Safety and tolerability characterization of maralixibat in infants with ALGS from 2 months of age: Interim results from the RISE study

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Introduction

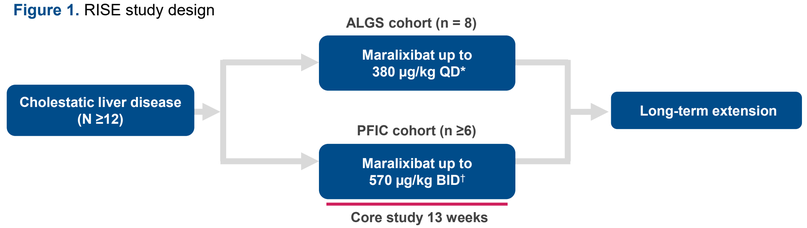
- Alagille syndrome (ALGS) is a rare cholestatic liver disease associated with high disease burden due to chronic cholestasis and pruritus.[1]
- Maralixibat (MRX) is an ileal bile acid transporter inhibitor (IBATi) approved by the Food and Drug Administration (FDA) for the treatment of cholestatic pruritus in patients with ALGS 1 year of age and older.[2]
- MRX has a well-characterized safety profile with >5 years of data in >150 children with cholestasis 1 year of age and older.[2]

Aim

- To evaluate the safety of MRX in infants with ALGS and progressive familial intrahepatic cholestasis (PFIC) <1 year of age in an ongoing, open-label, Phase 2 trial.
- An interim analysis for the ALGS cohort only is reported here.

Methods

Figure 1. RISE study design



*Maralixibat 380 µg/kg is equivalent to 400 µg/kg maralixibat chloride.†Maralixibat 570 µg/kg is equivalent to 600 µg/kg maralixibat chloride.
BID, twice daily; QD, once a day.

- Participants in the ALGS cohort received MRX (380 µg/kg once daily) in addition to standard-of-care.
- Infants with ALGS and cholestasis who were <1 year of age were enrolled.
- Eligibility criteria included: body weight ≥2.5 kg; gestational age ≥36 weeks; and clinical and laboratory evidence of cholestasis. Children with decompensated cirrhosis were excluded.
- Safety during the study was assessed by the incidence of treatment-emergent adverse events (TEAEs) and change from baseline to week 13 in laboratory parameters.
- Plasma pharmacokinetics (PK) of MRX were also evaluated.

Results

Table 1. Baseline characteristics

Variable	Participants with ALGS (N = 8)
Age, months	7.0 (5.0, 8.0)
Sex, n (%)	
Male	7 (87.5)
Race, n (%)	
White	5 (62.5)
Not applicable	3 (37.5)
Height z-score	–2.66 (–3.89, –1.95)
Weight z-score	–2.27 (–3.29, –1.92)
ALT, U/L	117.0 (96.5, 182.0)
AST, U/L	136.0 (117.5, 205.5)
Direct bilirubin, µmol/L	118.0 (87.3, 178.6)
Total bilirubin, µmol/L	158.8 (82.1, 227.7)
Total sBA, µmol/L	259.9 (199.5, 366.3)

All data are median (Q1, Q3) unless otherwise specified. Age is at the time of study enrollment.
ALGS, Alagille syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Q1, quartile 1; Q3, quartile 3; sBA, serum bile acid.

Results

Table 2. Overview of TEAEs

Participants, n (%)	N = 8
Participants with at least 1 TEAE	7 (87.5)
TEAE related to study drug*	2 (25.0)
Grade ≥3 TEAE	4 (50.0)
Grade ≥3 TEAE related to study drug*	0
Serious TEAE	4 (50.0)
Serious TEAE related to study drug*	0
TEAE that led to study drug discontinuation	0
TEAE that led to death	0

*Relatedness of TEAE is assessed by the investigator.
TEAE, treatment-emergent adverse event.

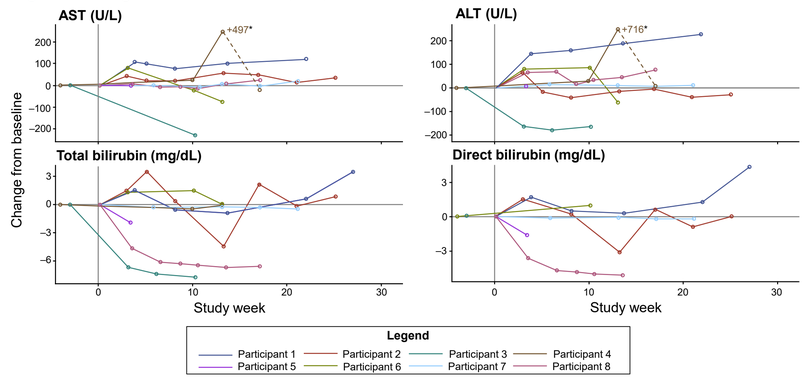
- The median duration of exposure to MRX was 136.5 days.
- Seven participants (87.5%) experienced ≥1 TEAE.
- Most TEAEs were Grade 1 in severity and unrelated to MRX; 2 participants (25%) had a TEAE related to MRX (both Grade 1 diarrhea, resolved).
- Four participants (50%) experienced 7 serious adverse events (SAEs), which were unrelated to MRX, all resolved and did not require a change in MRX dose.
- All TEAEs were self-limiting and resolved with no drug interruption or change in dose
  - No drug discontinuations or deaths were reported.
- Infections and gastrointestinal disorders were the most frequent TEAEs.

Table 3. Incidence of TEAEs occurring in ≥2 participants

Participants, n (%)*	N = 8
Gastrointestinal disorders	5 (62.5)
Abdominal pain	3 (37.5)
Diarrhea	3 (37.5)
Teething	3 (37.5)
General disorders and administration site conditions	4 (50.0)
Pyrexia	3 (37.5)
Infections and infestations	6 (75.0)
Nasopharyngitis	4 (50.0)
Respiratory, thoracic and mediastinal disorders	3 (37.5)
Rhinorrhea	2 (25.0)

*Adverse events were coded according to System Organ Class preferred term, using MedDRA version 22.1.
TEAE, treatment-emergent adverse event.

Figure 2. Change from baseline in AST, ALT, total bilirubin, and direct bilirubin



*Participant 4 experienced an increase in ALT/AST at week 13. The Principal Investigator attributed this finding to a concurrent viral upper respiratory infection. Subsequent local labs, represented by the dashed lines, returned back to baseline.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

- Fluctuations in aspartate transaminase (AST) and alanine transaminase (ALT) were observed; none resulted in dose reduction, dose interruption, or discontinuation.
- Bilirubin reductions of –28.1%, –30.2%, –96.3% were seen in 3 participants.
- All eight participants had elevated serum bile acid (sBA) at baseline. The baseline mean (SD) sBA was 347 (275.1) µmol/L. The mean (SD) change in sBA from baseline at week 13 was –89 (113.3) µmol/L.

Plasma PK analysis

- In previous studies of patients with ALGS >12 months of age, the vast majority of plasma drug level results were below the limit of quantification (BLQ‡), and the maximum measured value was 5.93 ng/mL.
- The majority of plasma drug levels were BLQ for all tested doses, and the maximum measured value was 2.27 ng/mL.
- These results are consistent with previous studies in participants with ALGS >12 months of age and with a minimally absorbed drug.

Table 4. Summary of PK data in patients with ALGS

		Baseline		Week 6		Week 8		Week 10		Week 13	
Study Participant	Age (months)	Pre-dose	2.5 hrs post-dose*	Pre-dose	2.5 hrs post-dose†	Pre-dose	2.5 hrs post-dose†	Pre-dose	2.5 hrs post-dose†	Pre-dose	2.5 hrs post-dose†
1	6			`		BLQ	1.55				
2	10	BLQ	BLQ			BLQ	0.824			BLQ	BLQ
3	7		BLQ	BLQ	0.698			BLQ	0.558	BLQ	0.315
4	8		BLQ						1.01		
5	8		0.598								
6	4	BLQ	BLQ					BLQ	2.27	BLQ	1.54
7	7	BLQ	BLQ	BLQ	0.535					BLQ	0.613
8	2		0.539		BLQ	BLQ			0.365	0.873	BLQ

All data are ng/mL, unless otherwise stated. *The initial dose of MRX was 190 µg/kg. †The final dose of MRX was 380 µg/kg. ‡BLQ = 0.250 ng/mL.
BLQ, below the limit of quantification; PK, pharmacokinetics.

Conclusions

- **MRX was well tolerated in infants with ALGS aged <1 year, with body weight of ≥2.5 kg, and TEAEs were mostly grade 1 in severity and unrelated to MRX.**
- **There were fluctuations in ALT, AST, and total bilirubin compatible with the natural history of ALGS.**
- **These data characterize the safety, tolerability, and PK of MRX in infants with ALGS, indicating that MRX may be used in children as young as 2 months of age.**

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