Maralixibat treatment response in Alagille syndrome is associated with improved health-related quality of life

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Objective The objective of this study was to assess the impact of treatment response to the ileal bile acid transporter inhibitor maralixibat on health-related quality of life (HRQoL) in children with Alagille syndrome.

Study design This analysis used data from the ICONIC trial, a phase 2 study with a 4-week double-blind, placebo-controlled, randomized drug withdrawal period in children with Alagille syndrome with moderate-to-severe pruritus. Clinically meaningful treatment response to maralixibat was defined a priori as a ≥1-point reduction in the Itch-Reported Outcome (Observer) score, from baseline to week 48. HRQoL was assessed using the Pediatric Quality of Life Inventory Generic Core, Family Impact, and Multidimensional Fatigue scale scores, which were collected via the caregiver. The minimal clinically important difference for HRQoL ranged from 4 to 5 points, depending on the scale.

Results Twenty of the 27 patients (74%) included in this analysis achieved an Itch-Reported Outcome (Observer) treatment response at week 48. The mean (SD) change in Multidimensional Fatigue score was +25.8 (23.0) for responders vs −3.1 (19.8) for nonresponders (P = .03). Smaller and non-statistically significant mean changes were observed for the Pediatric Quality of Life Inventory Generic Core and Family Impact scores. Controlling for baseline Family Impact score, responders' Family Impact scores increased an average of 16.9 points over 48 weeks compared with non-responders (P = .05). Smaller and non-statistically significant point estimates were observed for the Pediatric Quality of Life Inventory Generic Core and Multidimensional Fatigue scores.

Conclusion The significant improvements in pruritus seen with maralixibat at week 48 of the ICONIC study are clinically meaningful and are associated with improved HRQoL. *(J Pediatr 2022;■:1-8).*

Trial registration ClinicalTrials.gov: NCT02160782.

Children with Alagille syndrome typically present with chronic cholestasis manifested by pruritus and failure to thrive, and extrahepatic features such as characteristic facies, cardiovascular, vertebral, ocular, and renal abnormalities.[1,2] The pruritus experienced by children with Alagille syndrome is considered among the most severe of any cholestatic disease and is a major driver of reduced physical and emotional well-being. Children with Alagille syndrome have been shown to have significant impairments in health-related quality of life (HRQoL) compared with an age-matched healthy pediatric population,[3] and HRQoL scores have been negatively correlated with pruritus severity.[3] Cholestatic pruritus related to Alagille syndrome is often refractory to commonly used off-label therapies.[4] Ultimately, the majority of children with Alagille syndrome will require a liver transplant by adulthood, with intractable pruritus as a leading indication.[5,6]

Maralixibat (Livmarli, Mirum Pharmaceuticals, Inc) is an oral, minimally absorbed ileal bile acid transporter inhibitor that interrupts the enterohepatic circulation of bile acids.[7,8] This is the first agent to demonstrate significant, durable, and clinically meaningful improvements in pruritus among children with Alagille syndrome. In the pivotal ICONIC phase 2b study, maralixibat treatment resulted in significant improvements in pruritus in children with Alagille syndrome

HRQoL	Health-related quality of life
ItchRO(Obs)	Itch-Reported Outcome (Observer)
MCID	Minimal clinically important difference
PedsQL	Pediatric Quality of Life Inventory

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Portions of this study were presented as posters during the North American Society for Pediatric Gastroenterology (NASPGHAN) Annual Meeting, December 12–18, 2021, Virtual, USA and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Annual Meeting; June 22–25, 2022, Copenhagen, Denmark. (NASPGHAN: Poster 305; ESPGHAN Poster H-P-057).

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at weeks 18 and 48 of therapy.[9] Briefly, pruritus scores in participants who received placebo during the randomized withdrawal period returned to levels similar to baseline, whereas the treatment effect was maintained in patients who continued with maralixibat treatment. Further significant improvements in pruritus were observed with maralixibat up to week 48 and in participants who continued with the long-term extension study to week 204. Maralixibat is now approved in the US for the treatment of cholestatic pruritus in patients with Alagille syndrome aged 1 year or older.[10]

This study analyzed data collected during the ICONIC study to assess the impact of maralixibat treatment response on changes in HRQoL among children with Alagille syndrome.

Methods

This analysis used data from the ICONIC trial (LUM001-304; NCT02160782), an international, multicenter, long-term, phase 2b, placebo-controlled, randomized drug-withdrawal study with an open-label extension, in children with Alagille syndrome experiencing moderate-to-severe pruritus.[9] Patients were included from 9 locations in Europe and Australia. This prespecified subanalysis of ICONIC compares HRQoL data at baseline and at week 48, in children between the ages of 1 and 18 years with a clinical diagnosis of Alagille syndrome.

Key inclusion criteria of the ICONIC trial were evidence of cholestasis (total serum bile acid >3x the upper limit of normal for age [defined as 8 μmol/L], and intractable pruritus [defined as an Itch-Reported Outcome (Observer) [ItchRO{Obs}] score >2 for 2 consecutive weeks during the screening period, prior to dosing]). ItchRO(Obs) is a pruritus scale assessed by the caregiver, with higher scores indicating increased itch severity (0 = none to 4 = very severe). Key exclusion criteria were previous surgical interruption of the enterohepatic circulation, liver transplantation (including listing for transplantation), decompensated liver cirrhosis, or history of another associated liver disease. Patients receiving concomitant antipruritic medications had to remain on stable dosage until completion of the randomized withdrawal period or week 22.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by institutional review boards and ethics committees. Written informed consent (and assent) was obtained from the patients' legal guardian (and patients when appropriate).

Treatment Response

Treatment response to maralixibat was defined a priori as a ≥1-point reduction in ItchRO(Obs) score (a pruritus response), from baseline to week 48, where a ≥1-point reduction has been validated as a clinically meaningful improvement.[11] Caregivers reported the itch severity for patients in the mornings using an eDiary. Weekly morning average scores were calculated as the average of the morning scores of the 7 days before the scheduled visit.

End points

HRQoL was measured in all patients, irrespective of response to maralixibat, using the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales. PedsQL is a 23-item modular instrument designed to measure HRQoL in children and adolescents, encompassing physical functioning, emotional functioning, social functioning, and school functioning.[12] The reliability and feasibility of the PedsQL instrument has been validated in several pediatric populations, including those that are healthy, and those with chronic health conditions.[13-16] PedsQL questionnaires, including the PedsQL Generic Core Scale, PedsQL 2.0 Family Impact Module, and PedsQL Multidimensional Fatigue Scales were prospectively collected via a caregiver proxy report at baseline and weeks 18, 22, and 48 during the ICONIC study, and analyzed retrospectively. Measurements from baseline and week 48 were included in this analysis. For each item of the PedsQL instrument (parent and patient), a 5-point response scale was used (0 = never, 1 = almost never, 2 = sometimes, 3 = often, 4 = almost always). Items were reverse-scored and linearly transformed to a 0–100 scale, so that higher scores indicated better HRQoL.[17] The minimal clinically important difference (MCID) for the PedsQL scales ranged from 4 to 5 points, depending on the scale. This was validated based on previous analyses.[13]

As these scales were not specifically developed for an Alagille syndrome population, a subset of individual items from the HRQoL scales deemed most relevant to patients with Alagille syndrome was independently selected by clinical experts for assessment with treatment response.

Statistical Analyses

Patient demographics, baseline clinical characteristics, and changes from baseline to week 48 in HRQoL total scores and selected individual scale items were described and stratified by treatment response status. Frequencies and proportions were reported for categorical variables, and means and SDs were reported for continuous variables. Statistical comparisons were conducted using t tests or ANOVA for continuous variables and χ^2 tests for categorical variables. Multivariable linear regression models were used to assess the relationship between the mean change from baseline in HRQoL score (dependent variable) and treatment response (independent variable), adjusting for baseline HRQoL (model 1), and an interaction term between treatment response and baseline HRQoL (model 2). Adjustment for additional covariates was also explored for the following baseline variables: age, sex, bilirubin, rifampicin use, height z-score, weight z-score, ItchRO(Obs), and serum bile acid (model 3). Adjustments for multiplicity were not performed in this analysis. Data were analyzed using R, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The ICONIC study population included 31 patients enrolled between October 2014 and August 2015.[9] A total of 27 patients, 18 (67%) men, with Alagille syndrome were included in this analysis up to week 48 (3 patients withdrew from the study due to adverse events and 1 patient was missing Family Impact Scale scores). At baseline, patients had a mean (SD) age of 5.7 (4.3) years, total bilirubin of 5.0 (4.7) mg/dL, and serum bile acid of 266.1 (213.9) μmol/L (**Table I**). The mean (SD) ItchRO(Obs) score was 2.9 (0.6) (**Table I**). All but 1 patient were taking stable concomitant medications at baseline (ursodeoxycholic acid, n = 21; rifampicin, n = 21).

At week 48, a clinically meaningful ItchRO(Obs) treatment response, defined as a ≥1-point reduction in the ItchRO(Obs) score, was observed in 20 patients (74%); hereafter referred to as "responders." Baseline characteristics, including HRQoL and pruritus scores, were generally well balanced among responders and nonresponders (patients who did not show an ItchRO[Obs] response to maralixibat treatment), with no statistically significant differences between groups (**Figure 1**, **Table I**; **Table II** available at www.jpeds.com).

The baseline mean (SD) PedsQL Generic Core Total Scale score was 58.8 (17.9) in responders and 61.2 (15.1) in nonresponders (**Figure 1**, **Table II**). The baseline Family Impact Total Scale score among responders and nonresponders was 56.1 (19.2) and 50.8 (18.5), respectively. Responders had a baseline mean (SD) Multidimensional Fatigue Total Scale score of 48.9 (22.0), which was lower than that of nonresponders; 67.4 (20.9); $P = .15$ (**Figure 1**, **Table II**).

HRQoL

Clinically meaningful improvements across HRQoL scales from baseline to week 48 were experienced by responders to maralixibat treatment (those with an ItchRO[Obs] response) (**Figure 1**, **Table II**). In contrast, the average change in HRQoL scores from baseline to week 48 for nonresponders was not clinically meaningful. The mean (SD) change in the Multidimensional Fatigue Total Scale score was +25.8 (23.0) for responders vs −3.1 (19.8) for nonresponders; $P = .03$. Similar results were seen with the Family Impact Total Scale score (mean [SD] +17.8 [23.4] for responders vs +3.9 [7.8] for nonresponders; $P = .14$) and PedsQL Generic Core Total Scale score (mean [SD] +11.6 [20.3] for responders vs +1.2 [11.1] in nonresponders; $P = .21$).

Individual patient data showed that ItchRO(Obs) treatment response at week 48 was consistently associated with clinically meaningful improvements in PedsQL Generic Core Scale and Family Impact Total Scale scores (**Figure 2**; **Figure 3** available at www.jpeds.com).

Absolute changes in PedsQL Generic Core Scale, Family Impact, and Multidimensional Fatigue Total Scale scores, according to change in ItchRO(Obs) score from baseline for each patient, are shown in **Figure 3**. A 5-point change in the PedsQL Generic Core Total Scale score was observed in 13 of 20 (65%) responders and 3 of 7 (43%) nonresponders; $P = .39$; a 10-point change in the PedsQL Generic Core Total Scale score was observed in 10 of 20 (50%) responders and 2 of 7 (29%) nonresponders; $P = .41$. A similar pattern was reported for the Family Impact Total Scale score and Multidimensional Fatigue Scale score, with a higher proportion of responders achieving 5- and 10-point changes compared with nonresponders (data not shown).

Multivariable linear regression analysis demonstrated that the ItchRO(Obs) treatment response was associated with a clinically meaningful improvement in all 3 HRQoL measures (defined as a change greater than the MCID of 4–5 points)[13] from baseline to week 48. These results were most striking for the Family Impact Total Scale score. Controlling for the baseline Family Impact Total Scale score, responders' ItchRO(Obs) scores increased by an average of 16.9 points, more than 3 times the MCID of 5 points,[13] over the 48 weeks, compared with nonresponders; $P < .05$ (**Table III**). When adjusting for the interaction term between treatment response and baseline HRQoL, model results indicate that responders with a lower Family Impact Total Scale score at baseline had, on average, larger improvements in HRQoL at week 48, compared with responders who had a higher

Table I. Baseline characteristics in maralixibat responders and nonresponders

Characteristic	Baseline, overall (n = 27)	ItchRO(Obs)* treatment response at wk 48		*P* value	Change from baseline to wk 48, overall (n = 27)
		Responders (n = 20)	Nonresponders (n = 7)		
Age, y	5.70 ± 4.30	6.55 ± 4.17	3.29 ± 3.99	.08	–
Male, n (%)	18 (66.67)	14 (70.00)	4 (57.14)	.65	–
Height z-score	−1.52 ± 1.24	−1.41 ± 1.33	−1.85 ± 0.92	.43	0.18 ± 0.51
Weight z-score	−1.48 ± 0.97	−1.48 ± 1.04	−1.49 ± 0.81	.99	0.03 ± 0.43
BMI z-score	−0.61 ± 0.84	−0.70 ± 0.81	−0.35 ± 0.93	.36	−0.15 ± 0.56
sBA, μmol/L	266.05 ± 213.86	271.62 ± 236.61	250.15 ± 143.19	.82	−96.44 ± 166.63
Total bilirubin, mg/dL	5.04 ± 4.73	4.47 ± 4.13	6.67 ± 6.22	.30	0.07 ± 1.90
CSS score	3.26 ± 0.94	3.25 ± 1.02	3.29 ± 0.76	.93	−1.81 ± 1.30
ItchRO(Obs)*	2.90 ± 0.56	2.97 ± 0.55	2.68 ± 0.58	.25	−1.64 ± 1.32

BMI, body mass index; *CSS*, Clinician Scratch Scale; *sBA*, serum bile acid.
Data are mean ± SD unless otherwise indicated. *P* value is for the comparison of baseline characteristics according to treatment response status.
*ItchRO(Obs) is a clinical outcome assessment measure of pruritus, reported by the caregiver.

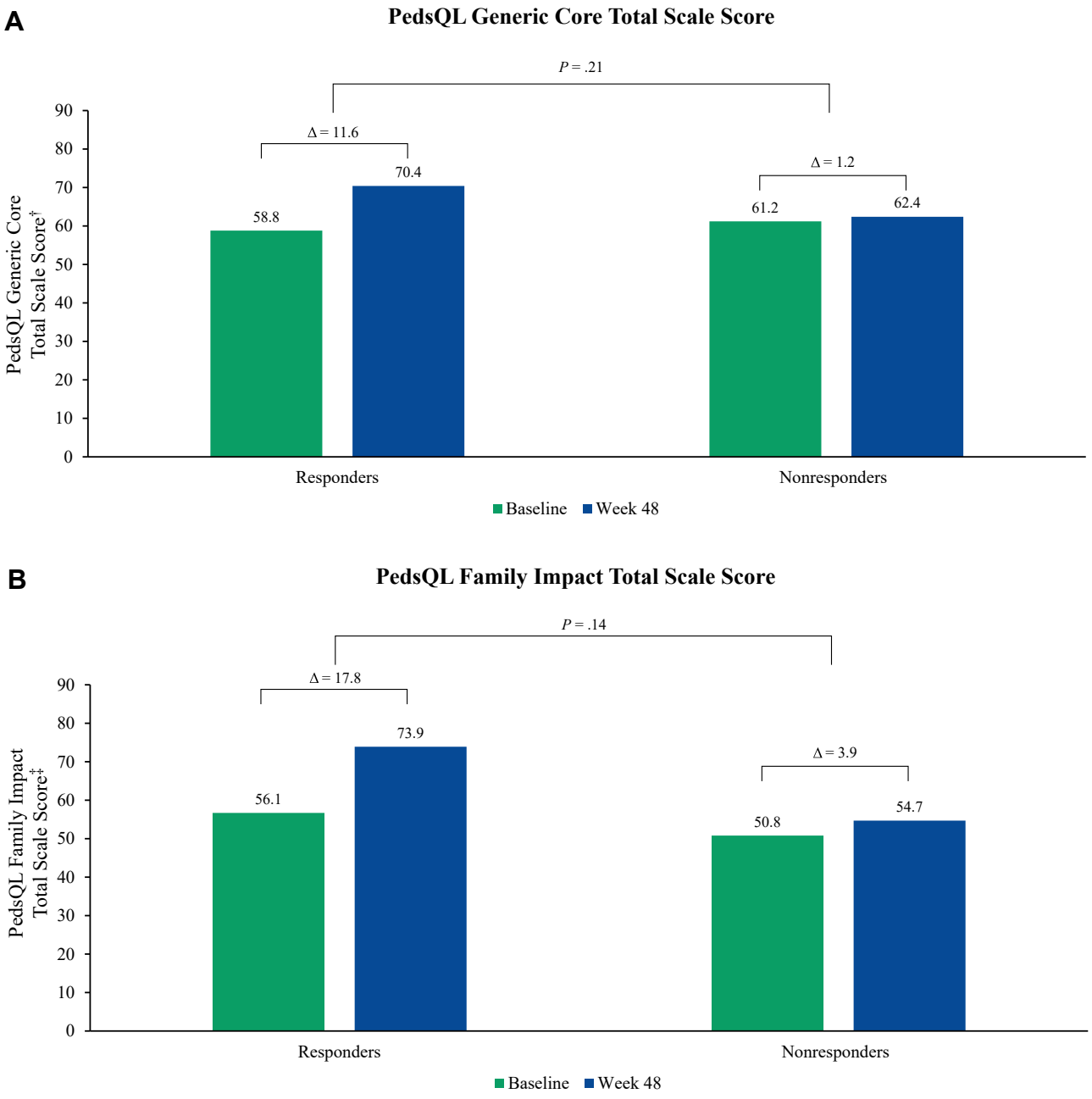

Figure 1. Change in HRQoL measures from baseline to week 48 in ItchRO(Obs)* responders and nonresponders to maralixibat treatment. **A,** Change in PedsQL Generic Core Total Scale score; **B,** Family Impact Total Scale score; and **C**, Multidimensional Fatigue Total Scale score. Data are mean ± SD. *ItchRO(Obs) is a clinical outcome assessment measure of pruritus, reported by the caregiver. †n = 27 patients had PedsQL Generic Core Total Scale data available at baseline and week 48; ‡n = 26 patients had Family Impact Total Scale data available at baseline and week 48; one patient had missing data at week 48; §n = 21 patients had Multidimensional Fatigue Total Scale data available at baseline and week 48; 6 patients had missing data at week 48.

total score at baseline (**Table IV**; available at www.jpeds.com).

Smaller and nonstatistically significant point estimates were observed for the PedsQL Generic Core Scale (**Table III**, **Table V**; available at www.jpeds.com) and Multidimensional Fatigue Total Scale scores (**Table III**, **Table VI**; available at www.jpeds.com). Controlling for baseline PedsQL Generic Core Total Scale score, responders' total score increased on average by 8.8 points (P = .19), almost 2 times the MCID, compared with nonresponders. Responders with the same Multidimensional Fatigue Total Scale score at baseline had an average total score increase of 13.9 points (P = .11),

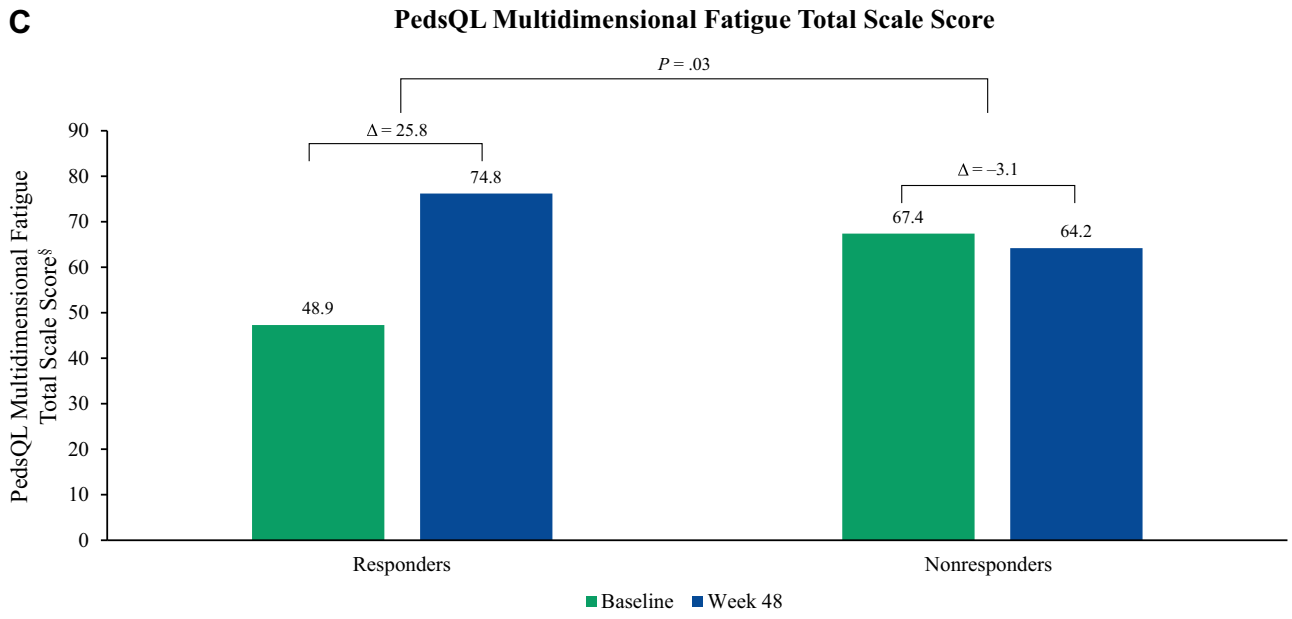

Figure 1. Continued.

nearly 3 times the MCID, compared with nonresponders. These results remained robust even after controlling for demographic and clinical characteristics.

Of the 19 HRQoL items selected for individual analysis, 6 sleep-related items demonstrated significantly larger changes from baseline to week 48 in responders compared with nonresponders: trouble sleeping ($\Delta = 45.4$, $P = .001$), feeling tired ($\Delta = 40.1$, $P = .03$), sleeping a lot ($\Delta = 55.2$, $P = .014$), difficulty sleeping through the night ($\Delta = 52.9$, $P = .003$), feeling tired upon waking ($\Delta = 72.4$, $P < .001$), and taking a lot of naps ($\Delta = 40.4$, $P = .02$) (**Table VII**; available at www.jpeds.com).

Discussion

In this cohort of children with Alagille syndrome, ItchRO(Obs) treatment response at week 48 was associated with clinically meaningful improvement in HRQoL from baseline to week 48. Responders experienced a significantly greater change in the Family Impact Total Scale score and Multidimensional Fatigue Total Scale score, and a numerically higher increase in the PedsQL Generic Core Total Scale score compared with nonresponders. Across all domains evaluated, the average increase in responders' HRQoL scores from baseline to week 48 well exceeded the MCID: by over 3 times for Family Impact, over 5 times for Multidimensional Fatigue, and over 2 times for the PedsQL Generic Core scales. In comparison, the average increase in scores in each domain among nonresponders did not meet the MCID. These data indicate a robust and clinically meaningful improvement in HRQoL among patients who responded to maralixibat, which is correlated with a reduction in pruritus.

In a previous study, pruritus did not influence HRQoL.[18] This may be due to the fact that clinician scratch scales were relied on to quantify pruritus, rather than a patient/caregiver scale. Further, the Family Impact and Multidimensional Fatigue scales were not utilized in that study potentially contributing to those results. In this analysis, the baseline demographic was one of moderate-to-severe pruritus at study entry, despite the majority (96%) of patients taking stable concomitant antipruritic medications at baseline. However, this analysis demonstrated a clear association between pruritus and HRQoL, with improved scores across all domains in patients who responded to maralixibat, thereby demonstrating that successful treatment of pruritus in patients with Alagille syndrome can have a positive impact on their quality of life. A key strength of this analysis is that reductions in pruritus were measured over 48 weeks. Thus, the associated increases in HRQoL are durable over a long time frame. A previous cross-sectional study found no correlation between pruritus severity and HRQoL in patients with Alagille syndrome when measured at baseline, prior to treatment with maralixibat[19]; however, that analysis explored only baseline scores where all patients had severe pruritus with high ItchRO(Obs) scores, likely impeding demonstration of the correlation between pruritus severity and HRQoL, particularly as only one pretreatment data point was assessed.

These findings are further reinforced by multivariable linear regression analysis, which showed the most striking association between ItchRO(Obs) treatment response and HRQoL improvement at week 48 in the Family Impact Scale. In this domain, responders had an increase of over 3 times the MCID compared with nonresponders. Results were consistent when controlling for additional baseline covariates. Patients with lower HRQoL at baseline appeared to

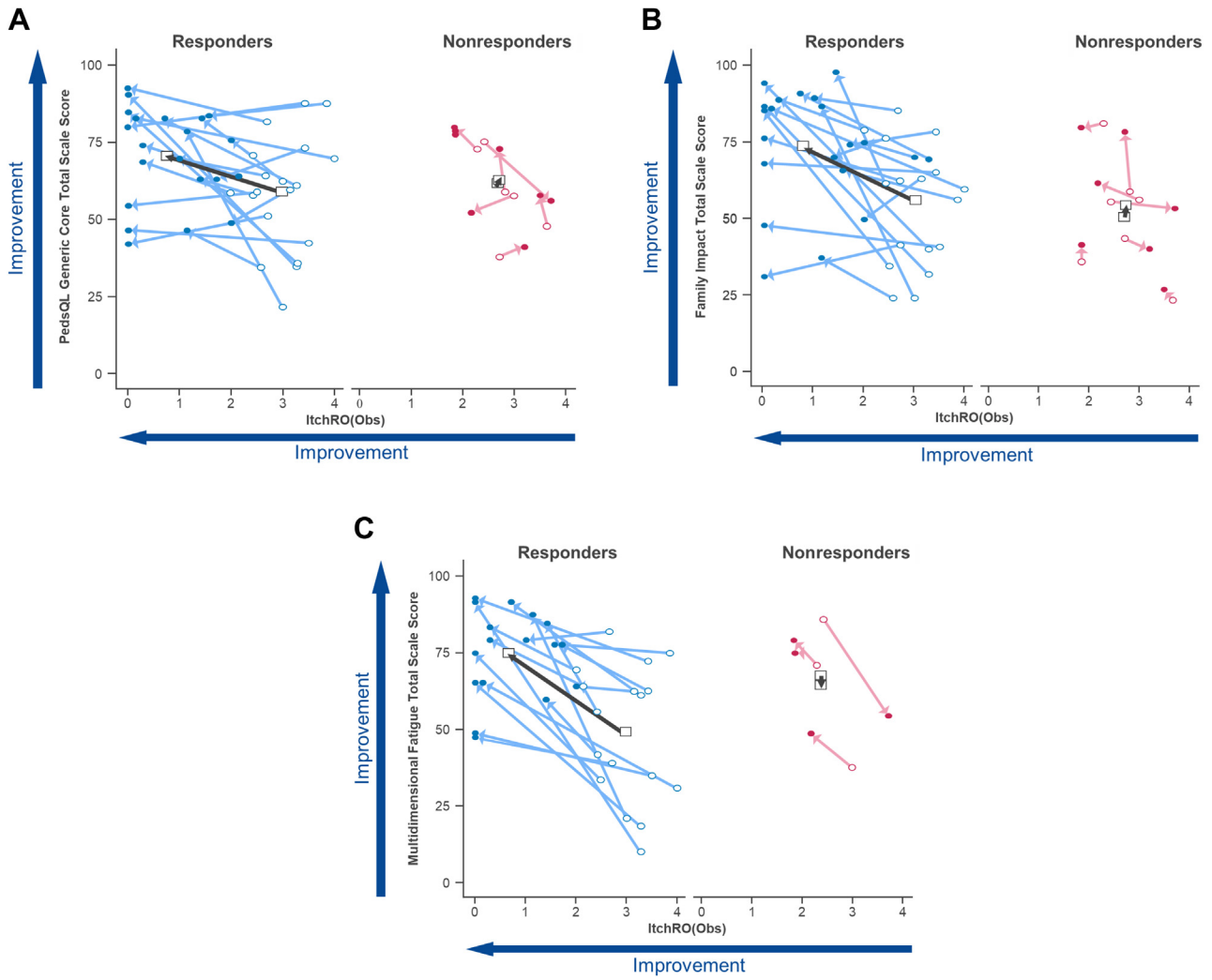

Figure 2. HRQoL scores at baseline and week 48 according to ItchRO(Obs)* treatment response status. **A**, PedsQL Generic Core Total Scale score; **B**, Family Impact Total Scale score; and **C**, Multidimensional Fatigue Total Scale score. Unfilled squares and black arrows represent the mean treatment response and HRQoL values at baseline and week 48 among all responders and nonresponders. Individual changes from baseline (unfilled circles) to week 48 (filled circles) are shown for responders (blue circles and arrows) and nonresponders (pink circles and arrows). All arrows are directional according to score increases/decreases. *ItchRO(Obs) is a clinical outcome assessment measure of pruritus, reported by the caregiver.

derive the greatest benefit of the treatment effects of maralixibat on HRQoL, compared with responders who had a higher HRQoL at baseline.

Patients with Alagille syndrome have disrupted sleep as a result of pruritus, and lower scores on HRQoL measures.[19,20] Of the 19 HRQoL items selected for individual analysis, 6 sleep-related items in particular demonstrated significantly larger changes from baseline to week 48 in responders compared with nonresponders.

Although investigations of HRQoL in Alagille syndrome and other causes of chronic pediatric liver disease are limited, children with Alagille syndrome have significantly impaired HRQoL compared with healthy children, or those with alpha-1-antitrypsin deficiency, and modestly impaired HRQoL scores when compared with children with other causes of chronic intrahepatic cholestasis.[18] For comparison, the HRQoL scores that have been described in patients with Alagille syndrome are also notably lower than those among pediatric patients with functional and organic gastrointestinal disorders.[14]

To date, maralixibat has been studied in 86 pediatric patients with cholestatic liver disease, including 31 patients in the phase 2b ICONIC study, and was generally well tolerated.[9,21] Diarrhea and abdominal pain were the most common adverse events. These were mild-to-moderate in severity and transient in nature, occurring mostly in the first 4 weeks of treatment and resolving within 1 week and therefore are unlikely to have had a significant impact on the patients' HRQoL.

Table III. Multivariable linear regression models of ItchRO(Obs)* treatment response at week 48 vs. Total Scale scores for the PedsQL Generic Core Scale, Family Impact Scale, and Multidimensional Fatigue Scale at week 48

	PedsQL generic core scale total scale score (n = 27; AIC = 226.34)		PedsQL family impact total scale score (n = 26; AIC = 229.26)		PedsQL multidimensional fatigue total scale score (n = 21; AIC = 175.86)	
Effect	**Beta (95% CI)**	***P* value**	**Beta (95% CI)**	***P* value**	**Beta (95% CI)**	***P* value**
Intercept	8.82 (−2.64; 20.27)	.15	4.31 (−9.12; 17.74)	.54	11.03 (−3.80; 25.87)	.16
ItchRO(Obs)* treatment response at wk 48 Yes vs No	8.76 (−3.86; 21.38)	.19	16.85 (1.01; 32.68)	.05	13.92 (−2.49; 30.32)	.11
HRQoL score, baseline (centered at 50)	−0.68 (−1.01; −0.35)	< .001	−0.56 (−0.94; −0.17)	.01	−0.82 (−1.11; −0.52)	< .001†

AIC, Akaike information criterion
Baseline HRQoL scores were centered at 50 (the median of the HRQoL scales) by subtracting 50 from each patient's individual HRQoL score to ease interpretation. One patient was missing PedsQL Family Impact Total Scale scores at baseline or week 48 and was not included in the models. Six patients were missing PedsQL Multidimensional Fatigue Total Scale scores at baseline or week 48 and were not included in the models.
*ItchRO(Obs) is a clinical outcome assessment measure of pruritus, reported by the caregiver.
†Statistical significance.

Certain limitations of this subanalysis should be noted. First, PedsQL has not been optimized for pediatric patients with cholestatic diseases. However, as shown previously, PedsQL remains a common instrument of choice for measurement of HRQoL in pediatric populations. The feasibility, reliability, and validity of PedsQL as a pediatric population health outcome measure have been demonstrated.[13] Another limitation is that the ICONIC study was designed so that patients in the placebo arm received placebo only during the randomized-withdrawal period, rather than for the full 48-week period, therefore a HRQoL comparison between treated and untreated patients was not possible.[9] This analysis was also limited by small sample sizes, in some cases due to missing data, meaning some of the analyses may have been underpowered. In addition to this, the long-term assessment, beyond 48 weeks of treatment response on HRQoL, was not feasible due to patient attrition over time. Additional research could assess whether maralixibat treatment response translates to improvements in HRQoL that last beyond 48 weeks. In addition, this study did not adjust for multiplicity. However, prior analyses using these data also did not adjust for multiplicity, and the consistent directional and statistical trends across outcomes and items instill confidence in the conclusions.[9]

The extrahepatic involvement of Alagille syndrome, which may also contribute to the lower HRQoL in these patients, was not accounted for in this analysis. However, it is not expected that these extrahepatic conditions would be affected by maralixibat treatment. The recent approval of maralixibat in the clinical setting[10] will lead to the generation of real-world data exploring the impact of maralixibat on HRQoL.

In conclusion, patients with Alagille syndrome who experienced a pruritus response while receiving maralixibat treatment, on average, achieved greater improvements in HRQoL from baseline to week 48, vs pruritus nonresponders. Using multivariable linear regression analysis, changes in the Family Impact Total Scale score were statistically significant and clinically meaningful. Individual sleep-related items also showed a statistically significant improvement, possibly because the reductions in pruritus resulted in fewer disruptions to, and a better quality of sleep.

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' HRQoL. As pruritus is a leading indication for liver transplant among patients with Alagille syndrome, ongoing evaluation of outcomes in this pediatric population should include assessment of the future impact of treatment on the burden of liver transplantation. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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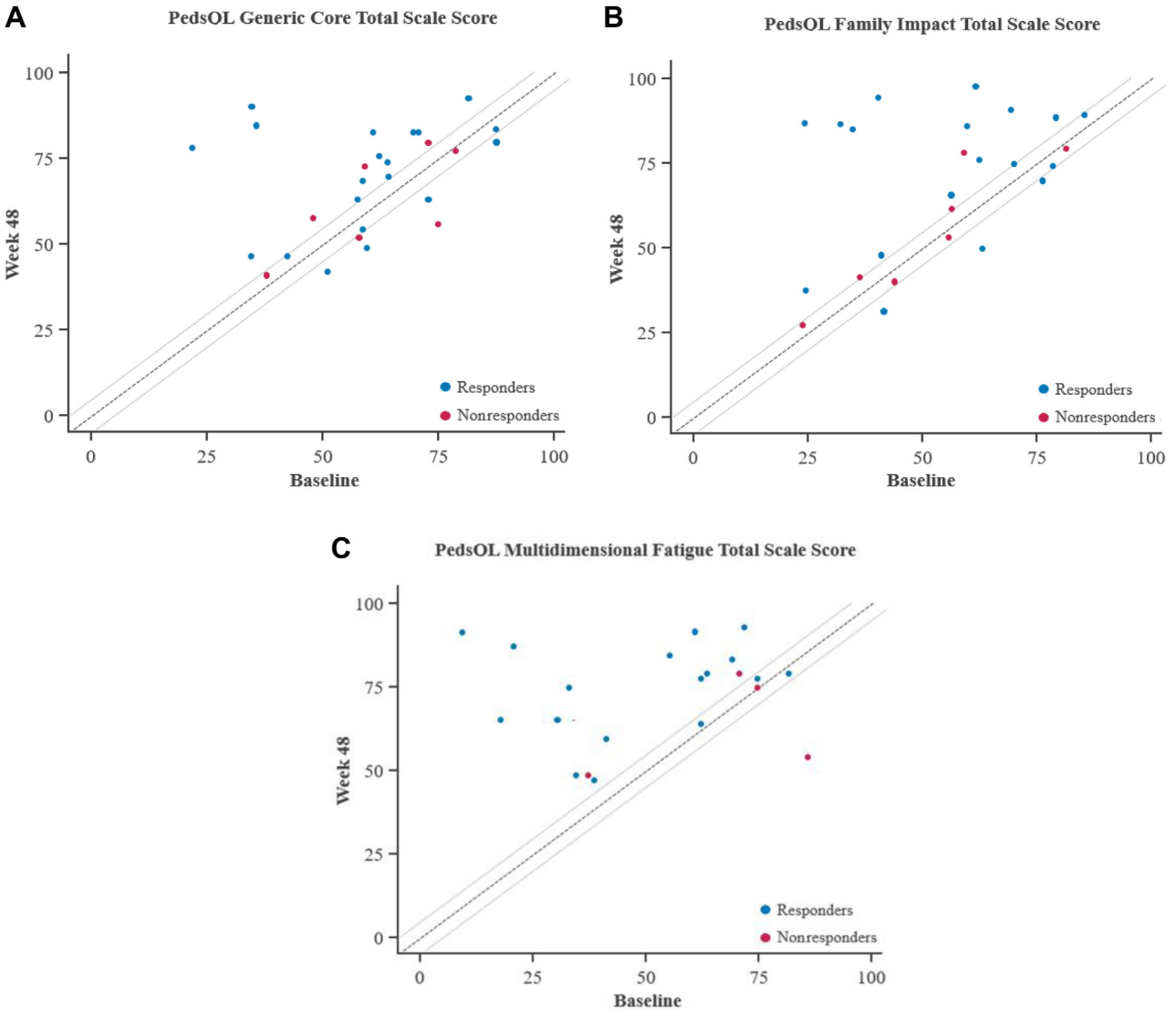

Figure 3. HRQoL scores at baseline vs week 48 according to change in ItchRO(Obs)* score. **A**, PedsQL Generic Core Total Scale score; **B**, Family Impact Total Scale score; and **C**, Multidimensional Fatigue Total Scale score. Gray dashed lines represent 1-point MCID change in HRQoL from baseline to week 48 (±5 points). Each circle represents 1 patient (blue circle = responder; pink circle = nonresponder). Patients outside of the grey dashed lines experienced a change in HRQoL greater than the MCID. The dotted black line represents no change in HRQoL from baseline to week 48. Any patients to the left of the black line experienced an increase in their HRQoL from baseline, and patients to the right of the black line experienced a decrease in their HRQoL from baseline. *ItchRO(Obs) is a clinical outcome assessment measure of pruritus, reported by the caregiver.

Table II. Change in HRQoL measures from baseline to week 48 in ItchRO(Obs)* responders and nonresponders to maralixibat treatment

	HRQoL at baseline				HRQoL at wk 48				HRQoL change from baseline to wk 48			
PedsQL scale	Overall (n = 27)	Responders (n = 20)	Nonresponders (n = 7)	*P* value	Overall (n = 27)	Responders (n = 20)	Nonresponders (n = 7)	*P* value	Overall (n = 27)	Responders (n = 20)	Nonresponders (n = 7)	*P* value
PedsQL Generic Core Total Scale score†	59.4 ± 17.0	58.8 ± 17.9	61.2 ± 15.1	.75	68.3 ± 15.5	70.4 ± 15.7	62.4 ± 14.5	.25	8.9 ± 18.7	11.6 ± 20.3	1.2 ± 11.1	.21
Family Impact Total Scale score‡	54.7 ± 18.8	56.1 ± 19.2	50.8 ± 18.5	.53	68.7 ± 21.1	73.9 ± 19.6	54.7 ± 20.0	.04	14.0 ± 21.2	17.8 ± 23.4	3.9 ± 7.8	.14
Multidimensional Fatigue Scale Total Scale score§	52.5 ± 22.5	48.9 ± 22.0	67.4 ± 20.9	.15	72.8 ± 14.7	74.8 ± 14.3	64.2 ± 15.1	.21	20.3 ± 24.9	25.8 ± 23.0	−3.1 ± 19.8	.03

Data are mean ± SD.
*ItchRO(Obs) is a clinical outcome assessment measure of pruritus, reported by the caregiver.
†n = 27 patients had PedsQL Generic Core Total Scale data available at baseline and week 48.
‡n = 26 patients had Family Impact Total Scale data available at baseline and week 48; one patient had missing data at week 48.
§n = 21 patients had Multidimensional Fatigue Total Scale data available at baseline and week 48; six patients had missing data at week 48.

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Table IV. Multivariable linear regression models of ItchRO(Obs)* treatment response and week 48 PedsQL Family Impact Total Scale score

	Model 1 (n = 26; AIC = 229.26)		Model 2 (n = 26; AIC = 228.32)		Model 3 (n = 26; AIC = 239.09)	
Effect	**Beta (95% CI)**	***P* value**	**Beta (95% CI)**	***P* value**	**Beta (95% CI)**	***P* value**
Intercept	4.31 (−9.12; 17.74)	.54	3.87 (−9.11; 16.86)	.57	6.35 (−60.65; 73.35)	.86
ItchRO(Obs)* treatment response at wk 48 Yes vs. No	16.85 (1.01; 32.68)	.05†	18.32 (2.91; 33.72)	.03†	21.26 (−0.15; 42.67)	.07
PedsQL Family Impact Total Scale score, baseline (centered at 50)	−0.56 (−0.94; −0.17)	.01†	−0.01 (−0.76; 0.75)	.99	0.06 (−0.99; 1.11)	.91
Interaction: ItchRO(Obs)* treatment response and PedsQL Family Impact Total Scale score			−0.72 (−1.59; 0.15)	.12	−0.83 (−2.01; 0.35)	.19
Age at baseline, y					−0.01 (−2.32; 2.30)	.99
Male					−2.23 (−27.55; 23.08)	.87
Total bilirubin, mg/dL					0.22 (−2.28; 2.73)	.86
Rifampicin usage at baseline					14.31 (−14.05; 42.66)	.34
Height z-score					−3.24 (−16.52; 10.05)	.64
Weight z-score					2.39 (−15.78; 20.55)	.80
ItchRO(Obs)* weekly Morning Severity score					−2.68 (−22.36; 17.01)	.79
sBA, μmol/L					−0.03 (−0.08; 0.02)	.20

AIC, Akaike information criterion; *sBA*, serum bile acid.
Baseline HRQoL scores were centered at 50 (the median of the HRQoL scales) by subtracting 50 from each patient's individual HRQoL score to ease interpretation. One patient was missing PedsQL Family Impact Total Scale scores at baseline or week 48 and was not included in the models.
*ItchRO(Obs) is a clinical outcome assessment measure of pruritus, reported by the caregiver.
†Statistical significance.

Table V. Multivariable linear regression models of ItchRO(Obs)* treatment response and week 48 PedsQL Generic Core Total Scale score

	Model 1 (n = 27; AIC = 226.34)		Model 2 (n = 27; AIC = 227.14)		Model 3 (n = 27; AIC = 230.29)	
Effect	**Beta (95% CI)**	***P* value**	**Beta (95% CI)**	***P* value**	**Beta (95% CI)**	***P* value**
Intercept	8.82 (−2.64; 20.27)	.15	4.72 (−9.14; 18.59)	.51	−19.95 (−66.02; 26.12)	.41
ItchRO(Obs)* treatment response at wk 48 Yes vs No	8.76 (−3.86; 21.38)	.19	13.58 (−2.03; 29.19)	.10	21.66 (3.42; 39.91)	.03†
PedsQL Generic Core Total Scale score, baseline (centered at 50)	−0.68 (−1.01; −0.35)	< .001†	−0.31 (−1.09; 0.46)	.44	0.23 (−0.64; 1.11)	.61
Interaction: ItchRO(Obs)* treatment response and PedsQL Generic Core Scale Total Scale score			−0.45 (−1.31; 0.41)	.32	−1.13 (−2.12; −0.14)	.04†
Age at baseline, y					−0.48 (−2.04; 1.08)	.56
Male					−4.43 (−21.52; 12.65)	.62
Total bilirubin, mg/dL					−0.11 (−1.79; 1.57)	.90
Rifampicin usage at baseline					19.42 (−0.11; 38.95)	.07
Height z-score					−3.97 (−12.77; 4.82)	.39
Weight z-score					5.1 (−7.50; 17.70)	.44
ItchRO(Obs)* weekly Morning Severity score					5.57 (−6.90; 18.03)	.40
sBA, μmol/L					−0.02 (−0.05; 0.01)	.26

Baseline HRQoL scores were centered at 50 (the median of the HRQoL scales) by subtracting 50 from each patient's individual HRQoL score to ease interpretation.
*ItchRO(Obs) is a clinical outcome assessment measure of pruritus, reported by the caregiver.
†Statistical significance.

Table VI. Multivariable linear regression models of ItchRO(Obs)* treatment response and week 48 PedsQL Multidimensional Fatigue Total Scale score

	Model 1 (n = 21; AIC = 175.86)		Model 2 (n = 21; AIC = 177.71)		Model 3 (n = 21; AIC = 174.25)	
Effect	**Beta (95% CI)**	***P* value**	**Beta (95% CI)**	***P* value**	**Beta (95% CI)**	***P* value**
Intercept	11.03 (−3.80; 25.87)	.16	8.79 (−11.00; 28.58)	.40	−0.4 (−45.90; 45.09)	.99
ItchRO(Obs)* treatment response at wk 48 Yes vs. No	13.92 (−2.49; 30.32)	.11	16.13 (−4.84; 37.11)	.15	11.41 (−14.14; 36.96)	.40
PedsQL Multidimensional Fatigue Scale Total Scale score, baseline (centered at 50)	−0.82 (−1.11; −0.52)	< .001†	−0.69 (−1.48; 0.10)	.11	−0.59 (−1.77; 0.58)	.35
Interaction: ItchRO(Obs)* treatment response and PedsQL Multidimensional Fatigue Scale Total Scale score			−0.15 (−1.00; 0.70)	.73	−0.34 (−1.49; 0.82)	.58
Age at baseline, y					−1.21 (−3.23; 0.82)	.27
Male					−16.73 (−36.32; 2.85)	.13
Total bilirubin, mg/dL					−0.42 (−2.35; 1.50)	.68
Rifampicin usage at baseline					33.8 (12.91; 54.69)	.01†
Height z-score					−1.79 (−16.37; 12.79)	.82
Weight z-score					−6.07 (−21.06; 8.92)	.45
ItchRO(Obs)* weekly Morning Severity score					2.70 (−9.66; 15.06)	.68
sBA, μmol/L					−0.04 (−0.07; −0.01)	.05†

Baseline HRQoL scores were centered at 50 (the median of the HRQoL scales) by subtracting 50 from each patient's individual HRQoL score to ease interpretation. Six patients were missing PedsQL Multidimensional Fatigue Scale Total Scale scores at baseline or week 48 and were not included in the models.
*ItchRO(Obs) is a clinical outcome assessment measure of pruritus, reported by the caregiver.
†Statistical significance.

Table VII. Change from baseline to week 48 HRQoL item scores, overall and stratified by ItchRO(Obs)* treatment response

		ItchRO(Obs)* treatment response at wk 48*		
	Overall (n = 27)	Responders (n = 20)	Nonresponders (n = 7)	*P* value
PedsQL Generic Core Scale				
Emotional: Trouble sleeping	40.74 ± 34.07	52.50 ± 27.98	7.14 ± 27.82	.001†
Physical: Problem participating in active play or exercise	12.96 ± 40.65	12.50 ± 38.47	14.29 ± 49.70	.92
School: Missing school/daycare to go to the doctor or hospital	13.16 ± 25.51	12.50 ± 27.39	16.67 ± 14.43	.80
Social: Problem playing with other children	0.00 ± 31.08	2.63 ± 33.22	−12.50 ± 14.43	.39
Social: Not able to do things that other children his/her age can do	6.52 ± 33.89	7.89 ± 35.41	0.00 ± 28.87	.68
PedsQL Family Impact Scale				
Communication: Hard to talk about child's health with others	14.42 ± 33.30	19.74 ± 32.89	0.00 ± 32.27	.19
Emotional: Feeling anxious	15.38 ± 42.47	17.11 ± 39.13	10.71 ± 53.73	.74
Physical: Feeling tired during the day	27.88 ± 31.88	32.89 ± 33.39	14.29 ± 24.40	.19
Social: Isolated from others	3.85 ± 34.42	6.58 ± 36.17	−3.57 ± 30.37	.52
Social: Hard to find time for social activities	13.46 ± 35.52	14.47 ± 39.37	10.71 ± 24.40	.82
Social: Not enough energy for social activities	13.46 ± 36.22	14.47 ± 41.93	10.71 ± 13.36	.82
Worry: Worried about child's future	15.38 ± 29.22	14.47 ± 31.53	17.86 ± 23.78	.80
PedsQL Multidimensional Fatigue Scale				
Cognitive: Difficulty keeping his/her attention on things	28.57 ± 34.72	32.35 ± 35.09	12.50 ± 32.27	.32
General: Feeling tired	26.19 ± 33.98	33.82 ± 26.43	−6.25 ± 47.32	.03†
Sleep/Rest: Sleeping a lot	7.14 ± 41.94	17.65 ± 35.09	−37.50 ± 43.30	.014†
Sleep/Rest: Difficulty sleeping through the night	42.86 ± 34.59	52.94 ± 30.47	0.00 ± 0.00	.003†
Sleep/Rest: Feeling tired when he/she wakes up in the morning	27.38 ± 42.50	41.18 ± 27.87	−31.25 ± 47.32	< .001†
Sleep/Rest: Resting a lot	15.48 ± 44.35	23.53 ± 39.99	−18.75 ± 51.54	.09
Sleep/Rest: Taking a lot of naps	20.24 ± 32.23	27.94 ± 30.47	−12.50 ± 14.43	.02†

Means and SDs are shown for continuous characteristics. *P* values are for the comparison of mean scores according to treatment response status and were calculated using t-test or ANOVA for continuous variables.
*ItchRO(Obs) is a clinical outcome assessment measure of pruritus, reported by the caregiver.
†Statistical significance.