Long-Term Maintenance of Response and Improved Liver Health With Maralixibat in Patients With Progressive Familial Intrahepatic Cholestasis

Introduction

• Progressive familial intrahepatic cholestasis (PFIC) is a collection of disorders in bile formation that can lead to intrahepatic cholestasis, chronic liver disease, and severe pruritus.

• Maralixibat (MRX) is a minimally absorbed bile acid transporter (BSEP) inhibitor that prevents enterohepatic bile acid recirculation and is approved for the treatment of cholestatic pruritus in patients with Alagille syndrome ≥9 months of age in the US and ≥2 months of age in the EU.

• MRX is Phase 3, randomized, double-blind, placebo-controlled, double-blind trial, investigating the efficacy and safety of maralixibat in patients with PFIC.

• Maralixibat achieved significant improvements in pruritus, levels of sBA, bilirubin, and growth in patients across the broad range of PFIC types studied to date.

• MARC-ON is an open-label, long-term extension study for patients who completed the MARC-1 study.

Objectives

• To assess the long-term maintenance response to maralixibat in patients who were randomized to receive maralixibat (MRX/ROM) or placebo (PBO/ROM) in MARC and continue treatment with maralixibat in MARC-ON.

Methods

• Double-blind, placebo-controlled, randomized, double-blind extension study.

• 120 patients were randomized to placebo or maralixibat (250 mg) in MARC-ON.

• Of the 120 patients randomized to placebo or maralixibat in MARC-ON, 81 completed all planned visits.

• All patients who completed the 120-week treatment period in MARC were eligible for enrollment in MARC-ON (n=75).

• Patients were monitored for 120 weeks in MARC and continued to be monitored in MARC-ON for up to 52 weeks.

Baseline Characteristics Were Well Balanced Between Treatment Arms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MRX/ROM</th>
<th>PBO/ROM</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>4.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Sex, male, %</td>
<td>43</td>
<td>42</td>
</tr>
<tr>
<td>PFIC, IRQ(GEO) score</td>
<td>2.6</td>
<td>2.5</td>
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<tr>
<td>Total sBA, µmol/L</td>
<td>263</td>
<td>253</td>
</tr>
<tr>
<td>USCAP, %</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>Bilirubin, µmol/L</td>
<td>55</td>
<td>58</td>
</tr>
<tr>
<td>Total bilirubin, µg/dL</td>
<td>102</td>
<td>102</td>
</tr>
<tr>
<td>Direct bilirubin, µg/dL</td>
<td>4.1</td>
<td>4.1</td>
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<tr>
<td>ALT, IU/L</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Direct bilirubin, µmol/L</td>
<td>0.8</td>
<td>0.8</td>
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<tr>
<td>Weight, kg</td>
<td>11.2</td>
<td>11.2</td>
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</tbody>
</table>

Results

Significant Improvements in Pruritus Severity Were Sustained in the MRX-MRX Group

- Significant improvements in sBA levels were observed in the MRX-MRX group across the 120-week treatment period.
- Patients in the MRX-MRX group achieved a mean reduction of 85% in pruritus severity scores compared to baseline.

Newly Gained Statistically Significant Reductions in Pruritus Severity Were Observed in the PBO-MRX Group

- In the PBO-MRX group, patients achieved a mean reduction of 70% in pruritus severity scores compared to baseline.

Significant Improvements in Key Endpoints Were Observed From Baseline to Week 52 in the MRX-MRX Group and Baseline to Week 26 in the PBO-MRX Group

- Heart rate from baseline
  - MRX-MRX group: 90 (±10) to 80 (±10)
  - PBO-MRX group: 90 (±10) to 85 (±10)

- Significant improvements were observed in the MRX-MRX group compared to the PBO-MRX group.

Conclusions

- Significant and sustained improvements in pruritus severity, sBA levels, and bilirubin, as well as growth, were observed with 52 weeks of maralixibat treatment across the broad range of genetic PFIC types studied to date.
- The PBO-MRX group showed significant improvement in pruritus severity and sBA levels, which was observed in the original MARC-1 study.
- These data suggest overall improved liver health with maralixibat treatment in patients with PFIC, which can be maintained over time.