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

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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.[2–4]
- Maralixibat (LIVMARLI®) is an ileal bile acid transporter inhibitor (IBATi) 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.[5]
- 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.[6,7]

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:[8–12]
  - Studies LUM001-301 (NCT02057692) and LUM001-302 (NCT01903460) were 13-week, randomised, placebo-controlled, Phase 2 studies.
  - Studies LUM001-305 (NCT02117713) and LUM001-303 (NCT02047318) were optional long-term treatment 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 Z-score, 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

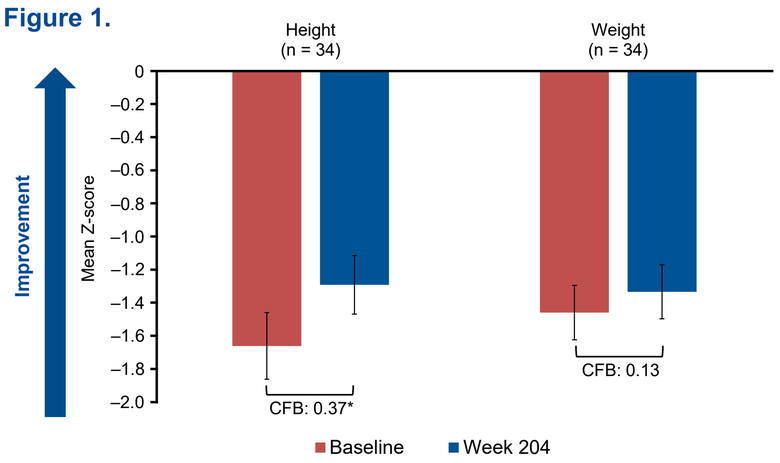
Table 1. Patient demographics and baseline characteristics.

	N = 34
Age, years (SD)	6.7 (3.82)
Male, n (%)	18 (52.94)
Treatment duration, months (SD)	58.61 (6.39)
Weight, kg (SD)	21.14 (10.94)
Weight Z-score (SD)	−1.46 (0.95)
Height, cm (SD)	112.8 (23.29)
Height Z-score (SD)	−1.66 (1.17)
sBA, µmol/L (SD)	184.23 (151.96)
ItchRO(Obs) score, weekly morning average (SD)	2.57 (0.80)
Clinician Scratch Scale score (SD)	3.10 (0.86)

ItchRO(Obs), Itch-Reported Outcome (Observer); sBA, serum bile acid; SD, standard deviation.

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

Figure 1.

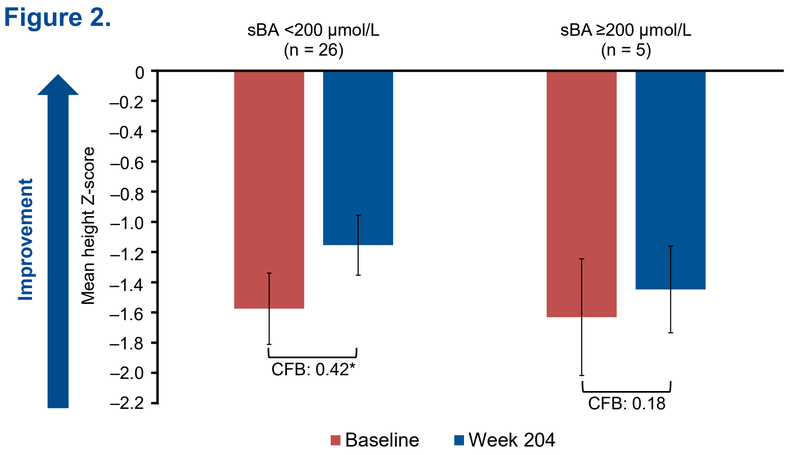


*p=0.0004.
CFB, change from baseline.

- 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.

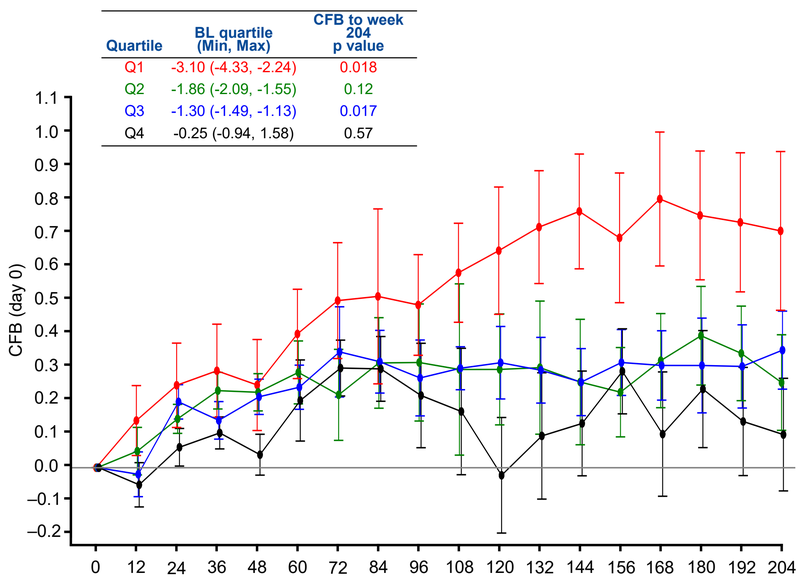


*p=0.0013.
CFB, change from baseline; sBA, serum bile acid.

- Mean height Z-scores significantly increased from baseline to week 204 in patients with an sBA response (<200 µmol/L) at week 48 (p=0.0013; **Figure 2**).
- There was no significant change in height Z-score among patients with sBA ≥200 µmol/L (**Figure 2**).

Greater height gain observed in patients with lower baseline height

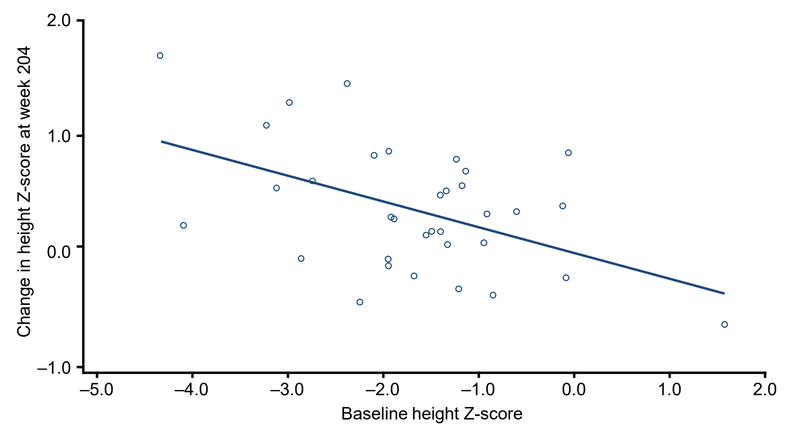
Figure 3.



Mean (±SE) CFB in height Z-score according to baseline height Z-score quartile.
BL, baseline; CFB, change from baseline; SE, standard error.

Significant correlation observed between baseline height and change in height

Figure 4.

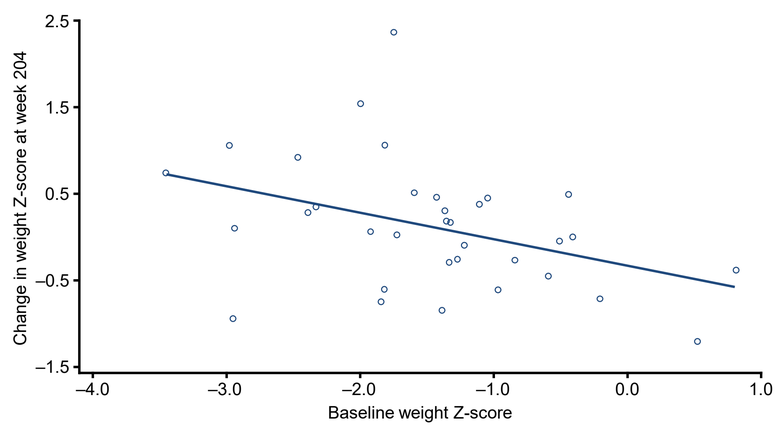


Shapiro–Wilk p value of normality at baseline=0.4490; the change at week 204=0.7850.
Pearson correlation coefficient: –0.4801 (p=0.004); Spearman correlation coefficient: –0.3231 (p=0.0623).

- A significant correlation was observed between change in height and baseline height across the whole cohort (baseline to week 204; Pearson's r = −0.48; p=0.004; **Figure 4**).

Significant correlation observed between baseline weight and change in weight

Figure 5.

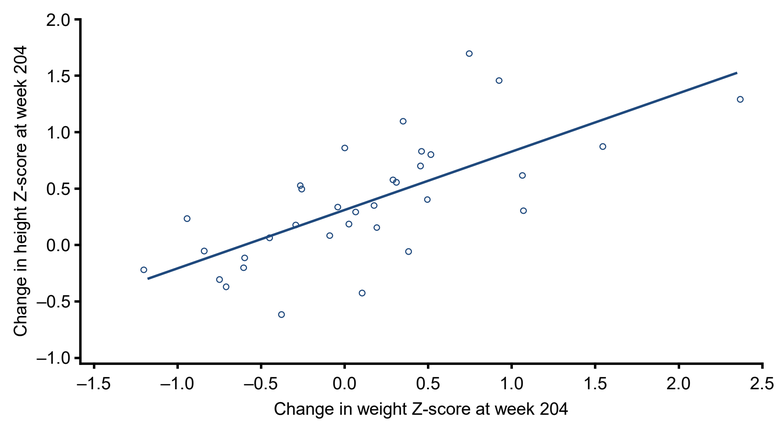


Shapiro–Wilk p value of normality at baseline=0.7748; the change at week 204=0.2694.
Pearson correlation coefficient: –0.3936 (p=0.02); Spearman correlation coefficient: –0.4093 (p=0.0162).

- 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**).

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

Figure 6.



Shapiro–Wilk p value of normality for weight=0.2694; for height=0.7850. Pearson correlation coefficient: 0.6946 (p<0.0001); Spearman correlation coefficient: 0.7345 (p≤0.0001).

- A signification correlation was observed between change in height Z-scores and change in weight Z-scores across the whole cohort (baseline to week 204; Pearson's r = 0.69; p<0.0001; **Figure 6**).

Nutritional status

- 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..

Contact information

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