Durability of Treatment Effect with Long-Term Maralixibat in Children with Alagille Syndrome: 4-Year Safety and Efficacy

ICONIC Study

Emmanuel Gonzales

Conflicts of interests

- Consultancy: Albireo, CTRS, Mirum Pharmaceuticals
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8. Hospital Universitario La Paz, Servicio de Hepatologia y Trasplante, Madrid, Spain
9. Mirum Pharmaceuticals, Basel, Switzerland
10. Mirum Pharmaceuticals, Foster City, CA
11. Takeda Pharmaceuticals, Lexington & Cambridge, MA
12. Stanford University, Palo Alto, California
13. Amplyx Pharmaceuticals, San Diego, CA
14. The Paediatric Liver Centre, Department of Child Health, King’s College Hospital, Denmark Hill, London, UK
Alagille syndrome is a rare cause of pediatric cholestasis

Alagille syndrome (ALGS) is a genetic, multisystem, developmental disease
- Autosomal dominant, with mutations in JAG1 (> 90% of cases) or NOTCH2
- Characterized by abnormalities of the liver, heart, eyes, vertebrae, kidney and facies
- Associated with growth deficit

Bile duct paucity leads to chronic cholestasis, severe pruritus and xanthomas
- Currently no approved pharmacological treatment options
- Liver transplantation (and at times partial external biliary diversion) are used to treat pruritus

Pharmacological inhibition of enterohepatic bile acid circulation may:
- Decrease serum bile acid (sBA) levels and pruritus
- Reduce cholesterol levels and xanthomas
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-α-hydroxy-4-cholesten-3-one; CYP7A1, cholesterol 7α-hydroxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; PBC, primary biliary cholangitis.

Objective: to explore the long-term efficacy and safety of maralixibat (400 µg/kg QD and BID) in children with ALGS.
Key eligibility criteria

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

Efficacy and safety assessments

- The following were assessed during the core study and at 12 weekly intervals during long-term extension:
  - 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 score (investigator rated; 0–4)
  - Pediatric Quality of Life Inventory (PedsQL) fatigue scale score (caregiver rated; 0–100)
  - Height and weight z-score
  - Safety (treatment-emergent adverse events)
Disposition from the core to extension period

<table>
<thead>
<tr>
<th>Disposition</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>31</td>
</tr>
<tr>
<td>Discontinued due to TEAE in core study a</td>
<td>3</td>
</tr>
<tr>
<td>Included in week 48 analysis</td>
<td>29</td>
</tr>
<tr>
<td>Consented to long-term extension</td>
<td>23</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>4</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>2</td>
</tr>
<tr>
<td>Renal failure unrelated to maralixibat</td>
<td>1</td>
</tr>
<tr>
<td>Liver enzyme elevations</td>
<td>1</td>
</tr>
<tr>
<td>Included in week 191 efficacy analysis (3.7 years)</td>
<td>15</td>
</tr>
</tbody>
</table>

a Infection; intracranial bleeding; increased bilirubin levels; all unrelated to maralixibat

TEAE, treatment-emergent adverse event.
## Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Enrolled participants (N = 31)</th>
<th>Extension participants (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>5.0 (1–15)</td>
<td>5.0 (1–12)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>19 (61.3)</td>
<td>10 (66.7)</td>
</tr>
<tr>
<td>JAG1 mutation, n (%)</td>
<td>31 (100.0)</td>
<td>15 (100.0)</td>
</tr>
<tr>
<td>Serum bile acid level, µmol/L</td>
<td>283.4 (37.8)</td>
<td>259.0 (55.3)</td>
</tr>
<tr>
<td>Total Bilirubin mg/dL</td>
<td>6.1 (1.0)</td>
<td>3.2 (0.9)</td>
</tr>
<tr>
<td>ItchRO(Obs) score (0-4)</td>
<td>2.9 (0.1)</td>
<td>2.8 (0.1)</td>
</tr>
<tr>
<td>CSS score (0-4)</td>
<td>3.3 (0.2)</td>
<td>3.2 (0.3)</td>
</tr>
<tr>
<td>Height z-score</td>
<td>−1.7 (0.2)</td>
<td>−1.8 (0.3)</td>
</tr>
</tbody>
</table>

Data presented as mean (SE) unless otherwise specified.
Study drug exposure for each participant

14/15 participants increased to 800 µg/kg/day
Reduction in mean serum bile acid levels was maintained long-term

Change from baseline, * \( p \leq 0.05 \), ** \( p \leq 0.01 \), *** \( p \leq 0.001 \) (overall population)
Mean pruritus scores reduced in the core study and were maintained in the extension.

Change from baseline, **** $p \leq 0.0001$ (overall population)
Serum bile acid levels and pruritus improved in the subgroup of patients treated long-term with maralixibat

Change from BL in sBA levels

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 15)</th>
<th>Core study (n = 15)</th>
<th>Long-term extension (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SE):</td>
<td>259.0 (55.3)</td>
<td>111.4 (33.9)</td>
<td>97.3 (33.8)</td>
</tr>
<tr>
<td>Change from BL</td>
<td></td>
<td>p = 0.0067 (BL to week 48)</td>
<td>p = 0.0047 (BL to week 191)</td>
</tr>
</tbody>
</table>

Change from BL in ItchRO(Obs) score (0–4)

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 15)</th>
<th>Core study (n = 15)</th>
<th>Long-term extension (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SE):</td>
<td>2.8 (0.1)</td>
<td>0.92 (0.2)</td>
<td>0.33 (0.2)</td>
</tr>
<tr>
<td>Change from BL</td>
<td></td>
<td>p &lt; 0.0001 (BL to week 48)</td>
<td>p &lt; 0.0001 (BL to week 193)</td>
</tr>
</tbody>
</table>
CSS and fatigue improved in the subgroup of patients treated long-term with maralixibat.

**Change from BL in CSS score (0–4)**

- **Baseline** (n = 15): Mean (SE): 3.2 (0.3)
- **Core study** (n = 15): 1.5 (0.4)  
  \( p = 0.0003 \) (BL to week 48)
- **Long-term extension** (n = 15): 0.8 (0.4)  
  \( p < 0.0001 \) (BL to week 191)

**Change from BL in PedsQL fatigue scale score (0–100)**

- **Baseline** (n = 14): 47.8 (5.9)
- **Core study** (n = 13): 74.8 (4.0)  
  \( p = 0.0005 \) (BL to week 48)
- **Long-term extension** (n = 14): 65.9 (4.7)  
  \( p = 0.0053 \) (BL to week 191)
Improvements from baseline in cholesterol levels and clinician xanthoma scores

Serum cholesterol and C4 levels

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 48</th>
<th>Week 191</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol, mg/dL</td>
<td>414.3 (182.1)</td>
<td>340.3 (149.9)</td>
<td>277.5 (65.7)</td>
</tr>
<tr>
<td>C4, ng/mL</td>
<td>7.4 (8.7)</td>
<td>20.4 (32.2)</td>
<td>30.4 (44.6)</td>
</tr>
</tbody>
</table>

*p value<sup>a</sup>:

- Serum cholesterol: < 0.01 and < 0.01
- C4: 0.1 and 0.04

<sup>a</sup> Change from baseline
Increased height z-scores with long-term maralixibat treatment

Baseline z-score: $-1.82$ (SE, 0.3)

Week 191 z-score: $-1.37$ (SE, 0.3)

Change from baseline, * $p \leq 0.05$, ** $p \leq 0.01$
Long-term maralixibat treatment was well-tolerated

14 participants remain on maralixibat with median treatment duration of 1469.5 days (210 weeks; 4 years)

<table>
<thead>
<tr>
<th>Number of participants, n (%)</th>
<th>Core Study (week 0–18) (N = 31)</th>
<th>Core Study (week 19–22)</th>
<th>Core Study (week 23–48) (N = 29)</th>
<th>Extension Phase (week 49–present) (N = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maralixibat (n = 13)</td>
<td>Placebo (n = 16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any TEAE</td>
<td>30 (96.8)</td>
<td>7 (53.8)</td>
<td>12 (75.0)</td>
<td>25 (86.2)</td>
</tr>
<tr>
<td>Grade 3 or 4 TEAE</td>
<td>6 (19.4)</td>
<td>0</td>
<td>1 (6.3)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Serious TEAE (all unrelated to maralixibat)</td>
<td>4 (12.9)</td>
<td>1 (7.7)</td>
<td>1 (6.3)</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>TEAE leading to death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAE leading to study drug discontinuation</td>
<td>2 (6.5)a</td>
<td>0</td>
<td>0</td>
<td>1 (3.4)a</td>
</tr>
<tr>
<td>TEAE potentially related to study drug</td>
<td>12 (38.7)</td>
<td>1 (7.7)</td>
<td>3 (18.8)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>22 (71.0)</td>
<td>2 (15.4)</td>
<td>3 (18.8)</td>
<td>14 (48.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 (41.9)</td>
<td>1 (7.7)</td>
<td>1 (6.3)</td>
<td>5 (17.2)</td>
</tr>
</tbody>
</table>

a Infection; intracranial bleeding; increased bilirubin levels; all unrelated to maralixibat
b Elevated ALT and/or AST levels (n = 2); hypertension/renal failure unrelated to maralixibat (n = 1)
c Third discontinuation occurred after the data cut-off, bringing n to 14

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Four years of maralixibat treatment in the ICONIC study: summary and conclusions

- Long-term maralixibat treatment in ALGS patients was associated with significant and durable improvement in:
  - Pruritus and serum bile acids
  - Quality of life, cholesterol and xanthoma
  - Height growth

- Maralixibat was generally well tolerated up to 800 µg/kg per day for up to 4 years (total 73.1 patient years exposure)

- Treatment emergent adverse events did not increase in frequency or severity with long-term treatment
Acknowledgements

• Hôpital Universitaire Bicêtre, Paris, France
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• Children’s Hospital at Westmead, Sydney, Australia
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• Royal Children’s Hospital Melbourne, Parkville, Australia
• Hôpital Universitaire Necker-Enfants malades, Paris, France
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