum Pharmaceuticals, Inc.
- FO is a speaker for Alexion Pharmaceuticals and Valenteck Pharma
- AAA is a consultant for Mirum Pharmaceuticals, Inc., Albireo, and Sarepta Therapeutics
- ES is the founder and chairman of Cellaion; an investigator for Mirum Pharmaceuticals, Inc., Albireo, and Intercept; and an advisor for Albireo
- UB is a consultant for Mirum Pharmaceuticals, Inc., Albireo, and Vivet Pharmaceuticals
- LD’A is a consultant and advisor for Mirum Pharmaceuticals, Inc., Albireo, Selecta, Vivet Pharmaceuticals, Tome, Spark, Genespire, and Alexion
- NK is a consultant for Mirum Pharmaceuticals, Inc.
- NM is an investigator for Mirum Pharmaceuticals, Inc.
- SPH is a hepatic safety adjudication committee (HSAC) member at Albireo and has received a research grant from Mirum Pharmaceuticals, Inc.
- AVL, SWR, TN, AL, LL, DBM, WG, and PV are employees of and shareholders in Mirum Pharmaceuticals, Inc.
- RPG-P has received a research grant from Mirum Pharmaceuticals, Inc. and is an advisor, teacher, and educator for Mirum Pharmaceuticals, Inc. and Albireo
- UE is a steering committee member for Mirum Pharmaceuticals, Inc.
- NO is a consultant for Albireo and received research support to her institution from Mirum Pharmaceuticals, Inc., Albireo, and Travere
- RJT is a consultant for Mirum Pharmaceuticals, Inc., Albireo, Generation Bio, Rectify Therapeutics, and Alnylam and a shareholder in Generation Bio and Rectify Therapeutics
- AM, GP, JCE, PC, MC, RHS, DD’A, N Laborde, CA, C-HL, SG, FKC, W-DH, VFH, JH, and N Laverdure have nothing to disclose
- Previously presented as an oral presentation at the Annual Meeting of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 2023 and at The Liver Meeting® (AASLD) 2022.
Thank You!