Maralixibat treatment response is associated with improved health-related quality of life in patients with bile salt export pump deficiency

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Introduction

- Progressive familial intrahepatic cholestasis (PFIC) is a group of rare disorders which are caused by defects in bile secretion and present with intrahepatic cholestasis.[1]
- Bile salt export pump (BSEP) deficiency (PFIC2), the most common genetic cause of the disease,[2] results in the accumulation of bile acids,[3] leading to a broad range of manifestations that usually present in early childhood, including jaundice, pruritus, failure to thrive, and progressive liver disease.[2,3]
- In particular, the pruritus associated with BSEP deficiency (PFIC2) can have a profound impact on patients' health-related quality of life (HRQoL).[4,5]
- Maralixibat is a novel, oral, minimally absorbed ileal bile acid transporter inhibitor (IBATi) under evaluation for the treatment of PFIC and is approved by the US FDA for the treatment of cholestatic pruritus in patients with Alagille syndrome ≥1 year of age.[6–8]

Aim

- Assess the impact of maralixibat treatment response on HRQoL among children with BSEP deficiency (PFIC2).

Methods

Study design and participants

- INDIGO (LUM001-501; NCT02057718) was an international, multicenter, long-term, Phase 2, open-label study that evaluated the efficacy and safety of maralixibat in children aged 12 months to 18 years with familial intrahepatic cholestasis 1 (FIC1) or BSEP deficiency (PFIC2).[9–11]
  - The study consisted of an initial maralixibat dose-escalation period up to a 266 µg/kg/day oral once-daily dose (equivalent to 280 µg/kg/day of maralixibat chloride), followed by long-term stable dosing where patients were allowed to increase to twice-daily dosing from week 72.[9–11]
- This analysis focused exclusively on children with BSEP deficiency (PFIC2).

Endpoints

- Response to treatment with maralixibat was defined *a priori* as a >75% decrease from baseline or reduction in serum bile acid (sBA) to <102 µmol/L from baseline to week 48.
  - 48 weeks was the defined endpoint as it was the closest timepoint to week 72 where these data were available.
- HRQoL was assessed using the Pediatric Quality of Life (PedsQL) Inventory Generic Core, Family Impact Scale, and Multidimensional Fatigue Scale questionnaires (PedsQL; 0–100 scale, 100 = best quality of life). Data were collected prospectively via caregivers at baseline and week 48, and analyzed retrospectively.
  - The minimal clinically important difference (MCID) for the HRQoL assessments ranges from 4 to 5 points, depending on the scale, as validated in previous analyses.[12]
- A subset of individual items from the HRQoL scales was also selected independently by clinical experts prior to reviewing responses, for their relevance to BSEP deficiency (PFIC2).

Statistical analysis

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

Results

- 22 patients from the INDIGO trial with PFIC2 had HRQoL data available at week 48, and were included in this analysis (patient baseline characteristics are shown in **Table 1**).
- At 48 weeks, 6 patients (28.6%) had achieved a treatment response; 1 patient's week 48 sBA response status was unknown and was therefore excluded; 15 participants did not meet the criteria for sBA response and were categorized as non-responders.
  - Baseline HRQoL was lower among responders than non-responders. Other baseline characteristics were similar between the two groups.

Table 1. Patient baseline characteristics in maralixibat responders and non-responders.

	sBA treatment response at week 48*†		
	Responders (N = 6)‡	**Non-responders (N = 15)**	**p-value**
Age (years)	4.5 ± 3.2	5.0 ± 3.6	0.77
Male, n (%)	2 (33.3)	4 (26.7)	1.00
Height z-score	–1.2 ± 0.7	–1.3 ± 1.0	0.73
Weight z-score	–0.6 ± 0.9	–0.6 ± 0.9	0.90
sBA (µmol/L)	281.6 ± 212.6	390.2 ± 108.9	0.13
PedsQL Generic Core Total Scale Score	58.9 ± 8.3	66.7 ± 14.9	0.25
PedsQL Family Impact Total Score	52.0 ± 13.4	65.2 ± 15.4	0.09
PedsQL Multidimensional Fatigue Scale Score	42.5 ± 11.7	68.5 ± 22.1	0.03
ItchRO(Obs)	2.5 ± 0.6	2.1 ± 0.9	0.33

*One patient was lost to follow-up at week 48 and was therefore not evaluable for sBA treatment response; †18 patients had non-truncating BSEP mutations, and 4 patients had truncating BSEP mutations; ‡Six responders all had non-truncating BSEP mutations.

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

ItchRO(Obs), Itch-Reported Outcome (Observer); PedsQL, Pediatric Quality of Life; sBA, serum bile acid; SD, standard deviation; µmol/L, micromoles/liter.

HRQoL analysis

- Responders experienced an improvement from baseline to week 48 across all HRQoL measures compared with non-responders
  - Statistically significant differences between responders and non-responders were observed in PedsQL Generic Core Score and Multidimensional Fatigue Scores (**Table 2**).
  - The change in Family Impact Score from baseline to week 48 for responders was clinically meaningful, at >1.5 times the MCID, but the difference between responders and non-responders was not statistically significant.
  - Significant differences were observed in PedsQL Generic Core Total Scale Score and Multidimensional Fatigue Total Scale Scores, with a mean (standard deviation) change in score from baseline to week 48 of 20.3 (17.7) and 35.8 (15.1) for responders, compared with –0.8 (10.9) and 0.7 (16.7) for non-responders; p=0.01 and p<0.01, respectively.
  - More responders experience a change of ≥5 points in the PedsQL Generic Core Total Scale Score compared with non-responders (80.0%* vs 15.4%; p=0.02).
  - A ≥10-point change in PedsQL Multidimensional Fatigue Total Scale Score was experienced by all responders (100%) and two non-responders (16.7%).*
- sBA treatment response at week 48 for individual patients was strongly associated with clinically meaningful improvements in PedsQL Generic Core Total Scale Score and Multidimensional Fatigue Total Scale Score (**Figure 1**).

  *One patient and three patients had missing data for these metrics, respectively.

Table 2. HRQoL at baseline, week 48, and change from baseline to week 48, for sBA responders and non-responders to maralixibat treatment.

		PedsQL Generic Core Scale (N = 18)*	**Multi-dimensional Fatigue Scale (N = 16)***	**Family Impact Scale (N = 20)***
HRQoL score at baseline	Responders	59.0 ± 9.3	40.3 ± 12.3	52.0 ± 13.4
	Non-responders	66.8 ± 15.5	68.5 ± 22.1	65.2 ± 15.4
	p-value	0.31	0.03	0.09
HRQoL score at week 48	Responders	79.3 ± 9.5	76.0 ± 13.4	60.0 ± 15.5
	Non-responders	65.9 ± 13.8	69.2 ± 18.5	62.7 ± 16.0
	p-value	0.07	0.51	0.73
HRQoL score change from baseline to week 48	Responders	20.3 ± 17.7	35.8 ± 15.1	8.0 ± 20.7
	5-point change, n (%)†	4 (80.0)	4 (100)	4 (66.7)
	10-point change, n (%)†	3 (60.0)	4 (100)	4 (66.7)
	Non-responders	–0.8 ± 10.9	0.7 ± 16.7	–2.5 ± 9.8
	5-point change, n (%)†	2 (15.4)	3 (25.0)	1 (7.1)
	10-point change, n (%)†	2 (15.4)	2 (16.7)	1 (7.1)
	p-value	0.01	<0.01	0.13

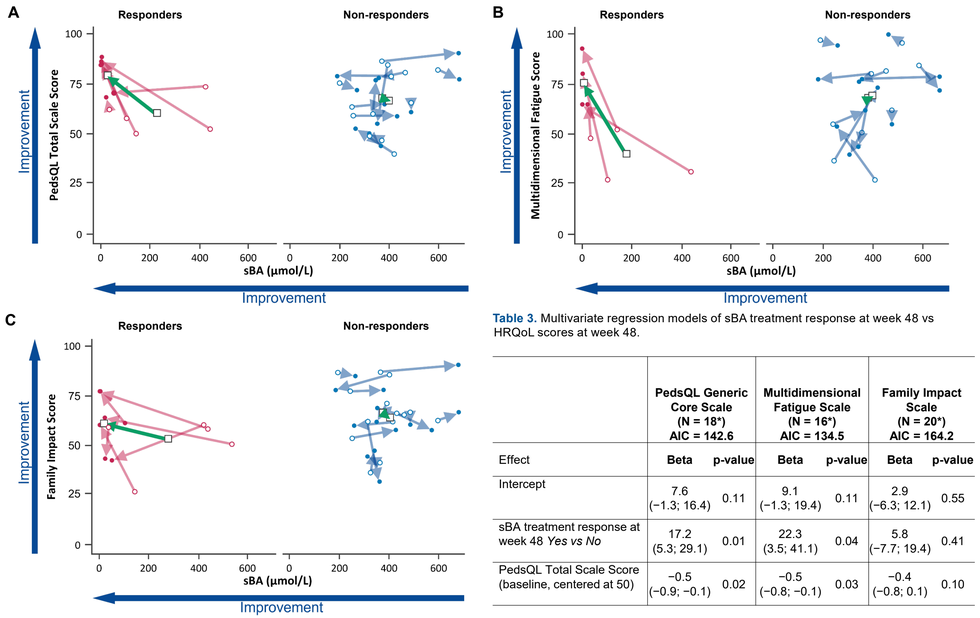
*Of the 21 patients included in the sample, 18 (85.7%), 16 (76.2%), and 20 (95.2%) had available data on PedsQL Generic Core Total Scale Score, Multidimensional Fatigue Total Scale Score, and Family Impact Total Scale Score, respectively, at week 48; †Proportions provided for 5- and 10-point changes were calculated among the number of patients with non-missing week 48 HRQoL data.

All data are mean ± SD unless otherwise stated.

HRQoL, health-related quality of life; PedsQL, Pediatric Quality of Life; sBA, serum bile acid; SD, standard deviation.

- Controlling for baseline PedsQL Generic Core Total Scale Score, multivariate regression analyses found that sBA responders' scores increased by a mean of 17 points, more than three times the MCID,[10] over the 48 weeks compared with non-responders (p<0.05) (**Table 3**).
  - Similarly, for the Multidimensional Fatigue Scale, responders' total scores increased by an average of 22 points compared with non-responders (p<0.05).
  - Smaller and non-statistically significant differences were observed for the Family Impact Total Scale Score.
- Five of the 10 individual HRQoL items in the PedsQL Family Impact Scale, demonstrated significant changes from baseline to week 48 in sBA responders compared with non-responders: feeling tired during the day (p=0.03); worried about how my child's illness is affecting other family members (p<0.01); difficulty sleeping through the night (p<0.01); feeling tired upon waking (p<0.01); and taking a lot of naps (p<0.01).

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



HRQoL, health-related quality of life; PedsQL, Pediatric Quality of Life; sBA, serum bile acid; µmol/L, micromoles/liter.

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 to week 48 are shown for responders (pink dots and arrows) and non-responders (blue dots and arrows). All arrows are directional according to baseline and week 48.

Table 3. Multivariate regression models of sBA treatment response at week 48 vs HRQoL scores at week 48.

	PedsQL Generic Core Scale (N = 18*) AIC = 142.6		**Multidimensional Fatigue Scale (N = 16*) AIC = 134.5**		**Family Impact Scale (N = 20*) AIC = 164.2**	
Effect	**Beta**	**p-value**	**Beta**	**p-value**	**Beta**	**p-value**
Intercept	7.6 (−1.3; 16.4)	0.11	9.1 (−1.3; 19.4)	0.11	2.9 (−6.3; 12.1)	0.55
sBA treatment response at week 48 *Yes vs No*	17.2 (5.3; 29.1)	0.01	22.3 (3.5; 41.1)	0.04	5.8 (−7.7; 19.4)	0.41
PedsQL Total Scale Score (baseline, centered at 50)	−0.5 (−0.9; −0.1)	0.02	−0.5 (−0.8; −0.1)	0.03	−0.4 (−0.8; 0.1)	0.10

*Of the 21 patients included in the sample, 18 (85.7%), 16 (76.2%), and 20 (95.2%) had available data on PedsQL Generic Core Total Scale Score, Multidimensional Fatigue Total Scale Score, and Family Impact Total Scale Score, respectively, at week 48.

AIC, Akaike information criterion; PedsQL, Pediatric Quality of Life; sBA, serum bile acid.

Conclusions

- **Patients with BSEP deficiency (PFIC2) who responded to maralixibat treatment had statistically significant and clinically meaningful improvements in HRQoL (PedsQL Generic Core Total Scale Score, Multidimensional Fatigue Total Scale Score).**
  - **Clinically meaningful improvements were also found in the Family Impact Total Scale Score.**
- **Statistically significant improvements were also seen in sleep and fatigue measures in patients who were maralixibat responders compared with non-responders.**
- **This analysis demonstrates that maralixibat treatment response at week 48, as measured by sBA, in patients with BSEP deficiency (PFIC2), is associated with a statistically significant and clinically meaningful improvement in HRQoL across multiple dimensions.**

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A Goldstein, R Howard, and W Garner are full-time employees of and shareholders in Mirum Pharmaceuticals, Inc.
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