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 their family.[2,3]
- Maralixibat is an ileal bile acid transporter inhibitor (IBATi) that has been shown to significantly reduce levels of sBA and pruritus via interruption of the enterohepatic circulation.[4,5]
- Maralixibat has been approved by the US FDA for the treatment of cholestatic pruritus in patients with ALGS ≥1 year of age.[6]
- So far, absolute values of pruritus intensity and cholestasis biomarkers have been shown to poorly correlate in children with ALGS.[7]
- Here, we evaluate how change in pruritus intensity correlates with change in cholestasis biomarkers in children with ALGS receiving maralixibat (ICONIC study; NCT02160782).

Aim

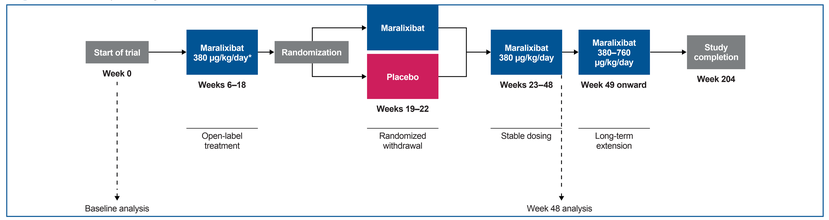
- To characterize correlations between pruritus, as measured by the Itch-Reported Outcome (ItchRO) Observer tool, and multiple parameters, including sBA and sBA subspecies, autotaxin (ATX), and quality of life measures following maralixibat treatment in children with ALGS.

Methods

Study design

- ICONIC is a long-term, Phase 2b, double-blind study assessing the effect of maralixibat treatment in children with ALGS, with a placebo-controlled, randomized withdrawal period (**Figure 1**).[5] 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 (height z-score). All assessments were collected at baseline and week 48 of the study.

Figure 1. Study design.



*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 >3× the upper limit of normal.
  - Moderate-to-severe ALGS-associated pruritus, which was measured as >2.0 points on the ItchRO scale.

Pruritus measurements

- Pruritus intensity was reported using the validated ItchRO and CSS scores.
- The ItchRO assessment (a five-point scale where 0 = "no itch" and 4 = "very severe itch") was completed by caregivers using an electronic diary.[8]
- 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.[9]

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 tool.
  - sBA, ATX, the CSS score, height z-score, and the PedsQL™ assessments were also evaluated.

Statistical methods

- *Post hoc* data analysis assessed pairwise correlations between pruritus intensity (defined by the ItchRO 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 48 weeks of treatment, with 27 evaluated for this analysis.
- Baseline characteristics for the analysis population are shown in **Table 1**.

Table 1. Baseline characteristics for the analysis population.

All participants (N)	Mean (SD) age (years)	Mean (SD) CSS score* (points)	Mean (SD) sBA† (µmol/L)	Mean (SD) ItchRO score‡ (points)
27	5.7 (4.30)	3.3 (0.94)	266 (213.9)	2.9 (0.56)

*CSS score range 0–4; †Normal value of sBA <10 µmol/L; ‡ItchRO score range 0–4.
CSS, Clinician Scratch Scale; ItchRO, Itch-Reported Outcome; L, liter; sBA, serum bile acid; SD, standard deviation; µmol, micromoles.

Pruritus associations

- At week 48, statistically significant correlations with the ItchRO score included CSS score, sBA, growth (height z-score), and ATX, with a trend toward significance with PedsQL™ Family Impact Total Scale (PedsQL™ Impact) scores, 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,[10] also exhibited significant correlations with pruritus in patients with ALGS (**Table 2**).
- A statistically significant correlation between the ItchRO 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 coefficient data exhibiting associations between ItchRO score and key parameters.

	Patients (N)	*r*	p-value
Parameters correlated with ItchRO score at week 48			
CSS	27	0.64	0.0003
TCA	27	0.60	0.0010
GCA	27	0.53	0.0047
sBA	27	0.47	0.0123
Height z-score	27	–0.44	0.0209
ATX	27	0.44	0.0213
PedsQL™ Impact	26	–0.38	0.0574
Parameters correlated with ItchRO score as a change from baseline to week 48			
PedsQL™ Fatigue	21	–0.59	0.0053

ATX, autotaxin; CSS, Clinician Scratch Scale; GCA, glycocholic acid; ItchRO, Itch-Reported Outcome; 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 acid; TCA, taurocholic acid.

Effect of sBA reductions on intensity of pruritus

- The overall average ItchRO score reduction was 1.6 points at week 48.
- Increasing proportional sBA reductions after 50% appeared to be associated with greater ItchRO score reductions (**Table 3**).
- One participant normalized with an ItchRO 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
Patients (N)	8	8	6	3	1
Change in ItchRO score (points)	–1.90	–2.12	–2.31	–2.79	–2.71

ItchRO, Itch-Reported Outcome; sBA, serum bile acid.

Conclusions

- **Maralixibat treatment in study participants with ALGS led to significant and clinically meaningful improvements in pruritus, using ItchRO 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 toward significance with the PedsQL™ Impact scores.**
- **Pruritus was significantly correlated with PedsQL™ Fatigue scores when assessing change from baseline to week 48, suggesting that sleep is improved with decreased pruritus.**
- **Overall, the positive treatment effects of maralixibat in patients with ALGS demonstrate important correlations with multiple clinically relevant parameters at week 48.**

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Presented at the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Annual Meeting (Virtual); USA; December 12–18, 2021.

Previously presented at The Liver Meeting Digital Experience™ (TLMdX), American Association for the Study of Liver Diseases (AASLD); November 13–16, 2020; 0341. Reused with permission.

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Acknowledgments
The authors would like to thank the clinical trial participants, their families, and investigators for their participation in the ICONIC study. Maralixibat is owned by Mirum Pharmaceuticals, Inc.
This analysis was funded by Mirum Pharmaceuticals, Inc.
Medical-writing support for the development of this poster was provided by Gopika Jones of Alpharmaxim Healthcare Communications, and Helen Singleton, PhD, of Health Interactions, and funded by Mirum Pharmaceuticals, Inc.

Disclosures
E Gonzales is a consultant for Mirum Pharmaceuticals, Inc., Albireo Pharma, Inc., and Laboratoires CTRS.
P Vig, E Tucker, and W Garner are full-time employees of and shareholders in Mirum Pharmaceuticals, Inc.
T Jaecklin was a full-time employee of and shareholder in Mirum Pharmaceuticals, Inc. at the time of the study.
E Jacquemin is a consultant for Laboratoires CTRS and Vivet Therapeutics.
B M Kamath has received unrestricted educational grants from Mirum Pharmaceuticals, Inc., and Albireo Pharma, Inc., and is a consultant for Mirum Pharmaceuticals, Inc., Albireo Pharma, Inc., Audentes Therapeutics, Inc., and Third Rock Ventures.