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 Libanes, 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 - Cardio, Bogota, Colombia; 7Ospedale Pediatrico Bambino Gesu Ircs, Lazio, Italy; 8University of Texas Southwestern Medical Center, Dallas, Texas; 9Pediatrics, UPMC Children’s Hospital of Pittsburgh, Pittsburgh, Pennsylvania; 10Pediatric Hepatology, UCLouvain, Cliniques Universitaires St-Luc, Brussels, Belgium; 11Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; 12Pediatric Gastroenterology and Hepatology, Hannover MediHepatological 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; 18Pediatric, 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, AdvonHealth 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 Mere 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>
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<td>GenerationBio</td>
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<td>Rectify Therapeutics</td>
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</tr>
</tbody>
</table>
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 cholestasis¹

• Debilitating pruritus, impaired growth, reduced QoL and progressive liver disease, with most children undergoing liver transplantation²⁻⁵

• 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 inhibitors⁶⁻⁸,*

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.

Maralixibat: IBAT Inhibitor That Interrupts Enterohepatic Circulation

Interrupts recirculation of bile acids to the liver

Redirects bile acid flow by inhibiting reuptake by IBAT

Increases faecal bile acid excretion

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.
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, Copyright (2021), with permission from Elsevier.
**MARCHANT-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

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*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.
**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>Exploratory cohort (n = 29)</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* (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>

*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

**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

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

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.

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)

<table>
<thead>
<tr>
<th>Change from Baseline</th>
<th>Maralixibat</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
<td>-1.7</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

Δ: -1.0 (-1.8, -0.3)★

Primary endpoint p = 0.0098†

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

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

Study week

<table>
<thead>
<tr>
<th>Patients</th>
<th>14</th>
<th>14</th>
<th>14</th>
<th>13</th>
<th>14</th>
<th>14</th>
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<tr>
<td></td>
<td>17</td>
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<td>17</td>
<td>17</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

Change from Baseline

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**

<table>
<thead>
<tr>
<th></th>
<th>Maralixibat</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 19)</td>
<td>(n = 14)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maralixibat</td>
<td>-1.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

Δ: -1.3 (-2.1, -0.5)*

p = 0.0029†

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

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. 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

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

Pruritus Score (ItchRO[Obs]) MMRM Analysis

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

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

Maralixibat (n = 12)  Placebo (n = 17)

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Change from Baseline, μmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maralixibat</td>
<td>-176</td>
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<tr>
<td>Placebo</td>
<td>11</td>
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</tbody>
</table>

Δ: -187 μmol/L (-293.5, -80.0)*

p = 0.0013†

Average sBA Over Time

<table>
<thead>
<tr>
<th>Study week</th>
<th>Maralixibat</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
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<td></td>
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<tr>
<td>6</td>
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<tr>
<td>14</td>
<td></td>
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<tr>
<td>18</td>
<td></td>
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<tr>
<td>22</td>
<td></td>
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<tr>
<td>26</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Maralixibat (n = 19)</th>
<th>Placebo (n = 14)</th>
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</thead>
<tbody>
<tr>
<td>Improvement</td>
<td></td>
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<tr>
<td>Change from Baseline, µmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-132</td>
</tr>
<tr>
<td></td>
<td>-6</td>
</tr>
</tbody>
</table>

Δ: -126 µmol/L (-194.0, -58.2)*

**Average sBA Over Time**

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

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

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

sBA MMRM Analysis

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

Improvement Change from Baseline, µmol/L

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

Average sBA Over Time

Study week

Patients

Maralixibat Placebo

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])

- Maralixibat (n = 33): 63.6%
- Placebo (n = 31): 25.8%

p = 0.0023
Δ: 37.8 (11.3, 59.4)†

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

- Maralixibat (n = 33): 51.5%
- Placebo (n = 31): 6.5%

p < 0.0001
Δ: 45.1 (21.8, 64.0)†

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

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

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

Average Serum Total Bilirubin Over Time

- Maralixibat
- Placebo

Study week

Maralixibat Placebo

0 2 6 10 14 18 22 26

Change from Baseline, mg/dL

Maralixibat Placebo

0 2 6 10 14 18 22 26

Change from Baseline, mg/dL

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

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

Improvement

Change from Baseline, mg/dL

-3.0 -2.0 -1.0 0.0 1.0 2.0 3.0

Δ: -1.5 (-3.1, -0.01)*

p = 0.048†

Average Serum Direct Bilirubin Over Time

Maralixibat Placebo

Change from Baseline, mg/dL

0 0.0 1.0 2.0 3.0

Study week

Patients

Maralixibat Placebo

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

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.

No significant changes in ALT levels were observed following maralixibat treatment in the All-PFIC cohort.
Exploratory Endpoint: Change From Baseline in Weight and Height Z-Score in All-PFIC Cohort

Weight Z-score MMRM Analysis

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

Δ: 0.23 (0.01, 0.44)*

p = 0.039†

Improvement

Change from Baseline

Height Z-score MMRM Analysis

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

Δ: 0.21 (-0.04, 0.45)*

p = 0.094†

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)

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Maralixibat (n = 47)</th>
<th>Placebo (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE, n (%)</td>
<td>47 (100)</td>
<td>43 (93.5)</td>
</tr>
<tr>
<td>Severe TEAE, n (%)</td>
<td>3 (6.4)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Serious TEAE, n (%)</td>
<td>5 (10.6)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>TEAE leading to discontinuation, n (%)</td>
<td>1 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>TEAE leading to death, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Most common TEAE: diarrhoea, n (%)</td>
<td>27 (57.4)</td>
<td>9 (19.6)</td>
</tr>
</tbody>
</table>

- 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, NAtrual 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 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 Leerberghhe, 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

<table>
<thead>
<tr>
<th>Status or Category</th>
<th>BSEP Deficiency</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>Screened for eligibility, n</td>
<td>13 (92.9)</td>
<td>32 (96.9)</td>
<td>44 (93.6)</td>
</tr>
<tr>
<td>Screen failure, n</td>
<td>0</td>
<td>0</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Randomised, n</td>
<td>14 (100)</td>
<td>33 (100)</td>
<td>47 (100)</td>
</tr>
<tr>
<td>Safety population, n</td>
<td>14 (100)</td>
<td>33 (100)</td>
<td>47 (100)</td>
</tr>
<tr>
<td>Completed study treatment, n (%)</td>
<td>13 (92.9)</td>
<td>32 (96.9)</td>
<td>44 (93.6)</td>
</tr>
<tr>
<td></td>
<td>15 (88.2)</td>
<td>28 (90.3)</td>
<td>42 (91.3)</td>
</tr>
<tr>
<td>Reason for discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event, n (%)</td>
<td>0</td>
<td>0</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Liver transplant, n (%)</td>
<td>0</td>
<td>0</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Withdrawal of consent, n (%)</td>
<td>1 (7.1)</td>
<td>1 (3.0)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td></td>
<td>1 (5.9)</td>
<td>2 (6.5)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Disease progression, n (%)</td>
<td>0</td>
<td>1 (3.2)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1 (5.9)</td>
<td>1 (2.2)</td>
<td></td>
</tr>
</tbody>
</table>

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)

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**

- **Maralixibat (n = 3)**
  - Improvement: -2.6
  - Δ: -2.6 (-4.2, -1.0)*
  - p = 0.0087†

- **Placebo (n = 5)**
  - Improvement: 0.05

**sBA MMRM Analysis**

- **Maralixibat (n = 3)**
  - Improvement: -105 µmol/L
  - Δ: -106 µmol/L (-271.5, 60.0)*
  - p = 0.2004†

- **Placebo (n = 5)**
  - Improvement: 0.3

**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

<table>
<thead>
<tr>
<th>Maralixibat (n = 7)</th>
<th>Placebo (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from Baseline</td>
<td></td>
</tr>
<tr>
<td>Improvemen</td>
<td>1.0</td>
</tr>
<tr>
<td>0.0</td>
<td>-1.4</td>
</tr>
<tr>
<td>-1.0</td>
<td></td>
</tr>
<tr>
<td>-2.0</td>
<td></td>
</tr>
<tr>
<td>-3.0</td>
<td></td>
</tr>
</tbody>
</table>

Δ: -1.1 (-2.8, 0.5)*

p = 0.1559†

sBA MMRM Analysis

<table>
<thead>
<tr>
<th>Maralixibat (n = 7)</th>
<th>Placebo (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from Baseline, µmol/L</td>
<td></td>
</tr>
<tr>
<td>-83</td>
<td>40</td>
</tr>
</tbody>
</table>

Δ: -123 µmol/L (-231.4, -14.0)*

p = 0.0305†

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

<table>
<thead>
<tr>
<th></th>
<th>Maralixibat (n = 4)</th>
<th>Placebo (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
<td>-1.8</td>
<td>-1.2</td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>-2.0</td>
<td>-1.5</td>
</tr>
</tbody>
</table>

Δ: -0.6 (-1.9, 0.7)*

p = 0.3062†

sBA MMRM Analysis

<table>
<thead>
<tr>
<th></th>
<th>Maralixibat (n = 4)</th>
<th>Placebo (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from Baseline, µmol/L</td>
<td>-152</td>
<td>-9</td>
</tr>
</tbody>
</table>

Δ: -142 µmol/L (-311.7, 27.4)*

p = 0.0875†

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.