Safety and Tolerability of Maralixibat in Infants From 2 Months of Age With Alagille Syndrome or Progressive Familial Intrahepatic Cholestasis: Results From the RISE Study

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Introduction

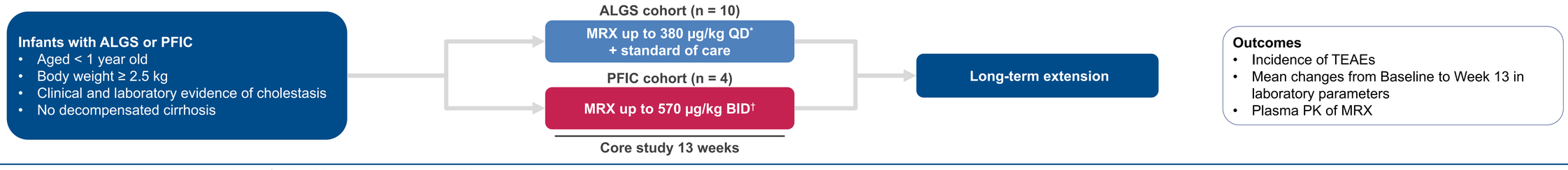
- Alagille syndrome (ALGS) and progressive familial intrahepatic cholestasis (PFIC) are rare cholestatic liver diseases associated with high disease burden due to chronic cholestasis and pruritus.[1,2]
- Maralixibat (MRX) is a minimally absorbed ileal bile acid transporter inhibitor (IBATi) approved for the treatment of cholestatic pruritus in patients with ALGS who are ≥ 2 months of age in the EU and ≥ 3 months of age in the US.[3,4]
- MRX has a well-characterised safety profile with > 5 years of data in > 150 children with cholestasis 1 year of age and older.[3]

Aim

- To evaluate the safety and tolerability of MRX in infants with ALGS or PFIC < 1 year of age in the open-label, Phase 2 RISE (Ma**R**alixibat **I**nfant **S**afety **E**valuation) study.

Methods

Figure 1. RISE study design: 13 week core study with long-term extension phase



*MRX 380 µg/kg is equivalent to 400 µg/kg MRX chloride. †MRX 570 µg/kg is equivalent to 600 µg/kg MRX chloride.
ALGS, Alagille syndrome; BID, twice daily; MRX, maralixibat; PFIC, progressive familial intrahepatic cholestasis; PK, pharmacokinetics; QD, once a day; RISE, Ma**R**alixibat **I**nfant **S**afety **E**valuation; TEAE, treatment-emergent adverse event.

Results

- The median duration of exposure to MRX was 128 days.
- All 14 participants had elevated serum bile acid (sBA) at Baseline.

Table 1. Baseline characteristics

Variable	ALGS (n = 10)	PFIC (n = 4)	All participants (N = 14)
Age, months	7.5 (6.0, 9.0)	8.5 (5.0, 10.5)	7.5 (6.0, 9.0)
Male, n (%)	9 (90.0)	2 (50.0)	11 (78.6)
PFIC genotype, n (%)			
ABCB11	NA	2 (50.0)	2 (14.3)
ATP8B1	NA	1 (25.0)	1 (7.1)
TJP2	NA	1 (25.0)	1 (7.1)
Height z-score	-3.02 (-3.93, -2.10)	-1.29 (-2.55, -0.38)	-2.66 (-3.84, -1.80)
Weight z-score	-2.27 (-2.74, -2.10)	-1.16 (-1.55, -0.67)	-2.12 (-2.73, -1.35)
ALT, U/L	121 (103.0, 187.0)	78 (56.5, 121.5)	109 (86.0, 177.0)
AST, U/L	152 (120.0, 253.0)	126 (72.5, 179.0)	152 (115.0, 180.0)
Direct bilirubin, µmol/L	118.0 (87.3, 151.9)	33.0 (13.2, 56.5)	87.3 (17.7, 151.9)
Total bilirubin, µmol/L	158.8 (48.4, 212.6)	45.8 (19.4, 72.5)	97.6 (25.9, 212.3)
Total sBA, µmol/L	252 (152.6, 320.9)	220 (133.4, 290.1)	241 (152.6, 320.9)
Rifampicin usage, n (%)	2 (20.0)	3 (75.0)	5 (35.7)
UDCA usage, n (%)	7 (70.0)	4 (100.0)	11 (78.6)

All data are median (Q1, Q3) unless otherwise specified. ALGS, Alagille syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable; PFIC, progressive familial intrahepatic cholestasis; Q1, quartile 1; Q3, quartile 3; sBA, serum bile acid; UDCA, ursodeoxycholic acid.

Table 2. Overview of TEAEs

Participants, n (%)[a]	ALGS (n = 10)	PFIC (n = 4)	All participants (N = 14)
Participants with ≥ 1 TEAE	9 (90.0)	4 (100.0)	13 (92.9)
TEAE related to study drug[a]	3 (30.0)	1 (25.0)	4 (28.6)
Grade ≥ 3 TEAE	5 (50.0)	0	5 (35.7)
Grade ≥ 3 TEAE related to study drug[a]	0	0	0
Serious TEAE	4 (40.0)	1 (25.0)	5 (35.7)
Serious TEAE related to study drug[a]	0	0	0
TEAE that led to study drug discontinuation	0	0	0
TEAE that led to death	0	0	0

[a]Relatedness of TEAE is assessed by the investigator.
ALGS, Alagille syndrome; PFIC, progressive familial intrahepatic cholestasis; TEAE, treatment-emergent adverse event.

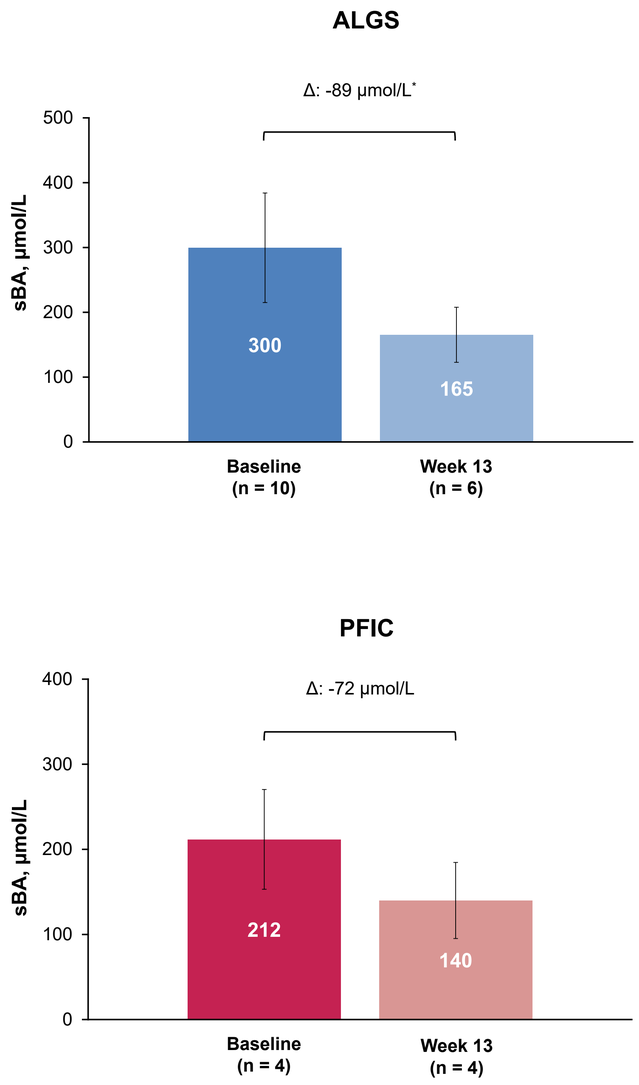
Table 3. Incidence of TEAEs occurring in ≥ 2 participants

Participants, n (%)[a]	ALGS (n = 10)	PFIC (n = 4)	All participants (N = 14)
Gastrointestinal disorders	5 (50.0)	2 (50.0)	7 (50.0)
Diarrhoea	3 (30.0)	1 (25.0)	4 (28.6)
Abdominal pain	3 (30.0)	0	3 (21.4)
Teething	3 (30.0)	0	3 (21.4)
Vomiting	1 (10.0)	1 (25.0)	2 (14.3)
General disorders and administration-site conditions	4 (40.0)	0	4 (28.6)
Pyrexia	3 (30.0)	0	3 (21.4)
Infections and infestations	6 (60.0)	3 (75.0)	9 (64.3)
Nasopharyngitis	4 (40.0)	0	4 (28.6)
Coronavirus infection	1 (10.0)	2 (50.0)	3 (21.4)
Gastroenteritis	1 (10.0)	1 (25.0)	2 (14.3)
Investigations	2 (20.0)	1 (25.0)	3 (21.4)
ALT increased	2 (20.0)	0	2 (14.3)
AST increased	2 (20.0)	0	2 (14.3)
Blood bicarbonate decreased	1 (10.0)	1 (25.0)	2 (14.3)
Respiratory, thoracic and mediastinal disorders	4 (40.0)	1 (25.0)	5 (35.7)
Rhinorrhoea	2 (20.0)	1 (25.0)	3 (21.4)
Cough	2 (20.0)	0	2 (14.3)

[a]Adverse events were coded according to System Organ Class preferred term, using MedDRA version 22.1.
ALGS, Alagille syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary tor Regulatory Activities; PFIC, progressive familial intrahepatic cholestasis; TEAE, treatment-emergent adverse event.

- The most frequently reported treatment-emergent adverse events (TEAEs) overall were infections (9 participants; 64.3.%).
- Most TEAEs were Grade 1 in severity and unrelated to MRX.
- Four participants (28.6%) had a TEAE related to MRX; most common were diarrhoea and abdominal discomfort, all Grade 1 in severity and resolved.

Figure 2. Mean sBA at Baseline and Week 13



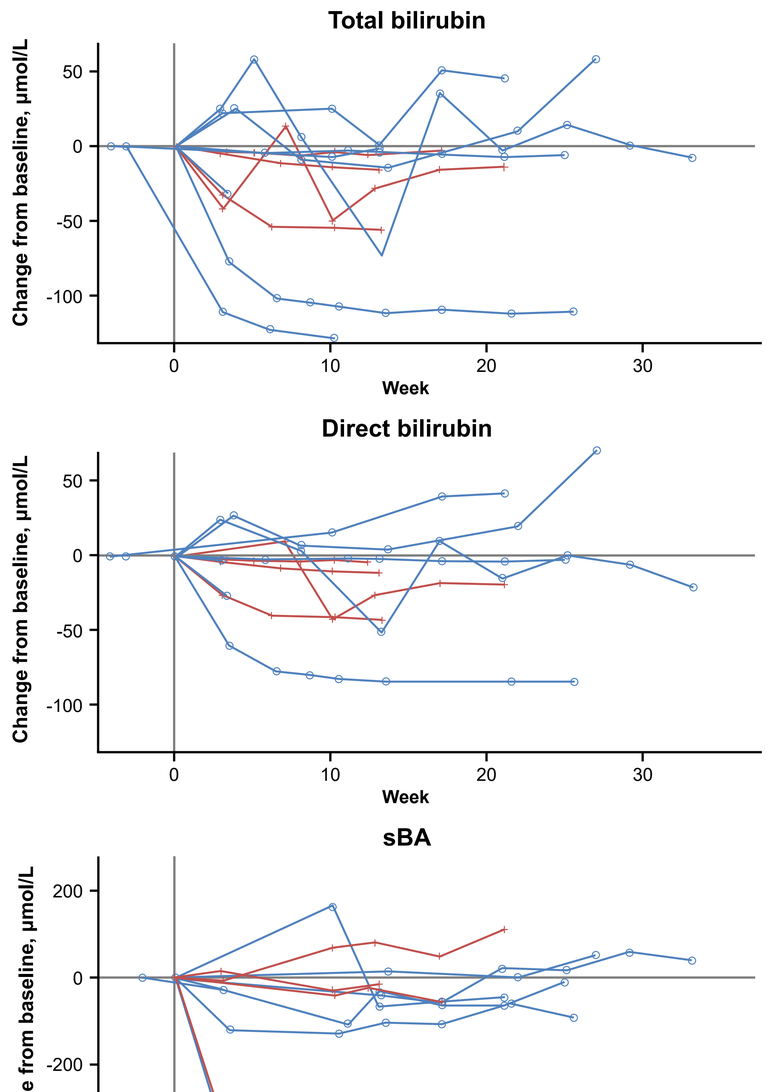
*Mean change from baseline to Week 13 based on participants who had Week 13 sBA results.
ALGS, Alagille syndrome; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.

- An overall mean change of -89 µmol/L and -72 µmol/L was observed in the ALGS and PFIC cohorts, respectively, by Week 13.
- More than half of the participants with Week 13 data had a reduction in total bilirubin > 30% in both ALGS and PFIC cohorts.
- Fluctuations in alanine aminotransferase (ALT) were observed; none resulted in dose reduction, dose interruption or discontinuation.
- The mean change in ALT from Baseline to Week 13 was 148 U/L for ALGS and -13 U/L for PFIC.

Plasma pharmacokinetics (PK) analysis

- The majority of plasma drug levels were below the level of quantification (BLQ [level of quantification 0.25 ng/mL]) for all tested doses for both cohorts.
- The maximum measured values were 2.27 ng/mL and 1.44 ng/mL in the ALGS and PFIC cohorts, respectively.
- These results are consistent with previous studies in ALGS and PFIC > 12 months of age and with a minimally absorbed drug.

Figure 3. Change from baseline in total bilirubin, direct bilirubin, sBA and ALT up to Week 33



*Extreme outliers for ALT were capped at 250 U/L for readability, with actual changes noted.
ALGS, Alagille syndrome; ALT, alanine aminotransferase; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.

Conclusions

- **MRX was minimally absorbed and well tolerated in infants with ALGS or PFIC < 1 year of age; TEAEs were mostly Grade 1 in severity and there were no ≥ Grade 3 or serious TEAEs related to MRX. In total, 4 out of 14 participants experienced diarrhoea, all Grade 1 in severity and resolved, with no drug discontinuations.**
- **Meaningful reductions in sBA were observed in both ALGS and PFIC cohorts.**
- **There were fluctuations in ALT compatible with the natural history of ALGS. Short-term increases in ALT were observed in the PFIC cohort, with results returning either below or back to Baseline by Week 13.**
- **These data characterise the safety, tolerability and PK of MRX in infants with ALGS or PFIC, indicating that MRX may be used in children as young as 2 months of age.**

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