Improvements in Pruritus After Maralixibat Treatment Are Associated With Improved Health-Related Quality of Life for Patients With Cholestatic Liver Disease

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Introduction

- Alagille syndrome (ALGS) and progressive familial intrahepatic cholestasis (PFIC) are rare cholestatic liver diseases associated with severe pruritus along with markedly reduced health-related quality of life (HRQoL).[1,2]
  - Pruritus can lead to self-mutilation, scarring, sleep disturbances, disruption of school activities, decreased school performance, and has a substantial impact on daily functioning, leading to impaired HRQoL.[3,4]
- Maralixibat (MRX) is a minimally absorbed ileal bile acid transporter inhibitor that prevents enterohepatic bile acid recirculation and is approved for[5,6]:
  - Treatment of cholestatic pruritus in patients with ALGS ≥3 months of age in the US and ≥2 months of age in the EU
  - Treatment of cholestatic pruritus in patients with PFIC ≥12 months of age in the US and treatment of PFIC in patients ≥3 months of age in the EU
- ICONIC was a placebo-controlled, randomized withdrawal period, phase 2b study that evaluated safety and efficacy of maralixibat in children (aged 1–18 years) with ALGS (NCT02160782).[7]
  - In ICONIC, participants who received maralixibat achieved significant improvements in sBA, pruritus, xanthomas, height, and HRQoL.[7]
- MARCH was a phase 3, randomized, double-blind, placebo-controlled, 26-week trial investigating the efficacy and safety of maralixibat in participants with PFIC across the broadest range of PFIC types studied to date (NCT03905330).[8,9]
  - In MARCH, participants who received maralixibat achieved statistically significant improvements in pruritus, levels of sBAs, bilirubin, and growth.[8]
  - Significant and sustained responses were observed with up to 2 years of maralixibat treatment in MARCH-ON, an open-label extension study for participants who completed the MARCH study (NCT04185363).[10,11]

Objective

- To report the results of a retrospective analysis assessing the relationship between pruritus and HRQoL measures after maralixibat treatment in:
  - Participants with ALGS in the ICONIC trial (18-week open-label period)
  - Participants with PFIC in the MARCH trial (26-week double-blind period)

Methods

- Pruritus and HRQoL data from the ICONIC and MARCH trials were retrospectively analyzed.
- Pruritus was assessed using the validated Itch-Reported Outcome (Observer) (ItchRO[Obs]) scale, which is a 0 to 4 scale, where 0 = no itch, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.[12] A ≥1-point reduction in ItchRO(Obs) is considered clinically meaningful.
- Impact on HRQoL, indicated by caregivers, was assessed using the Pediatric Quality of Life Inventory (PedsQL) Generic Core, Physical Health (PH), Psychosocial Health (PSH), and Multidimensional Fatigue (MF) scales.
  - PedsQL is a 0-100 scale, with higher scores indicating better QoL.
  - The minimal clinically important difference (MCID) of these assessments is 4-5 points, depending on the scale.
- Spearman correlation coefficients were determined to assess the relationship between ItchRO(Obs) and HRQoL.
  - In ICONIC, average change from Baseline (CFB) in ItchRO(Obs) and HRQoL scores were assessed from Baseline to Week 18 (open-label period).
  - In MARCH, average CFB in ItchRO(Obs) and HRQoL scores were assessed from Baseline to Weeks 18-26.

Results

Table 1. Key Baseline Demographics and Characteristics

Variable[a]	ICONIC[b] (N=31)		MARCH[c]							
			BSEP				All-PFIC			
	Baseline	CFB at Week 18[d]	PBO (n=17)	CFB at Week 26[d]	MRX (n=14)	CFB at Week 26[d]	PBO (n=31)	CFB at Week 26[d]	MRX (n=33)	CFB at Week 26[d]
Age, y	5.4 ± 4.2	-	4.2 ± 3.6	-	6.3 ± 5.2	-	4.4 ± 3.6	-	4.9 ± 4.1	-
Sex, male, %	61	-	35	-	50	-	42	-	52	-
sBA, µmol/L[e]	283 ± 211	-88 (-133, -42)[f]	312 ± 152	11 (-58, 80)	312 ± 158	-176 (-257, -94)[f]	272 ± 147	3 (-42, 48)	254 ± 140	-157 (-200, -115)[f]
ItchRO(Obs)[g]	2.9 ± 0.5	-1.7 (-2.1, -1.4)[f]	2.6 ± 0.9	-0.6 (-1.1, -0.1)[f]	2.9 ± 0.9	-1.7 (-2.3, -1.2)[f]	2.7 ± 0.9	-0.6 (-1.0, -0.2)[f]	2.9 ± 0.9	-1.8 (-2.2, -1.4)[f]
PedsQL[h]	60.3 ± 16.6	11.0 (4.0, 17.0)[f]	65.1 ± 19.4	1.5 (-7.3, 10.4)	47.8 ± 18.6	17.4 (2.2, 32.7)	63.3 ± 16.9	7.2 (0.7, 13.6)	55.8 ± 19.0	16.8 (7.7, 25.9)
PH	64.7 ± 20.0	NR	71.4 ± 23.7	-1.3 (-17.3, 14.8)	52.9 ± 23.5	13.7 (-7.0, 34.4)	65.4 ± 24.9	9.4 (-2.3, 21.1)	61.5 ± 22.4	15.6 (4.3, 26.9)
PSH	57.6 ± 16.7	NR	61.0 ± 19.2	2.9 (-4.0, 9.8)	44.7 ± 19.6	19.3 (5.9, 32.7)	61.6 ± 16.3	5.6 (0.6, 10.7)	52.0 ± 20.2	17.8 (9.3, 26.3)
MF	51.2 ± 22.6	20.0 (9.0, 32.0)[f]	64.2 ± 21.4	6.9 (-1.5, 15.4)	62.0 ± 28.3	17.4 (2.5, 32.2)	71.5 ± 19.8	4.2 (-1.7, 10.0)	57.8 ± 20.4	21.6 (14.6, 28.5)
EDQ sleep disturbance[i]	NR	NR	3.6 ± 1.1	-0.6 (-1.1, -0.05)[f]	3.7 ± 1.0	-1.4 (-2.1, -0.7)[f]	3.7 ± 1.0	-0.6 (-1.0, -0.11)[f]	3.7 ± 0.8	-1.7 (-2.2, -1.3)[f]

[a]Data are mean ± SD, except where otherwise indicated. Values are based on non-missing assessments among the overall populations in ICONIC and MARCH. [b]All participants had confirmed *JAG1* variant. [c]PFIC types included nt-BSEP (n=31), FIC1 (n=13), MDR3 (n=9), TJP2 (n=7), and MYO5B (n=4). [d]Data are mean (95% CI). [e]In MARCH, sBA CFB was assessed using mixed model repeated measures (MMRM) analysis of data from Weeks 18 to 26. [f]Significant 95% CIs (that exclude 0). [g]In MARCH, CFB for ItchRO(Obs) was assessed using MMRM analysis of data from Weeks 15 to 26. [h]In MARCH, PedsQL CFB was assessed at Week 26 using descriptive statistics. [i]The ICONIC study did not measure sleep quality using the exploratory diary questionnaire (EDQ). In MARCH, a subset of questions from the EDQ focused on sleep disturbance were assessed for their relationship to pruritus improvement. CFB was assessed using MMRM analysis of data from Weeks 15 to 26.

Significant Correlations Were Observed Between ItchRO(Obs) and HRQoL Scores After Treatment With Maralixibat

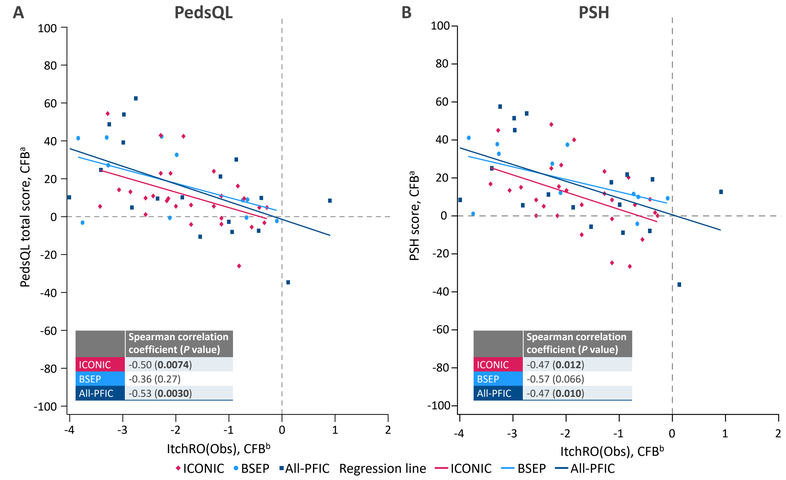
Table 2. Correlations Between ItchRO(Obs) and HRQoL Measures[a]

Variable[b]	ICONIC (N=31)	MARCH			
		BSEP		All-PFIC	
		PBO (n=17)	MRX (n=14)	PBO (n=31)	MRX (n=33)
PedsQL	-0.50 (**0.0074**)	0.28 (0.34)	-0.36 (0.27)	-0.11 (0.61)	-0.53 (**0.0030**)
PH	-0.31 (0.11)	0.56 (**0.037**)	-0.433 (0.18)	0.14 (0.51)	-0.50 (**0.0057**)
PSH	-0.47 (**0.012**)	-0.077 (0.79)	-0.57 (0.066)	-0.41 (**0.039**)	-0.47 (**0.010**)
MF	-0.71 (**0.0002**)	-0.40 (0.29)	-0.69 (0.058)	-0.012 (0.96)	-0.36 (0.11)
EDQ sleep disturbance[c]	NR	0.81 (**0.0014**)	0.88 (**0.0039**)	0.88 (<**0.0001**)	0.96 (<**0.0001**)

[a]Correlations are based on non-missing assessments among the overall populations in ICONIC and MARCH. [b]Data are Spearman correlation coefficient (*P* value). [c]The ICONIC study did not measure sleep quality. In MARCH, a subset of questions from the EDQ focused on sleep disturbance were assessed for their relationship to pruritus improvement.

Reductions in ItchRO(Obs) Scores After Maralixibat Treatment Are Directly Correlated With Improvements in QoL

Figure 1. Correlation of ItchRO(Obs) With (A) PedsQL Total Score and (B) PSH Score



[a]PedsQL and PSH CFB were assessed at Week 18 for ICONIC and were the average CFB of Weeks 18, 22, and 26 for MARCH. [b]ItchRO(Obs) CFB was based on weekly morning average CFB at Week 18 for ICONIC trial or monthly morning average CFB of Weeks 15-18, 19-22, and 23-26 for MARCH trial.

Conclusions

- Improvements in pruritus after treatment with maralixibat were strongly correlated with improvements in HRQoL across multiple domains both in participants with ALGS and in participants with PFIC.
- These results illustrate that the impact of maralixibat on pruritus and HRQoL is robust across different cholestatic liver diseases.

Abbreviations

ALGS, Alagille syndrome; BSEP, bile salt export pump; CFB, change from Baseline; EDQ, exploratory diary questionnaire; FIC1, familial intrahepatic cholestasis-associated protein type 1; HRQoL, health-related quality of life; ItchRO(Obs), Itch-Reported Outcome (Observer); MDR3, multidrug-resistance 3 protein; MF, Multidimensional Fatigue; MMRM, mixed model repeated measures; MRX, maralixibat; MYO5B, myosin VB; NR, not recorded; nt, nontruncated; PBO, placebo; PedsQL, Pediatric Quality of Life Inventory; PFIC, progressive familial intrahepatic cholestasis; PH, Physical Health; PSH, Psychosocial Health; sBA, serum bile acid; SD, standard deviation; TJP2, tight junction protein 2.

Disclosures

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