Response to treatment with maralixibat in Alagille syndrome is associated with improved health-related quality of life

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Introduction

- Alagille syndrome (ALGS) is a rare, life-threatening, autosomal dominant, multisystem disease, typically diagnosed within the first 3 months of life.[1,2]
- Children with ALGS present with chronic cholestasis, pruritus, failure to thrive, and xanthomas.[2]
  - The pruritus experienced by children with ALGS is considered among the most severe in any chronic liver disease and negatively impacts physical and emotional wellbeing.[3–5]
- Maralixibat is an oral, minimally absorbed ileal bile acid transporter inhibitor (IBATi) that interrupts the enterohepatic circulation of bile acids.[6–8]
- The Phase 2b ICONIC study (LUM001-304) showed that treatment with maralixibat significantly reduced pruritus compared with baseline at both weeks 18 and 48 (p<0.0001) in children with ALGS.[8–10]
- Maralixibat is the first agent to demonstrate significant, durable, and clinically meaningful improvements in pruritus in patients with ALGS,[10] and has been approved by the US FDA for the treatment of cholestatic pruritus in patients with ALGS ≥1 year of age.[11]

Aim

- Assess the impact of maralixibat treatment response on changes in health-related quality of life (HRQoL) among children with ALGS.

Methods

Study design and participants

- ICONIC (LUM001-304; NCT02160782) was an international, multicenter, long-term, Phase 2b, placebo-controlled, randomized drug-withdrawal study with an open-label extension, in children with ALGS experiencing moderate to severe pruritus.[8–10]
  - The overall study consisted of an initial 6-week dose-escalation period (maralixibat doses up to 380 µg/kg/day [equivalent to 400 µg/kg maralixibat chloride]), a 4-week randomized withdrawal period (weeks 18–22), and long-term stable dosing.[8–10]
  - The analysis presented here compares HRQoL data at baseline and at week 48.

Endpoints

- Treatment response to maralixibat was defined as a ≥1-point reduction in caregiver Itch-Reported Outcome (ItchRO) instrument score from baseline to week 48.[10]
- Pediatric Quality of Life (PedsQL) questionnaires (Generic Core PedsQL module, Family Impact Scale, and Multidimensional Fatigue Scale) were prospectively collected via a caregiver proxy report and analyzed retrospectively. Measurements from baseline and week 48 were included in this analysis.
  - The minimal clinically important difference (MCID) for the PedsQL scales ranges from 4 to 5 points, depending on the scale. This was validated from previous analyses.[12]
- A subset of individual items from the HRQoL scales, deemed to be most relevant to patients with ALGS, was independently selected by clinical experts for assessment with treatment response.

Statistical analysis

- Patient demographics, baseline clinical characteristics, and changes in HRQoL total scores and selected individual scale items from baseline to week 48 were described and stratified by treatment response status at week 48.
- Statistical comparisons were conducted using t-tests or analysis of variance for continuous variables and a chi-squared test for categorical variables.
- Multivariate linear regression models were used to assess the relationship between the mean change from baseline in HRQoL score and treatment response status, adjusting for baseline HRQoL.

Results

Study population

- A total of 27 patients with ALGS, with data at week 48, were included in this analysis.
- Baseline characteristics were similar between responders and non-responders (**Table 1**).
- At week 48, 20 patients (74%) met the definition of ItchRO response ('responders'), compared with seven patients (26%) who did not ('non-responders').

Table 1. Baseline demographic and clinical characteristics in maralixibat responders and non-responders.

	ItchRO treatment response at week 48		
	Responders (N = 20)	Non-responders (N = 7)	p-value
Age (years)	6.55 ± 4.17	3.29 ± 3.99	0.08
Male, n (%)	14 (70.00)	4 (57.14)	0.65
Height z-score	−1.41 ± 1.33	−1.85 ± 0.92	0.43
Weight z-score	−1.48 ± 1.04	−1.49 ± 0.81	0.99
BMI z-score	−0.70 ± 0.81	−0.35 ± 0.93	0.36
sBA (µmol/L)	271.62 ± 236.61	250.15 ± 143.19	0.82
Bilirubin (total), mg/dL	4.47 ± 4.13	6.67 ± 6.22	0.30
CSS	3.25 ± 1.02	3.29 ± 0.76	0.93
ItchRO	2.97 ± 0.55	2.68 ± 0.58	0.25

All data are mean ± SD unless otherwise indicated. p-value is for the comparison of baseline characteristics according to treatment response status.

BMI, body mass index; CSS, Clinician Scratch Score; dL, deciliters; ItchRO, Itch-Reported Outcome; L, liters; mg, milligrams; sBA, serum bile acid; SD, standard deviation; µmol, micromoles.

HRQoL analysis

- Numerically, responders had improved HRQoL measures compared with non-responders across all scales (**Table 2**).
- The change in Multidimensional Fatigue Total Scale Score from baseline to week 48 was significantly higher in responders compared with non-responders; **Table 2**).
- No clinically meaningful change was observed from baseline to week 48 across all scales in non-responders.

Table 2. Change in HRQoL measures from baseline to week 48 in ItchRO responders and non-responders to maralixibat treatment.

	HRQoL at baseline			HRQoL at week 48			HRQoL change from baseline to week 48		
	Responders (N = 20)	Non-responders (N = 7)	p-value	Responders (N = 20)	Non-responders (N = 7)	p-value	Responders (N = 20)	Non-responders (N = 7)	p-value
PedsQL Generic Core Scale*	58.8 ± 17.9	61.2 ± 15.1	0.75	70.4 ± 15.7	62.4 ± 14.5	0.25	11.6 ± 20.3	1.2 ± 11.1	0.21
Family Impact Scale†	56.7 ± 18.9	50.8 ± 18.5	0.48	73.9 ± 19.6	54.7 ± 20.0	0.04	17.8 ± 23.4	3.9 ± 7.8	0.14
Multidimensional Fatigue Scale‡	47.3 ± 22.4	67.4 ± 20.9	0.12	76.2 ± 15.1	64.2 ± 15.1	0.17	25.8 ± 23.0	−3.1 ± 19.8	0.03

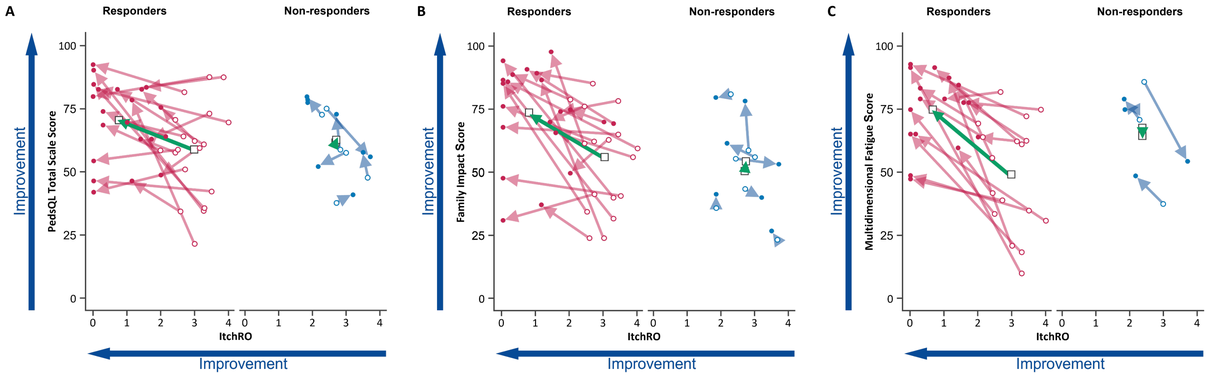
*N = 27 patients had a PedsQL Generic Core Scale score. †N = 26 patients had a Family Impact Scale score; ‡N = 21 patients had a Multidimensional Fatigue Scale score.

Data are mean ± SD.

HRQoL, health-related quality of life; PedsQL, Pediatric Quality of Life.

- Individual patient data showed that ItchRO treatment response at week 48 was consistently associated with clinically meaningful improvements in all measures of HRQoL (**Figure 1**).
- Multivariate regression analysis demonstrated that ItchRO treatment response was associated with a clinically meaningful improvement for all three HRQoL measures from baseline to week 48.
- Responders' Family Impact Scale scores increased an average of 16.9 points, more than three times the MCID, over the 48 weeks compared with non-responders (p=0.05) (**Table 3**).
- Responders' PedsQL Generic Core Total Scale Score increased on average by 8.8 points (p=0.19), almost two times the MCID, compared with non-responders. Similarly, for the Multidimensional Fatigue score, responders had an average total score increase of 13.9 points (p=0.11), more than two times the MCID, compared with non-responders (**Table 3**).
- Results remained robust even after controlling for demographic and clinical characteristics.
- Of the 19 HRQoL items selected for individual analysis, six sleep-related items demonstrated significantly larger changes from baseline to week 48 in responders compared with non-responders (**Table 4**).

Figure 1. HRQoL scores at baseline and week 48 according to ItchRO response status; PedsQL Generic Core Total Scale Score (**A**), Family Impact Total Scale Score (**B**) and Multidimensional Fatigue Total Scale Score (**C**).



HRQoL, health-related quality of life; ItchRO, Itch-Reported Outcome; PedsQL, Pediatric Quality of Life.

Unfilled squares and green arrows represent the mean treatment response and HRQoL values at baseline and week 48 among all responders and non-responders. Individual changes from baseline (unfilled circles) to week 48 (filled circles) are shown for responders (pink circles and arrows) and non-responders (blue circles and arrows). All arrows are directional according to baseline and week 48.

Table 3. Multivariate regression models of ItchRO treatment response at week 48 versus PedsQL Generic Core Total Scale Score, Family Impact Total Scale Score, and Multidimensional Fatigue Total Scale Score at week 48.

	PedsQL Generic Core Scale (N = 27) AIC = 226.34		Family Impact Scale (N = 26) AIC = 229.26		Multidimensional Fatigue Scale (N = 21) AIC = 175.86	
Effect	Beta	p-value	Beta	p-value	Beta	p-value
Intercept	8.82 (−2.64; 20.27)	0.15	4.31 (−9.12; 17.74)	0.54	11.03 (−3.80; 25.87)	0.16
ItchRO treatment response at week 48 *Yes vs No*	8.76 (−3.86; 21.38)	0.19	16.85 (1.01; 32.68)	0.05	13.92 (−2.49; 30.32)	0.11
HRQoL score, baseline, centered at 50	−0.68 (−1.01; −0.35)	<0.001	−0.56 (−0.94; −0.17)	0.01	−0.82 (−1.11; −0.52)	<0.001

One patient was missing Family Impact Scale scores at baseline or week 48 and six patients were missing Multidimensional Fatigue Scale scores at baseline or week 48 and were not included in the models.

AIC, Akaike information Criterion; HRQoL, health-related quality of life; ItchRO, Itch-Reported Outcome.

Table 4. Difference between responders and non-responders in change from baseline to week 48 in selected HRQoL items.

HRQoL item	Difference in change from baseline to week 48	p-value
Trouble sleeping	45.4	<0.01
Feeling tired	40.1	0.03
Sleeping a lot	55.2	0.01
Difficulty sleeping through the night	52.9	<0.01
Feeling tired upon waking	72.4	<0.001
Taking a lot of naps	40.4	0.02

HRQoL, health-related quality of life

Conclusions

- **Patients with ALGS who experienced a pruritus response while receiving maralixibat treatment, on average, achieved greater improvements in HRQoL from baseline to week 48, versus pruritus non-responders:**
  - **Changes in the Family Impact Scale were statistically significant and clinically meaningful using multivariate regression analysis**
  - **Improvements in the PedsQL Generic Core Scale were almost two times the MCID**
  - **Multidimensional Fatigue Scale changes were more than two times the MCID**
- **Significant improvements in six sleep-related items of the HRQoL scales seen in pruritus responders versus non-responders warrant further investigation into the relationship between response to maralixibat and improvements in sleep disturbance.**
- **These data demonstrate that the significant improvements in pruritus seen with maralixibat at week 48 of the ICONIC study are clinically meaningful and are associated with improvements in patients' quality of life.**

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