Phase 2 placebo-controlled withdrawal study of the ASBT inhibitor maralixibat in children with Alagille syndrome

48-week efficacy analysis

ICONIC Study

Author affiliations

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Alagille syndrome is a rare cause of pediatric cholestasis

Alagille syndrome (ALGS) is a genetic multisystemic developmental disease
- Also known as syndromic intrahepatic bile duct paucity or arteriohepatic dysplasia
- Autosomal dominant, with mutations in JAG1 (> 90% of cases) or NOTCH2
- Characterized by abnormalities of the liver, heart, eyes, vertebrae, kidney and facies

Bile duct paucity leads to chronic cholestasis, severe pruritus and xanthoma
- Liver transplantation may be indicated to improve quality of life in patients with severe pruritus

Pharmacological inhibition of enterohepatic bile acid circulation may:
- Decrease serum bile acid (sBA) and cholesterol levels
- Relieve pruritus and xanthoma
Maralixibat is an oral, minimally absorbed, selective inhibitor of ASBT (apical sodium-dependent bile acid transporter)

Clinical effects of ASBT inhibition

- ASBT inhibitors, including maralixibat, decrease pruritus, sBA and cholesterol, and increase C4 in PBC\(^2\)–\(^4\)
- Maralixibat shows a trend towards decreases in pruritus in ALGS\(^5\)

C4, 7-a-hydroxy-4-cholesten-3-one; CYP7A1, cholesterol 7α-hydroxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; PBC, primary biliary cholangitis

ICONIC: Phase 2 placebo-controlled double-blind drug-withdrawal study of maralixibat in children with ALGS

- Higher dose of maralixibat than previous ALGS trials
- Randomized placebo-controlled withdrawal design

Week 0–18 (18 weeks)
- Maralixibat up to 400 µg/kg po QD

Week 18–22 (4 weeks)
- Maralixibat (MRX)

Week 22–48 (26 weeks)
- Results from a pre-specified 48-week analysis

Week 48–long-term (2 years)
- Maralixibat
- Long-term Treatment

Key inclusion criteria

• Children 1–18 years with ALGS (clinical and/or genetic criteria)
• Chronic cholestasis (clinical/biochemical criteria)
• Significant pruritus (>2 on Itch Reported Outcome [Observer] - ItchRO[Obs]; 0–4)
• No biliary diversion, liver transplant or decompensated cirrhosis

Primary endpoint

• sBA change from week 18 to 22 in those with ≥50% sBA reduction from baseline at week 12 or 18

Additional endpoints

• Pruritus (caregiver-rated ItchRO[Obs]; 0–4)
• Clinician Scratch Scale (CSS) score (investigator rated; 0–4)
• Cholestasis and bile acid metabolism biomarkers (sBA, serum cholesterol, C4)
• Clinician xanthoma scale (CXS) score (investigator rated; 0–4)
• Pediatric Quality of Life Inventory (PedsQL) total score (caregiver rated; 0–100)
• Safety (adverse events, total bilirubin levels, alanine aminotransferase [ALT] levels)
### Disposition and demographics

<table>
<thead>
<tr>
<th>Disposition and demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled, n</td>
<td>31</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>5.4 (1–15)</td>
</tr>
<tr>
<td>Male, %</td>
<td>61.3</td>
</tr>
<tr>
<td>Genotype, n (%): JAG1</td>
<td>31 (100)</td>
</tr>
<tr>
<td>Randomized week 18, n&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29</td>
</tr>
<tr>
<td>Maralixibat</td>
<td>13</td>
</tr>
<tr>
<td>Placebo</td>
<td>16</td>
</tr>
<tr>
<td>Completed week 48, n&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28</td>
</tr>
</tbody>
</table>

### Baseline characteristics, mean (SD)

<table>
<thead>
<tr>
<th>Baseline characteristics, mean (SD)</th>
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</thead>
<tbody>
<tr>
<td>ItchRO(Obs) score, 0–4</td>
<td>2.9 (0.5)</td>
</tr>
<tr>
<td>CSS score, 0–4</td>
<td>3.3 (0.9)</td>
</tr>
<tr>
<td>sBA, µmol/L</td>
<td>283 (211)</td>
</tr>
<tr>
<td>C4, ng/mL</td>
<td>10.3 (14.7)</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>6.1 (5.8)</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>181 (109)</td>
</tr>
<tr>
<td>Clinician xanthoma scale score, 0–4</td>
<td>0.9 (1.26)</td>
</tr>
<tr>
<td>PedsQL score, 0–100</td>
<td>61.2 (17.3)</td>
</tr>
</tbody>
</table>

*Similar baseline characteristics in MRX-MRX-MRX and MRX-PBO-MRX group*

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<sup>a</sup> Early discontinuations of three patients due to adverse events, two before and one after the drug withdrawal period. All unrelated to maralixibat.
Significant improvements in sBA levels versus placebo and baseline

**p < 0.01, ***p < 0.001, change from baseline (overall population)
Improvements in ItchRO(Obs) scores maintained during randomized withdrawal with maralixibat

Baseline ItchRO(Obs)

2.9 (0.5)

MRX vs Pbo week 18 to week 22, p < 0.0001

MRX-MRX-MRX (n = 13)

MRX-PBO-MRX (n = 16)

Mean (SEM) change from baseline in ItchRO(Obs) score between week 18 and 22

LS Mean (SEM) change in ItchRO(Obs) score between week 18 and 22

****p < 0.0001, change from baseline (overall population)

††††p < 0.0001 maralixibat versus placebo
Improvements from baseline in Clinician Scratch Scale scores throughout the study

**Clinician Scratch Scale scores**

**Baseline**
- Mean (SD): 3.3 (0.90)
- Proportion of patients in overall population (%): [Bar chart showing distribution]

**Week 18**
- Mean (SD): 1.5 (1.33)
- Proportion of patients (change from baseline overall population): [Bar chart showing distribution]

**Week 48**
- Mean (SD): 1.5 (1.37)
- Proportion of patients (change from baseline overall population): [Bar chart showing distribution]

- **p < 0.0001**, change from baseline (overall population)

**Comparison**

**Week 22**
- **Maralixibat**
  - Mean (SD): 2.1 (1.12)
  - Proportion of patients (%): [Bar chart showing distribution]
- **Placebo**
  - Mean (SD): 2.9 (1.12)
  - Proportion of patients (%): [Bar chart showing distribution]

- **† p < 0.05** maralixibat versus placebo (change from week 18)
Improvements from baseline in cholesterol levels and clinician xanthoma scores

Serum cholesterol and C4

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>Baseline</th>
<th>Week 18</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol, mg/dL</td>
<td>512.1 (419.8)</td>
<td>417.1 (310.9)</td>
<td>413.7 (344.8)</td>
</tr>
<tr>
<td>p-value(^a)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>C4, ng/mL</td>
<td>10.3 (14.7)</td>
<td>24.3 (27.7)</td>
<td>16.9 (25.2)</td>
</tr>
<tr>
<td>p-value(^a)</td>
<td>&lt;0.01</td>
<td>0.07</td>
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\(^a\) Change from baseline (overall population)

**p < 0.01, change from baseline (overall population)**
Improvements over time in caregiver HRQoL scores

Health-related Quality of Life scale

- Caregiver-rated PedsQL score (0–100)

Open-label period (week 0–18 and week 22–48)

- Significant mean (SD) improvement at week 18: 11 (17) points, \( p = 0.001 \)
- Significant mean (SD) improvement at week 48: 10 (19) points, \( p = 0.016 \)
- Significant correlation between PedsQL and ItchRO(Obs) change from baseline at week 48: \(-0.43\) (95% CI \(-0.71\)–\(-0.15\); \( p = 0.046 \))

Randomized drug withdrawal period (week 18–22)

- No difference between placebo and maralixibat
Maralixibat was generally well tolerated

<table>
<thead>
<tr>
<th>AE, regardless of relatedness</th>
<th>Maralixibat week 0–18 (n = 31)</th>
<th>Withdrawal, week 18–22</th>
<th>Maralixibat week 22–48 (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>30 (96.8%)</td>
<td>7 (53.8%)</td>
<td>12 (75.0%)</td>
</tr>
<tr>
<td>Mild or moderate</td>
<td>24 (77.4%)</td>
<td>7 (53.8%)</td>
<td>11 (68.8%)</td>
</tr>
<tr>
<td>Grade 3-4 AEs</td>
<td>6 (19.4%)</td>
<td>0</td>
<td>1 (6.3%)</td>
</tr>
<tr>
<td>Leading to discontinuation (all unrelated to maralixibat)</td>
<td>2 (6.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Potentially related AEs</td>
<td>12 (38.7%)</td>
<td>1 (7.7%)</td>
<td>3 (18.8%)</td>
</tr>
<tr>
<td>Any serious AE (all unrelated to maralixibat)</td>
<td>4 (12.9%)</td>
<td>1 (7.7%)</td>
<td>1 (6.3%)</td>
</tr>
<tr>
<td>Gastrointestinal AEs</td>
<td>22 (71.0%)</td>
<td>2 (15.4%)</td>
<td>3 (18.8%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>13 (41.9%)</td>
<td>1 (7.7%)</td>
<td>1 (6.3%)</td>
</tr>
</tbody>
</table>
Summary and conclusions

- ICONIC investigated the highest dose of maralixibat in patients with ALGS to date
- Maralixibat significantly reduced pruritus and sBA levels over time and vs placebo in children with ALGS
- Maralixibat also improved xanthomas and quality of life
- Treatment effects were maintained over a 48-week period; 15 participants treated ≥3 years
- Maralixibat was generally well tolerated, with AEs of mainly mild or moderate severity
- Therapeutic benefits of maralixibat in children with ALGS and moderate to severe pruritus were clinically relevant and statistically significant
- A confirmatory phase 3 study is planned
Acknowledgments

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