Growth analysis in children with PFIC treated with the ASBT inhibitor maralixibat

INDIGO Study

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Treatment of children with progressive familial intrahepatic cholestasis

• **Progressive Familial Intrahepatic Cholestasis (PFIC)**
  - A progressive childhood cholestatic liver disease
  - Caused by rare genetic defects of bile acid excretion
  - Leading to debilitating pruritus, lipid-soluble vitamin deficiency, growth deficit

• **Standard of care**
  - Pharmacotherapy is only partially/temporarily effective and off-label
  - Partial external biliary diversion (PEBD) reduces serum bile acids (sBA) and pruritus, and improves growth, but may have serious complications
  - Liver transplantation can treat pruritus, but complications/recurrence are not uncommon in PFIC

• **Maralixibat**
  - A potent, minimally absorbed, selective ASBTi (inhibitor of the ileal apical sodium-dependent bile acid transporter)
  - Pharmacological interruption of enterohepatic bile acid recirculation may benefit patients with PFIC
Maralixibat is a potent, selective inhibitor of the ileal apical sodium-dependent bile acid transporter (ASBT)

Clinical effects of ASBT inhibition

- ASBT inhibitors, including maralixibat, decrease pruritus, sBA and cholesterol, and increase C4 in PBC\(^2\)-\(^4\) and improve growth in a cholestasis model\(^5\)
- Maralixibat studies show a trend towards decreases in pruritus in ALGS\(^6\)

Maralixibat interrupts recirculation of bile acids to the liver\(^1\)

Maralixibat redirects bile acid flow by inhibiting reuptake of bile acid

Maralixibat increases fecal bile acid excretion\(^1\)

ALGS, Alagille syndrome; C4, 7-α-hydroxy-4-cholesten-3-one; PBC, primary biliary cholangitis.

INDIGO: phase 2, open-label, safety and efficacy study of maralixibat in children with PFIC

Results from a pre-specified 48-week analysis are presented (subsequent data are preliminary and are not available for all patients)
Key entry criteria and efficacy endpoints

**Key inclusion criteria**
- 1–18 years old
- PFIC phenotype
- PFIC genotype (biallelic \textit{ABCB11} or \textit{ATP8B1} mutation)

**Key efficacy endpoints**
- Height and weight
- Cholestasis biomarkers
  - sBA (primary efficacy measure)
  - ALT, AST, bilirubin, C4
- Pruritus assessments
  - ItchRO(Obs) score (caregiver-rated pruritus; 0 = none, 4 = severe)
  - CSS score (investigator-rated, 0–4)
- HRQoL assessment
  - PedsQL total score (parent-rated, 0–100)

**Key exclusion criteria**
- PEBD or ileal exclusion
- Liver transplant
- Decompensated cirrhosis

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSS, clinician scratch scale; HRQoL, health-related quality of life; ItchRO(Obs), Itch-Reported Outcome (Observer); PedsQL, Pediatric Quality of Life Inventory
### Disposition, demographics, disease characteristics

#### Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>PFIC1, n = 8</th>
<th>PFIC2, n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATP8B1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ABCB11</strong></td>
<td></td>
<td></td>
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<tr>
<td>Median age (range), year</td>
<td>2.0 (1–7)</td>
<td>4.0 (1–13)</td>
</tr>
<tr>
<td>Boys, n (%)</td>
<td>6 (75)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>6 (75)</td>
<td>20 (80)</td>
</tr>
<tr>
<td>Mean (SD) z-scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>−2.96 (1.47)</td>
<td>−1.29 (0.98)</td>
</tr>
<tr>
<td>Weight</td>
<td>−2.70 (2.82)</td>
<td>−0.63 (0.88)</td>
</tr>
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</table>

#### Disposition to week 48

<table>
<thead>
<tr>
<th>Participants (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reached week 48</td>
</tr>
<tr>
<td>Efficacy data available</td>
</tr>
<tr>
<td>PFIC1</td>
</tr>
<tr>
<td>PFIC2</td>
</tr>
<tr>
<td>Maralixibat dose</td>
</tr>
<tr>
<td>280 µg/kg/day</td>
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<tr>
<td>140 µg/kg/day</td>
</tr>
<tr>
<td>&lt; 140 µg/kg/day</td>
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</tbody>
</table>

*One patient receiving 280 µg/kg/day had a treatment interruption and was re-escalating at week 48*
After 48 weeks of treatment:

- Significant pruritus\(^a\) improvement
- Trend towards sBA improvement
- Trend towards QoL improvement
- No change in ALT or bilirubin

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean (range)</th>
<th>Week 48 Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ItchRO(Obs)</td>
<td>2.3 (0.1, 3.8)</td>
<td>-1.1 (-1.5, -0.6)</td>
</tr>
<tr>
<td>CSS</td>
<td>2.9 (0, 4)</td>
<td>-1.3 (-2.0, -0.6)</td>
</tr>
<tr>
<td>sBA [µmol/L]</td>
<td>381 (34, 602)</td>
<td>-59 (-157, 39)</td>
</tr>
<tr>
<td>PedsQL total</td>
<td>62.9 (34.5, 85.9)</td>
<td>4.4 (-4.0, 12.7)</td>
</tr>
<tr>
<td>C4 [ng/L]</td>
<td>4.6 (0.3, 47.3)</td>
<td>7.7 (-0.8, 16.1)</td>
</tr>
</tbody>
</table>

\(^a\) Pruritus measured by ItchRO(Obs)

QoL: Quality of Life as measured by PedsQL; sBA: serum bile acids; CSS: Clinician Scratch Scale

Part of the data presented by Thompson et al., AASLD 2017
Profound/sustained treatment response in n = 6

**Response criteria:**
- sBA levels – normalized (≤ 8.5 µmol/L; n = 4) or reduced ≥ 70% from baseline (n = 2) AND
- ItchRO(Obs) – no pruritus (n = 2) or improved ≥ 1.0 points from baseline (n = 4)

**Responder characteristics:**
- All non-truncating PFIC2 (ABCB11) mutations, all on 280 µg/kg/day; no other predictive characteristics
- ALT, AST and bilirubin normalized, if elevated at baseline (ALT remained mildly elevated in responder F/1)

Intercurrent illnesses in responders F/4, M/3 and F/1
Height z-scores increased in PFIC2 responders vs decreased in partial/non-responders

*a z-score: number of standard deviations that a measure deviates from the mean value of healthy age-matched controls

*\( p < 0.05, **p < 0.001 \) vs partial/non-responders, post hoc ANCOVA
Weight z-scores increased in PFIC2 responders vs decreased in partial/non-responders

- Responders
- Partial/non-responders

Mean (SD) change from baseline in height z-score

* $p < 0.05$, ** $p < 0.001$ vs partial/non-responders, post hoc ANCOVA

Responder, n
6 6 6 6 6 6 5 5

Partial/non-responder, n
19 19 17 16 14 11 8

*z-score: number of standard deviations that a measure deviates from the mean value of healthy age-matched controls
Improvements in growth may be related to disease modifications induced by maralixibat

- Possible explanations for growth increases:
  - Pruritus relief?
  - Improved sleep?
  - Greater absorption of fats due to modified bile acid profile in the gut?

- Growth spurt with maralixibat comparable to those documented after PEBD\textsuperscript{1,2} or liver transplantation\textsuperscript{3,4}

Improvement of lipid profile in responders

- Response is associated with improvement in lipid profiles

**Change from baseline to week 72**

- Changes in the serum lipid profile with maralixibat are comparable to those reported after PEBD\(^1\)
- ASBT inhibition upregulates hepatic LDL-receptor mRNA levels in a piglet model\(^2\)

Higher doses may lead to higher response rate

- Protocol amendment doubled maralixibat dose to 280 µg/kg BID
- 7th responder with PFIC2 manifested on BID treatment
- Growth benefit was reproducible after meeting response criteria

- Change in z-scores after starting BID dosing:
  - Height: +0.93
  - Weight: +0.34
Summary and conclusions

• Maralixibat leads to marked treatment benefit in a subset of children with PFIC2
  - Improvement in growth
  - Normalization or substantial reduction in sBA levels
  - Disappearance or substantial reduction in pruritus
  - Normalization of bilirubin and liver enzyme levels, if elevated at baseline
  - Improvement in lipid profile
  - Improvement in HRQoL

• Improvement in growth may be related to reductions in pruritus, better sleep or better fat absorption and may indicate disease-modifying potential of maralixibat

• A phase 3 study will be conducted to further investigate maralixibat in children with PFIC
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