Clinical Benefits of Maralixibat for Patients With Alagille Syndrome Are Durable Through 7 Years of Treatment: Data From the MERGE Study

Abstract #1107

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Introduction

- Alagille syndrome (ALGS) is a rare, debilitating, autosomal dominant disorder that presents with a broad range of clinical manifestations.[1]
  - The key clinical manifestations include cholestasis, pruritus, failure to thrive, xanthomas, and progressive liver disease, all of which can lead to liver transplant or death.
- Maralixibat is a minimally absorbed ileal bile acid transporter inhibitor that prevents enterohepatic bile acid recirculation and is approved for the treatment of cholestatic pruritus in patients with ALGS ≥2 months of age in the EU.[2]
- Improvements in pruritus, sBA, and height were observed in prior clinical trials of maralixibat in participants with ALGS.[3,4]
  - In ICONIC (up to 380 µg/kg/twice daily), responses were durable for up to ~4 years.[3]
  - In IMAGO (280 µg/kg/daily) and its extension study IMAGINE and in ITCH (280 µg/kg/daily) and its extension study IMAGINE-II, responses were durable for up to ~1.5 years.[4,5]
- Participants from ICONIC, IMAGINE, and IMAGINE-II were invited to enrol in the MERGE study for additional follow-up to assess the long-term durability of response to maralixibat.[6]

Objective

- To report on the efficacy of maralixibat in reducing cholestasis in participants with ALGS with additional long-term follow-up from MERGE, including some participants who received treatment for 7 years.

Methods

- All participants from ICONIC, IMAGINE, and IMAGINE-II were included in the analysis; details of the study designs have been presented previously.
- Impact of maralixibat was assessed for pruritus, sBA, height and weight Z-scores, ALT, AST, and total and direct bilirubin.[a]
  - Pruritus was measured using the Itch-Reported Outcome (Observer) (ItchRO[Obs]) scale, which is a 0 to 4 scale where 0 = no itch, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.[7] A ≥1-point reduction in ItchRO(Obs) is considered clinically meaningful.
- Change from Baseline (CFB) was assessed by comparing median (Q1, Q3) values from enrolment in the initial trial (ie, ICONIC, IMAGO, or ITCH) with data from the visit in MERGE that best aligned with an annual visit.

[a]ALT and bilirubin were measured in serum.

Results

- Of the 86 participants for whom data were analysed, 85 had a genetic diagnosis of ALGS (*JAG1*, n=83; *NOTCH2*, n=2) and 1 participant had an unidentified variant.
- The median age of the cohort was 5 years, 57% were male.
- Sixty-eight (79.1%) participants were taking ursodeoxycholic acid (UDCA) and sixty-five (76%) were taking rifampicin at Baseline.
- Of 83 participants on either UDCA or rifampicin at Baseline, 94% (n=78) continued to take either one of them at any time during the study period.
- Of 22 participants on either UDCA or rifampicin at Year 7, 96% (n=21) continued to take either one of the two medications at any time during the study period.

Improvements in Clinical Outcomes Persist for up to 7 Years of Maralixibat Treatment

Table 1. Change From Baseline in Clinical Outcomes of Interest After Initiation of Maralixibat

Parameter[a]	Baseline (N=86)	Year 1 (n=76)	Year 2 (n=49)	Year 3 (n=45)	Year 4 (n=42)	Year 5 (n=40)	Year 6 (n=34)	Year 7 (n=23)
ItchRO(Obs)	2.7 (2.1, 3.1)	-1.6 (-2.1, -0.8)	-1.0 (-1.9, -0.3)	-1.0 (-2.0, -0.3)	-1.1 (-2.0, -0.5)	-2.0 (-2.9, -1.3)	-1.3 (-1.9, -0.6)	-2.1 (-2.6, -1.6)
		<0.001	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.004**
sBA, µmol/L	194 (83, 363)	-53 (-146, 8)	-62 (-137, 2)	-60 (-134, 0)	-61 (-152, -34)	-77 (-182, -21)	-113 (-235, -24)	-121 (-231, -41)
		<0.001	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Height Z-score[b]	-1.6 (-2.3, -0.9)	0.1 (-0.1, 0.3)	0.2 (0.0, 0.5)	0.4 (0.0, 0.6)	0.3 (0.0, 0.8)	0.4 (-0.1, 0.9)	0.5 (0.0, 1.1)	0.8 (0.0, 1.2)
		<0.001	**<0.001**	**<0.001**	**<0.001**	**0.002**	**<0.001**	**0.002**
Weight Z-score[b]	-1.4 (-2.2, -0.7)	0.1 (-0.2, 0.4)	0.2 (-0.4, 0.5)	0.1 (-0.2, 0.5)	0.3 (-0.3, 0.5)	0.2 (-0.4, 1.2)	0.4 (-0.4, 1.3)	0.1 (-0.5, 0.9)
		0.26	0.17	0.08	0.15	0.11	0.10	0.51

[a]All data are median (Q1, Q3); *P* value. *P* value is from a signed-rank test that used a within-group comparison to assess whether the CFB is significantly different from 0 (no change). [b]Height and weight Z-scores are based on a participant's sex and age at the Baseline visit. The World Health Organization growth charts were used to derive Z-scores for participants younger than 24 months, and the US Centers for Disease Control and Prevention growth charts were used to derive Z-scores for participants aged 24 months or older.

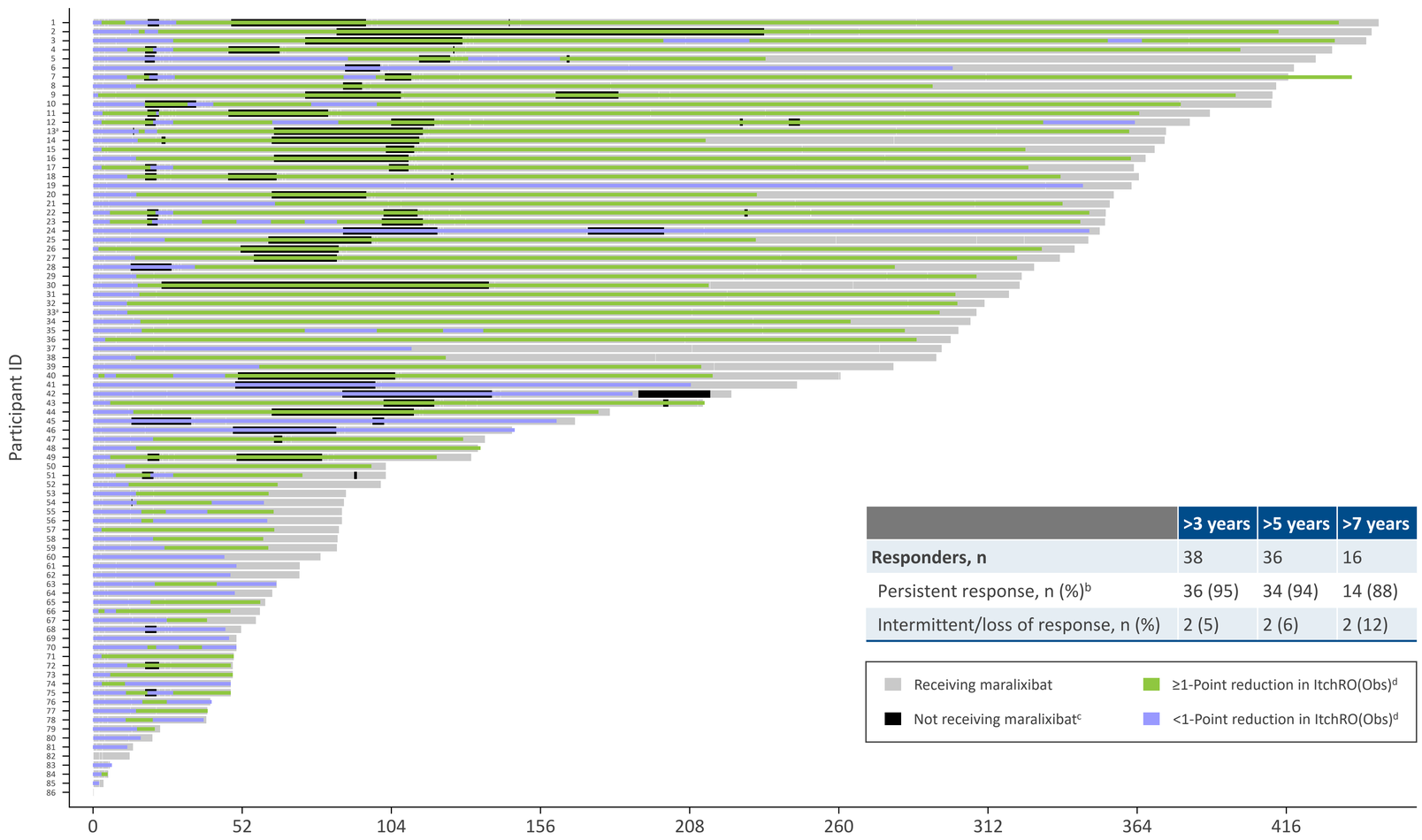
Table 2. Liver Function Tests at Baseline and Over 7 Years

Parameter[a]	Baseline (N=86)	Year 1 (n=76)	Year 2 (n=49)	Year 3 (n=45)	Year 4 (n=42)	Year 5 (n=40)	Year 6 (n=34)	Year 7 (n=23)
Total bilirubin, µmol/L	49.6 (17.1, 138.5)	37.6 (15.4, 140.2)	22.2 (15.4, 71.8)	27.4 (15.4, 80.4)	23.9 (15.4, 71.8)	23.9 (13.7, 70.1)	22.2 (15.4, 82.1)	22.2 (15.4, 92.3)
Direct bilirubin, µmol/L	42.8 (12.0, 128.3)	18.8 (8.6, 78.7)	17.1 (8.6, 58.1)	17.1 (10.3, 53.0)	15.4 (8.6, 47.9)	12.0 (8.6, 35.9)	13.7 (10.3, 59.9)	10.3 (6.8, 70.1)
ALT, U/L	140 (95, 196)	180 (125, 228)	165 (130, 254)	189 (126, 249)	173 (109, 271)	180 (122, 310)	168 (108, 342)	176 (123, 270)
AST, U/L	133 (89, 187)	155 (110, 216)	162 (114, 210)	140 (97, 227)	133 (107, 260)	170 (102, 229)	135 (95, 220)	130 (105, 245)

[a]All data are median (Q1, Q3) and are observed values.

Pruritus Response Persists for up to 7 Years of Maralixibat Treatment

Figure 1. Maralixibat Exposure and ItchRO(Obs) Response by Participant



	>3 years	>5 years	>7 years
Responders, n	38	36	16
Persistent response, n (%)[b]	36 (95)	34 (94)	14 (88)
Intermittent/loss of response, n (%)	2 (5)	2 (6)	2 (12)

[a]Participants with *NOTCH2* variant. [b]Response was evaluated among individuals who had an initial response and was considered durable if >85% of measurements showed a reduction of ≥1 point in ItchRO(Obs). [c]Gaps in maralixibat exposure are due to treatment interruption or participants receiving placebo during Weeks 18 to 22 in ICONIC. [d]Reduction in ItchRO(Obs) relative to Baseline (first dose of maralixibat).

Conclusions

- Of those participants who remained on maralixibat therapy out to 7 years, nearly all experienced benefits in key clinical outcomes, including reductions in pruritus and sBA, as well as improvements in growth.
- Significant ($P<0.05$) reductions in total and direct bilirubin were observed in some individuals following long-term therapy.
- No meaningful changes in ALT or AST were observed.
- Maralixibat had a sustained treatment response in improving pruritus and quality of life.

Abbreviations

ALGS, Alagille syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CFB, change from Baseline; ItchRO(Obs), Itch-Reported Outcome (Observer); *JAG1*, jagged canonical Notch ligand 1; *NOTCH2*, Notch receptor 2; sBA, serum bile acid; UDCA, ursodeoxycholic acid.

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