An integrated analysis of long-term clinical safety in maralixibat-treated participants with Alagille syndrome

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Introduction

- Alagille syndrome (ALGS) is a rare, life-threatening, autosomal dominant, multisystem disease.[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.[5–8]
- The safety database for MRX now comprises over 1600 participants, including 86 patients with ALGS, which is the largest database for an ASBTi.

Objectives

- To evaluate the overall clinical safety of MRX in an integrated population of patients with ALGS who received MRX.
- To conduct a sub-analysis of safety data in the 13-week placebo-controlled studies, LUM001-301 and LUM001-302.

Methods

Study design

- Patient-level data from three Phase 2 clinical studies (and their extension studies) of MRX-treated patients with ALGS were combined in an integrated analysis of adverse events (AEs).
  - Studies LUM001-301 (NCT02057692) 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 LUM001-302 up to 266 µg/kg/day.*
- In LUM001-304, MRX was administered according to a dose-escalation schedule over 6 weeks of treatment to a final dose of 380 µg/kg/day.* Patients were increased to BID dosing, starting after week 103.
- Ongoing patients from studies LUM001-303, LUM001-304, and LUM001-305 rolled over into the long-term safety study MRX-800 (MERGE; NCT04168385).
- Key entry criteria are shown in **Table 1**.

*Doses presented as MRX free base.

Study population

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

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

ALGS, Alagille syndrome; MRX, maralixibat; sBA, serum bile acid; ItchRO(Obs), Itch-Reported Outcome (Observer).

Statistical analysis

- Safety data were analyzed across the integrated safety population, including treatment-emergent AEs (TEAEs) and laboratory parameters (multiple Medical Dictionary for Regulatory Activities [MedDRA] preferred terms were utilized).
- AEs were analyzed for reported rates, including by severity and seriousness, and 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 data cut-off date for the present analysis was taken on December 1, 2019.

Results

Baseline characteristics and treatment duration

- In total, 86 patients with ALGS treated with MRX were included in this integrated safety analysis.
- Baseline patient characteristics for the main safety population and sub-analysis populations are shown in **Table 2**.
- The median duration of exposure was 32.2 months, with up to 60.9 months of treatment with MRX (>5 years).

Table 2. Baseline patient demographics and characteristics.[9]

	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)	3.0 (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)
Oral antihistamines	40 (46.5)	25 (64.1)	12 (66.7)
Mean CSS score (SD)	3.0 (0.9)	3.0 (0.9)	2.8 (0.9)
Mean ItchRO(Obs) severity score (SD)	2.7 (0.8)	2.7 (0.8)	–

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); MRX, maralixibat; sBA, serum bile acid; SD, standard deviation; UDCA, ursodeoxycholic acid.

Treatment-emergent adverse events (TEAEs)

- All 86 patients (100%) had ≥1 TEAE. A total of 62 patients (72.1%) had a TEAE reported to be potentially related to study treatment (**Table 3**). Most TEAEs were mild to moderate in severity.
- There were no deaths. Twenty-eight patients (32.6%) had a serious AE (SAE), of which three patients (3.5%) had a SAE reported to be related to MRX treatment (anemia/hematochezia in one patient; increased alanine aminotransferase (ALT) levels in one patient; autoimmune hepatitis in one patient) (**Table 3**).
- Fourteen patients (16.3%) had a TEAE that led to MRX discontinuation (**Table 3**).

Table 3. Overall incidence of TEAEs.

Patients, n (%)	Integrated MRX safety population (N = 86)*	Sub-analysis of 13-week placebo-controlled studies	
		13-week MRX (N = 39)	13-week placebo (N = 18)†
≥1 TEAE	86 (100.0)	35 (89.7)	16 (88.9)
≥1 TEAE potentially related to treatment	62 (72.1)	27 (69.2)	11 (61.1)
SAE	28 (32.6)	1 (2.6)	0
SAE potentially related to treatment	3 (3.5)	0	0
TEAE leading to treatment discontinuation‡	14 (16.3)	1 (2.6)	1 (5.6)
ALT increase§	7 (8.1)	1 (2.6)	0
Blood bilirubin increase	2 (2.3)	0	0

*Up to >5 years follow-up; †16 patients from the placebo group subsequently crossed over to MRX, and were also included within the N = 86 patients assessed for MRX safety; ‡Only TEAEs occurring in ≥2 patients are displayed; §Led to treatment discontinuation after meeting pre-specified protocol stopping criteria.
ALT, alanine aminotransferase; MRX, maralixibat; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

- The most common TEAEs were diarrhea and abdominal pain, and the incidence was highest during the first 4 weeks of treatment. The events were mild to moderate in severity, transient in nature, and resolved with no action taken with MRX (**Table 4**).
- The majority of gastrointestinal (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.

Table 4. Treatment-emergent GI events occurring in at least 5% of MRX patients.

Patients, n (%)	Integrated MRX safety population (N = 86)		Sub-analysis of 13-week placebo-controlled studies			
			Overall		Grade 3–4	
	Overall	Grade 3–4	13-week MRX (N = 39)	13-week placebo (N = 18)*	13-week MRX (N = 39)	13-week placebo (N = 18)*
Diarrhea	49 (57.0)	0	17 (43.6)	8 (44.4)	0	0
Abdominal pain	38 (44.2)	4 (4.7)	10 (25.6)	3 (16.7)	0	1 (5.6)
Vomiting	35 (40.7)	1 (1.2)	5 (12.8)	2 (11.1)	1 (2.6)	0
Abdominal pain upper	13 (15.1)	0	4 (10.3)	3 (16.7)	0	0
Abdominal discomfort	7 (8.1)	0	1 (2.6)	0	0	0
Nausea	7 (8.1)	0	2 (5.1)	0	0	0
Constipation	6 (7.0)	1 (1.2)	1 (2.6)	0	0	0
Hematochezia	6 (7.0)	1 (1.2)	0	1 (5.6)	0	0
Dental caries	5 (5.8)	1 (1.2)	0	0	0	0

There were no Grade 5 events reported. *16 patients from the placebo group subsequently crossed over to MRX, and were also included within the N = 86 patients assessed for MRX safety.
MRX, maralixibat.

- GI AEs of diarrhea and abdominal pain were also analyzed using grouped-term definitions (multiple MedDRA preferred terms). Safety data from the 13-week placebo-controlled studies showed that the rates of diarrhea and abdominal pain were similar between MRX and placebo, with a slight difference in abdominal pain (**Table 5**).

Table 5. Maximum severity of GI AEs with MRX or placebo, in the 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.
AE, adverse event; MRX, maralixibat.

Laboratory events

- Over 5 years, a total of 43 patients (50.0%) had treatment-emergent laboratory abnormalities.
- Consistent with the natural history of ALGS, asymptomatic spontaneous increases in serum ALT levels were observed in some patients; however, these were not MRX dose-dependent.
  - These were not associated with concomitant rises in bilirubin or with clinical sequelae.
- No other clinically significant trends or patterns in laboratory measures were observed, including in fat-soluble vitamins.

Conclusions

- **MRX was well-tolerated over 5 years across an integrated ALGS population (N = 86).**
- **Mild to moderate GI effects were observed in the first weeks of treatment and lasted less than 1 week in duration:**
  - **Placebo-controlled data indicate that GI events occur in the background of ALGS.**
  - **There were no discontinuations of MRX treatment due to diarrhea or abdominal pain.**
- **ALT elevations appear to be consistent with the natural history of ALGS.**
- **This integrated analysis demonstrated that up to >5 years of treatment with MRX is well tolerated and that MRX has an acceptable safety profile.**

Contact information

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R K Raman, W Garner, P Vig, and E Tucker are full-time employees and shareholders of Mirum Pharmaceuticals, Inc.