Pruritus intensity is associated with cholestasis biomarkers and quality of life measures after maralixibat treatment in children with Alagille syndrome

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Introduction

- Alagille syndrome (ALGS) is a rare, genetic, multisystem disorder that commonly presents in infancy.[1]
- Patients with ALGS experience severe cholestatic pruritus due to the accumulation of serum bile acids (sBA).[1]
- ALGS-associated pruritus can be extremely debilitating, resulting in bleeding, scarring, sleep disturbance, fatigue, and decreased quality of life, which can often have a significant impact on the patient and family.[2,3]
- Maralixibat is an apical sodium-dependent bile acid transporter inhibitor that has been shown to significantly reduce levels of sBA and pruritus via interruption of the enterohepatic circulation.[4]
- Absolute values of pruritus intensity and cholestasis biomarkers have been shown to poorly correlate.[5]
- Here, we evaluate how change in pruritus intensity correlates with change in cholestasis biomarkers in the ICONIC study (NCT02160782).

Aim

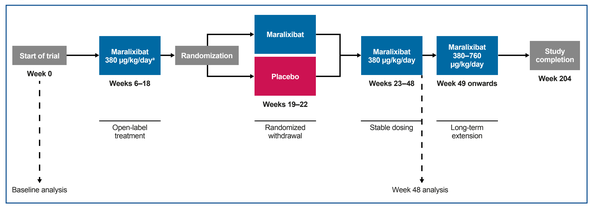
- To characterize correlations between pruritus, as measured by the Itch Reported Outcome Observer (ItchRO[Obs]) tool, and multiple parameters, including sBA and sBA subspecies, autotaxin (ATX), and quality of life measures following maralixibat treatment in children with ALGS.

Methods

Study design

- ICONIC is a long-term, Phase 2, double-blind study assessing the effect of maralixibat treatment in children with ALGS, with an initial placebo-controlled, randomized withdrawal period (**Figure 1**). Participants continue to receive maralixibat in an ongoing rollover study.
  - Participants received doses of 400 µg/kg/day of maralixibat chloride (equivalent to 380 µg/kg/day of maralixibat, and hereafter referred to as 380 µg/kg/day maralixibat) for 18 weeks.
  - During the double-blind, randomized withdrawal period, participants were randomized (1:1) to continue with maralixibat or switch to matching placebo for 4 weeks.
  - After the 4-week randomized withdrawal period, all participants received open-label maralixibat to Week 48.
  - Participants were allowed to enter the long-term extension study.
  - Study measurements included, but were not limited to, pruritus, total and subspecies of sBA, ATX, Pediatric Quality of Life Inventory™ (PedsQL™) assessments, Clinician Scratch Scale (CSS) score, and growth. All assessments were collected at Baseline and Week 48 of the study.

Figure 1. Study design



[a]Includes a 6-week dose escalation period for all participants during the first 6 weeks of the open-label treatment phase and for those who received placebo during the randomized withdrawal phase

Study population

- Key inclusion criteria were:
  - Male or female patients 12 months to 18 years of age, inclusive.
  - Confirmed clinical diagnosis of ALGS as per the ICONIC study protocol.
  - Evidence (biological and/or clinical) of cholestasis, including total sBA level of > 3x upper limit of normal.
  - Moderate-to-severe ALGS-associated pruritus, which was measured as ≥ 2.0 points on the ItchRO(Obs) scale.

Pruritus measurements

- Pruritus intensity was reported using the validated ItchRO(Obs) and CSS scores.
- The ItchRO(Obs) assessment (a five-point scale where 0 = 'no itch' and 4 = 'very severe itch') was completed by caregivers using an electronic diary.[6]
- The CSS score (a five-point scale where 0 = 'no evidence of scratching' and 4 = 'cutaneous mutilation with bleeding, hemorrhage, and scarring') was determined by physician assessment during study visits.

Data analyses

- Data collected and reported herein were taken from the first 48 weeks of treatment.
- Primary objective: to evaluate correlations between multiple parameters associated with pruritus in patients with ALGS:
  - Pruritus intensity was assessed at Baseline and Week 48 using the ItchRO(Obs) tool.
  - sBA, ATX, the CSS score, height z-score, and the PedsQL™ score assessments were also evaluated.

Statistical methods

- *Post-hoc* data analysis assessed pairwise correlations between pruritus intensity (defined by the ItchRO[Obs] score) and cholestasis parameters after Week 48 using Spearman's rank correlation coefficient (rho [*r*]).
- A significant correlation coefficient was confirmed by a p-value of < 0.05, which provided evidence to reject the null hypothesis of no pairwise correlation ($r = 0$).

Results

Baseline characteristics

- Twenty-nine of the 31 enrolled participants completed Week 48, with 27 evaluated for this analysis.
- Baseline characteristics for the analysis population are shown in **Table 1**.

Table 1. Baseline characteristics for analysis population

All participants, N	Mean age, years (SD)[a]	Mean CSS score,[b] points (SD)[a]	Mean sBA,[c] µmol/L (SD)[a]	Mean ItchRO(Obs) score,[d] points (SD)[a]
27	5.7 (4.30)	3.3 (0.94)	266 (213.9)	2.9 (0.56)

[a]SD was used rather than standard error, as stated in the abstract; [b]CSS score range 0–4; [c]normal value of sBA < 10 µmol/L; [d]ItchRO(Obs) score range 0–4
CSS, Clinician Scratch Scale; ItchRO(Obs), Itch Reported Outcome Observer; sBA, serum bile acids; SD, standard deviation

Pruritus associations

- At Week 48, statistically significant correlations with the ItchRO(Obs) score included CSS, sBA, growth (height z-score), and ATX, with a trend towards significance on the PedsQL™ Family Impact Total Scale (PedsQL™ Impact), as shown in **Table 2**.
- Taurocholic acid (TCA) and glycocholic acid (GCA), the subspecies of sBA previously reported to be associated with pruritus improvement in patients with progressive familial intrahepatic cholestasis treated with maralixibat,[7] also exhibited significant correlations with pruritus in patients with ALGS (**Table 2**).
- A statistically significant correlation between the ItchRO(Obs) and PedsQL™ Multidimensional Fatigue Scale (PedsQL™ Fatigue) scores was also noted as a change from Baseline to Week 48 ($r = -0.59$, $p = 0.0053$; **Table 2**).

Table 2. Spearman's rank correlation data exhibiting associations between ItchRO(Obs) score and key parameters

	r	p-value
Parameters correlated with ItchRO(Obs) score at Week 48		
CSS	0.65	0.0002
TCA	0.60	0.0010
GCA	0.53	0.0047
sBA	0.47	0.0123
Height z-score	–0.47	0.0116
ATX	0.44	0.0213
PedsQL™ Impact	–0.38	0.0574
Parameters correlated with ItchRO(Obs) score as a change from Baseline to Week 48		
PedsQL™ Fatigue	–0.59	0.0053

ATX, autotaxin; CSS, Clinician Scratch Scale; GCA, glycocholic acid; ItchRO(Obs), Itch Reported Outcome Observer; PedsQL™, Pediatric Quality of Life Inventory™; PedsQL™ Fatigue, PedsQL™ Multidimensional Fatigue Scale; PedsQL™ Impact, PedsQL™ Family Impact Total Scale; *r*, Spearman's rank correlation coefficient; sBA, serum bile acids; TCA, taurocholic acid

Effect of sBA reductions on intensity of pruritus

- Overall average ItchRO(Obs) score reduction was 1.6 points at Week 48.
- Increasing proportional sBA reductions after 50% appeared to be associated with greater ItchRO(Obs) score reductions (**Table 3**).
- One participant normalized with an ItchRO(Obs) score reduction of –3.5 points.

Table 3. Change in pruritus intensity in relation to changes in sBA

sBA reduction, %	50	60	70	80	90
Change in ItchRO(Obs) score, points	–1.86	–2.12	–2.31	–2.79	–2.71

ItchRO(Obs), Itch Reported Outcome Observer; sBA, serum bile acids

Conclusions

- **Maralixibat treatment in study participants with ALGS led to significant and clinically meaningful improvements in pruritus, using ItchRO(Obs) and CSS scores.**
- **sBA reductions correlated with reductions in pruritus intensity, further supporting the causal relationship between the two.**
- **Significant correlations were also found with ATX and height z-score, with a trend towards significance in the PedsQL™ Impact.**
- **Pruritus was significantly correlated with PedsQL™ Fatigue when assessing change from Baseline to Week 48, suggesting that improvement in sleep is reduced with increased pruritus.**
- **Overall, the positive treatment effects of maralixibat in patients with ALGS demonstrate important correlations with multiple clinically relevant parameters at Week 48.**

ALGS, Alagille syndrome; ATX, autotaxin; CSS, Clinician Scratch Scale; ItchRO(Obs), Itch Reported Outcome Observer; PedsQL™, Pediatric Quality of Life Inventory™; PedsQL™ Fatigue, PedsQL™ Multidimensional Fatigue Scale; PedsQL™ Impact, PedsQL™ Family Impact Total Scale; sBA, serum bile acids

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References
1. Saleh M, Kamath BM, Chitayat D. Alagille syndrome: clinical perspectives. *Appl Clin Genet* 2016;9:75–82
2. Kamath BM, Baker A, Houwen R, *et al*. Systematic review: the epidemiology, natural history, and burden of Alagille syndrome. *J Pediatr Gastroenterol Nutr* 2018;67(2):148–156
3. Elisofon SA, Emerick KM, Sinacore JM, Alonso EM. Health status of patients with Alagille syndrome. *J Pediatr Gastroenterol Nutr* 2010;51(6):759–765
4. Shneider BL, Spino C, Kamath BM, *et al*. Placebo-controlled randomized trial of an intestinal bile salt transport inhibitor for pruritus in Alagille syndrome. *Hepatol Commun* 2018;2(10):1184–1198
5. Kamath BM, Spino C, McLain RM, *et al*. Unraveling the relationship between itching, scratch scales, and biomarkers in children with Alagille syndrome. *Hepatol Commun* 2020;4(7):1012–1018
6. Kamath BM, Abetz-Webb L, Kennedy C, *et al*. Development of a novel tool to assess the impact of itching in pediatric cholestasis. *Patient* 2018;11(1):69–82
7. Zhao X, Vig P, Wardle AJ, Setchell KDR. Differential expression of bile acid subspecies with maralixibat treatment in pruritus responders with bile salt export pump deficiency. Presented at The Digital International Liver Congress™ (ILC), 27–29 August 2020

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