Maralixibat improves growth in patients with Alagille syndrome: A 4-year analysis

Binita M Kamath,1 Douglas B Mogul,2 Marshall Baek,2 Tiago Nunes,3 Pamela Vig2

1 Division of Gastroenterology, Hepatology & Nutrition, Hospital for Sick Children and University of Toronto, Toronto, ON, Canada; 2 Mirum Pharmaceuticals, Inc., Foster City, CA, USA; 3 Mirum Pharmaceuticals, Inc., Basel, Switzerland

Introduction

- Alagille syndrome (ALGS) is a rare, debilitating, autosomal-dominant, multisystem disease, typically diagnosed within the first 3 months of life.1,2
- Symptoms of ALGS include growth restriction as well as cholestatic pruritus that negatively impacts quality of life.1,4
- Maralixibat (LVMARLI®) is a bile acid sequestrant (BAS) recently approved by the US Food and Drug Administration (FDA) for the treatment of cholestatic pruritus in patients with ALGS 1 year of age and older.4
- Recent data indicate that maralixibat is associated with improved event-free survival in this population, suggesting that the drug may potentially improve liver disease outcomes beyond pruritus control in ALGS.1,2

Aim

To evaluate the impact of long-term maralixibat treatment on the growth and nutritional status of patients with ALGS.

Methods

- Height and weight Z-scores were evaluated in patients who participated in three clinical studies (and their long-term, open-label extensions) of maralixibat for the treatment of cholestatic pruritus in ALGS.4–12
  - Studies LUM001-301 (NCT02057692) and LUM001-302 (NCT01930460) were 13-week, randomised, placebo-controlled, Phase 2 studies.
  - Studies LUM001-300 (NCT02117713) and LUM001-303 (NCT02047318) were optional long-term extension studies to the LUM001-301 and LUM001-302 studies, respectively.
  - Study LUM001-304 (NCT02160782) was a 48-week study with a 4-week, randomised drug-withdrawal period, followed by an open-label, long-term extension study.
- Patients who had both baseline and week 204 assessments for all eight parameters (height, weight, Z-score, albumin, direct bilirubin, total bilirubin, cholesterol, serum bile acid [sBA] and 7 alpha-hydroxy-4-cholesten-3-one [C4]) were included in the analysis.
- Patients were divided into four subgroups based on baseline height or weight Z-score quartiles (Q1, Q2, Q3 and Q4).
- Spearman and Pearson correlation coefficients and t-tests were used to evaluate the association between height and other parameters known to correlate with growth.

Results

Table 1. Patient demographics and baseline characteristics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N = 34</th>
<th>Mean (±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>6.7 (3.82)</td>
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<tr>
<td>Male, n (%)</td>
<td>16 (52.94)</td>
<td></td>
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<tr>
<td>Treatment duration, months (SD)</td>
<td>21.14 (10.94)</td>
<td></td>
</tr>
<tr>
<td>Weight, kg (SD)</td>
<td>112.8 (23.29)</td>
<td></td>
</tr>
<tr>
<td>Height, cm (SD)</td>
<td>1.17 (0.10)</td>
<td></td>
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<tr>
<td>Height Z-score (SD)</td>
<td>-1.46 (0.96)</td>
<td></td>
</tr>
<tr>
<td>sBA, µmol/L (SD)</td>
<td>164.23 (131.96)</td>
<td></td>
</tr>
<tr>
<td>InroQ(0ther) score, weekly morning average (SD)</td>
<td>2.57 (0.80)</td>
<td></td>
</tr>
<tr>
<td>Clinician Scratch Scale score (SD)</td>
<td>3.10 (0.86)</td>
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</table>

Change from baseline in height and weight Z-scores with maralixibat treatment

Figure 1.

- Mean height Z-scores significantly increased from baseline to week 204 (p<0.0004; Figure 1).
- No significant change was observed in mean weight Z-scores between baseline and week 204 (Figure 1).

Relationship between sBA and height

Figure 2.

- Mean height Z-scores significantly increased from baseline to week 204 in patients who achieved an sBA response (<200 µmol/L) at week 204 (p=0.0013; Figure 2).
- There was no significant change in height Z-score among patients with sBA ≥200 µmol/L (Figure 2).

Significant correlation observed between baseline height and change in height

Figure 3.

- A significant correlation was observed between change in height and sBA at week 204; Pearson’s r = −0.39; p=0.02 (Figure 3).

Greater height gain observed in patients with lower baseline height

Figure 4.

- A significant correlation was observed between change in height and weight across the whole cohort (baseline to week 204; Pearson’s r = −0.39; p=0.02; Figure 5).

Figure 5.

- A significant correlation was observed between change in weight and baseline weight across the whole cohort (baseline to week 204; Pearson’s r = −0.39; p=0.02; Figure 5).

Significant correlation observed between baseline weight and change in weight

Figure 6.

- A significant correlation was observed between change in height and weight across the whole cohort (baseline to week 204; Pearson’s r = −0.39; p=0.02; Figure 6).

Greater changes in height correlate with greater changes in weight after maralixibat treatment

Figure 7.

- No changes beyond standard of care in supplementation occurred during the study.
- There were no clear changes in vitamin D levels or albumin throughout treatment.

Conclusions

- Patients with ALGS typically present with significant growth deficits.
- Patients with ALGS treated with long-term maralixibat (up to 4 years) showed significantly improved benefit in height.
- Patients with the lowest height and weight Z-scores at baseline had the greatest improvements in height and weight Z-scores.
- Individuals that had the greatest catch-up weight gain also had the greatest catch-up height growth.
- Maralixibat-treated patients who achieved an sBA threshold <200 µmol/L had greater accelerated height, suggesting bile acid homeostasis can facilitate improvement in height deficits.
- Further analyses, including comparison with a natural history cohort of patients with ALGS, are needed to fully characterize the impact of maralixibat treatment on growth.

References

6. Alagille syndrome: A 4-year analysis (23.29).}

Acknowledgements

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Contact information
Binita M Kamath, Binita Kamath@nicollaks.com
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