Gastrointestinal tolerability of maralixibat in patients with Alagille syndrome: An integrated analysis of short- and long-term treatment

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H-ePwP-030

Introduction

- Alagille syndrome (ALGS) is a rare, life-threatening, autosomal dominant, multisystem disease that is typically diagnosed within the first 3 months of life.[1,2]
- ALGS symptoms include cholestatic pruritus and failure to thrive; the pruritus associated with ALGS can be extremely debilitating and lead to sleep deprivation.[3,4]
- Maralixibat (MRX) is an apical sodium-dependent bile acid transporter inhibitor (ASBTi) that interrupts the enterohepatic circulation of bile acids, leading to significant and durable reductions in serum bile acids and cholestatic pruritus.[5–7]
- Consistent with ASBTis' mechanism of action, gastrointestinal (GI) disturbances are the most commonly reported adverse events (AEs).[8,9]

Objective

- To characterize treatment-emergent AEs of diarrhea and abdominal pain in an integrated population of patients with ALGS treated with MRX across three clinical trials and their extension studies.
- A sub-analysis of placebo-controlled studies was conducted to further illustrate the treatment-emergent AEs.

Methods

Study design

- Patient-level data from three Phase 2 clinical trials (and their extension studies) of MRX-treated patients with ALGS were combined in an integrated analysis of GI events.
  - Studies LUM001-301 (NCT02055768) and LUM001-302 (NCT01903460) were 13-week, randomized, placebo-controlled, Phase 2 studies.
  - Studies LUM001-305 (NCT02117713) and LUM001-303 (NCT02047318) were optional long-term treatment extension studies to the LUM001-301 and LUM001-302 studies, respectively.
  - Study LUM001-304 (NCT02160782) was a 48-week study with a 4-week randomized drug withdrawal period, followed by an open-label, long-term extension study.
- MRX was administered according to a dose-escalation schedule over the first 5 weeks of treatment in studies LUM001-301 and -302 up to 266 µg/kg/day.*
- In LUM001-304, MRX was administered according to a dose-escalation schedule over 6 weeks of treament to a final dose of 380 µg/kg/day.* Patients were increased to BID dosing in the long-term extension phase after week 103.
- Ongoing patients from studies LUM001-303, -304 and -305 rolled over into the long-term safety study MRX-800 (MERGE; NCT04168385).

*All doses presented as MRX free base.

Study population

Table 1. Key entry criteria for the MRX clinical trials.

Key entry criteria included:
• Aged 12 months to 18 years
• Diagnosis of ALGS based on specific diagnostic criteria and evidence of cholestasis
• sBA >3 x upper limit of normal
• ItchRO (Obs) severity score ≥2 (0–4 scale)
• No surgical interruption of the enterohepatic circulation
• No previous liver transplantation (LT), and not currently listed for LT
• No history or presence of other concomitant liver disease, or decompensated cirrhosis
• No chronic diarrhea requiring ongoing intravenous fluids or nutritional intervention

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

Statistical analysis

- Treatment-emergent AEs of diarrhea and abdominal pain were analyzed in all patients, irrespective of relatedness to treatment as judged by the investigator.
- Grouped term definitions (multiple Medical Dictionary for Regulatory Activities [MedDRA] preferred terms) were utilized for each event.
- GI events were analyzed for reported rates, including by severity and seriousness, actions taken with the study drug in response to the events (i.e. dose reductions/ discontinuations), time-to-first-onset and potential dose–response relationships.
- The incidence rate was calculated as the number of patients with an event reported within the 4-week period divided by the number of participants who remained in the study.
- The prevalence rate was the number of patients with an event ongoing (either newly reported or ongoing from the previous period) divided by the number of participants who remained in the study.

Results

- Overall, 86 patients received MRX and were included in this integrated MRX safety population.
- Patient baseline characteristics are shown in **Table 2**.
- The median duration of exposure was 32.2 months, with up to 60.9 months of treatment with MRX (up to >5 years).
- Across all studies and doses, MRX dose interruptions were reported in a total of 2 patients who experienced GI events (1 for diarrhea and 1 for abdominal pain).
- There were no discontinuations for any GI-related event over the 5 years of treatment.

Table 2. Baseline patient demographics and characteristics.

	Integrated MRX safety population (N = 86)	Sub-analysis of 13-week placebo-controlled studies	
		13-week MRX (N = 39)	13-week placebo (N = 18)*
Mean age, years (SD)	6.2 (4.5)	7.1 (4.9)	5.2 (3.6)
Sex			
Male	49 (57.0)	24 (61.5)	7 (38.9)
Race			
Asian	2 (2.3)	2 (5.1)	0
Black or African American	6 (7.0)	4 (10.3)	2 (11.1)
White	44 (51.2)	31 (79.5)	15 (83.3)
More than one race	2 (2.3)	1 (2.6)	1 (5.6)
Not reported†	32 (37.2)	1 (2.6)	0
Mean treatment duration, months (SD)	34.5 (21.0)	2.95 (0.5)	2.7 (0.7)
Mean sBA, µmol/L (SD)	250.4 (206.2)	240.0 (224.9)	223.2 (147.0)
Baseline antipruritic medications			
UDCA	74 (86.0)	36 (92.3)	15 (83.3)
Rifampicin	64 (74.4)	29 (74.4)	14 (77.8)
Colestyramine	0 (0.0)	0 (0.0)	0 (0.0)
Oral antihistamines	40 (46.5)	25 (64.1)	12 (66.7)
Mean CSS score (SD)	3.0 (0.94)	3.0 (0.93)	2.8 (0.92)
Mean ItchRO (Obs) severity score (SD)	2.7 (0.8)	2.7 (0.8)	–

Data cut-off: Dec 01 2019. All data are n (%) unless otherwise indicated. *16 patients from the placebo group subsequently crossed over to MRX, and were also included within the N = 86 patients assessed for MRX safety; †Data were not reported or not captured.
CSS, clinician scratch scale; ItchRO (Obs), Itch Reported Outcome (Observer); sBA, serum bile acid; SD, standard deviation; UDCA, ursodeoxycholic acid.

Maximum severity of GI events

Table 3. Maximum severity of GI events in the integrated population, with up to >5 years of follow-up.

Patients experiencing an AE, n (%)	**Integrated patient population (N = 86)**	
	Diarrhea*	**Abdominal pain***
Any severity	49 (57.0)	46 (53.5)
Mild	42 (48.8)	34 (39.5)
Moderate	7 (8.1)	8 (9.3)
Severe	0 (0.0)	4 (4.7)
Life threatening/fatal	0 (0.0)	0 (0.0)

*Includes multiple AE terms.

Table 4. Maximum severity of AEs with MRX or placebo in the integrated 13-week placebo-controlled population (N = 57).

Patients experiencing an AE, n (%)	**MRX (N = 39)**		**Placebo (N = 18)**	
	Diarrhea*	**Abdominal pain***	**Diarrhea***	**Abdominal pain***
Any severity	17 (43.6)	15 (38.5)	9 (50.0)	5 (27.8)
Mild	16 (41.0)	12 (30.8)	6 (33.3)	3 (16.7)
Moderate	1 (2.6)	3 (7.7)	3 (16.7)	1 (5.6)
Severe	0	0	0	1 (5.6)
Life threatening/fatal	0	0	0	0

*Includes multiple AE terms.

Incidence and prevalence of GI events

Figure 1. Incidence and prevalence of diarrhea in the integrated MRX safety population.

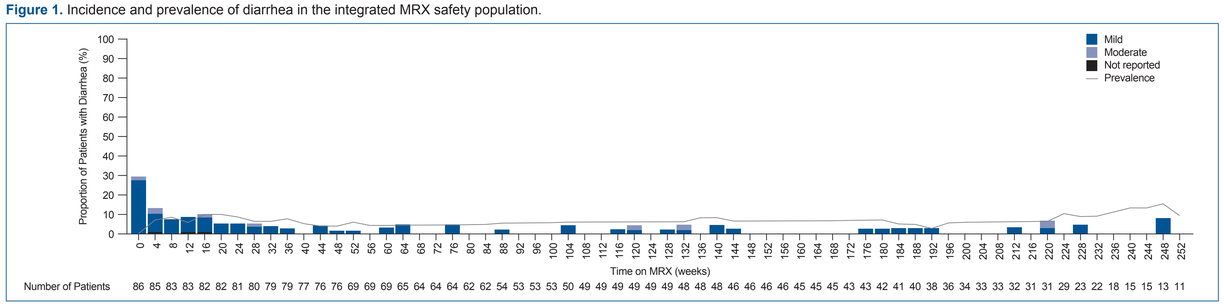


Figure 2. Incidence and prevalence of abdominal pain in the integrated MRX safety population.

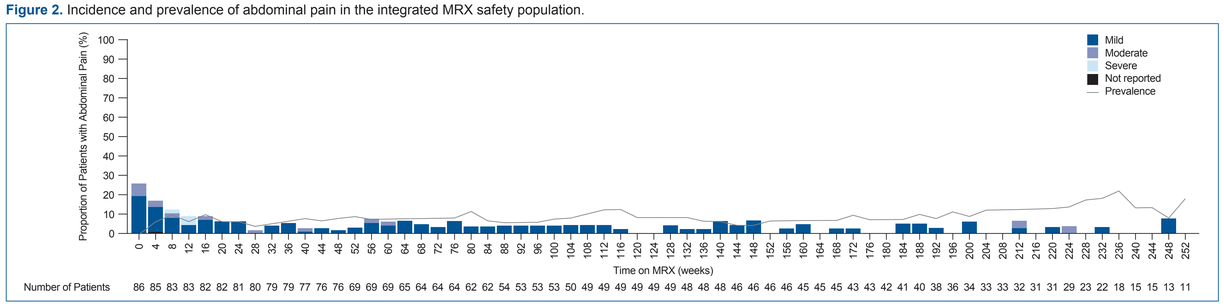
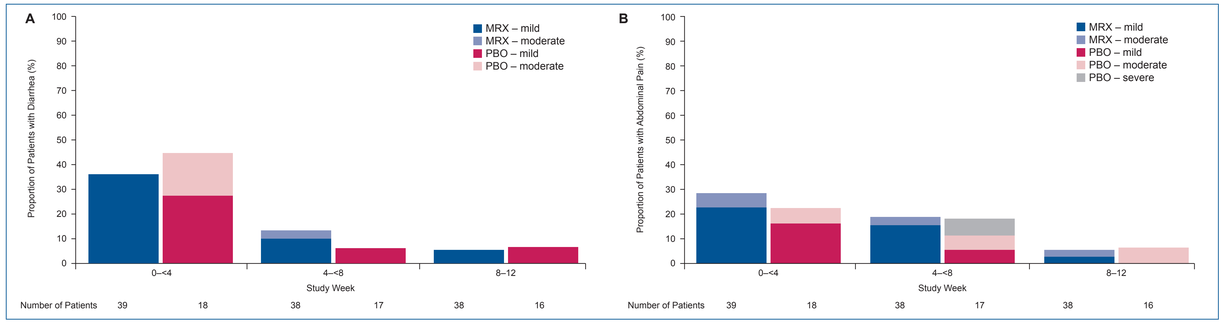


Figure 3. Incidence of (A) diarrhea and (B) abdominal pain in the subset of patients enrolled in 13-week placebo-controlled studies, providing a baseline level of GI AEs in this patient population, for comparison.



- Most patients experienced mild to moderate GI events (**Tables 3** and **4**), which resolved with no action taken with MRX.
- Safety data from the 13-week placebo-controlled studies showed that the rates of diarrhea were similar between MRX and placebo, with a slight difference in abdominal pain (**Table 4**).
- Median time-to-first-onset for diarrhea and abdominal pain were 3.9 and 4.2 weeks, respectively.
- The overall prevalence rate of GI events across the integrated patient population up to >5 years was low (**Figures 1 and 2**).
- Incidence of diarrhea and abdominal pain was highest during the first 4 weeks of treatment and was transient in nature, subsequently decreasing over time (**Figures 1–3**).
- The majority of GI events lasted for less than 1 week, with a median duration of events resolving within 2 days for diarrhea and 1 day for abdominal pain.

Conclusions

- **In this integrated safety analysis of 86 patients treated with MRX for up to >5 years:**
  - **The majority of GI AEs occurred within the first 4 weeks of treatment and lasted <1 week in duration.**
  - **The majority of diarrhea and abdominal pain AEs were mild to moderate in severity and transient in nature.**
  - **There were no GI-related discontinuations of MRX.**
- **Data from the 13-week placebo group demonstrate that GI events are common in untreated patients, and the rates of diarrhea were similar between MRX and placebo, with a slight difference in abdominal pain.**

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This poster was presented at the 6th World Congress of Pediatric Gastroenterology, Hepatology and Nutrition (WCPGHAN), 02–05 June 2021, Vienna, Austria

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Acknowledgments
We would like to thank clinical trial participants, their families and investigators for their participation in the 301,302, 303, 304 and 305 clinical studies.
Maralixibat is owned by Mirum Pharmaceuticals, Foster City, CA, US. This analysis was funded by Mirum Pharmaceuticals.
Medical writing support for the development of this poster was provided by Steven Duckett, Health Interactions, and funded by Mirum Pharmaceuticals.

Disclosures
R. Raman, W. Garner, E. Tucker and P. Vig are full-time employees and shareholders of Mirum Pharmaceuticals, Inc.
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., and Audentes Therapeutics, Inc.
E. Gonzales is a consultant for Mirum Pharmaceuticals, Inc., Albireo Pharma, Inc., and CTRS Laboratories.