Impact of Maralixibat on Cholestatic Pruritus in Adults Aged 16 Years and Older With Alagille Syndrome

Poster # WED-257

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Background

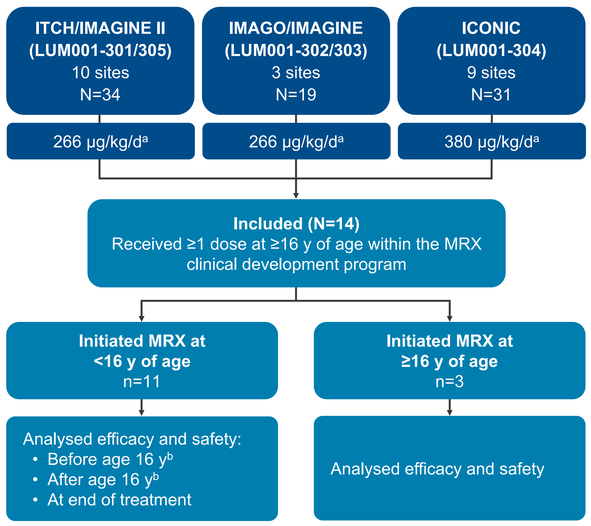
- ALGS is a rare, debilitating, autosomal dominant disorder that presents with a broad range of clinical manifestations.[1]
  - The key clinical manifestations include cholestasis, pruritus, failure to thrive, xanthomas, and progressive liver disease, all of which can lead to liver transplant or death.[1]
- Cholestatic pruritus is the most debilitating symptom of ALGS and among the most severe of any chronic liver disease.[2]
- Maralixibat (MRX), an IBAT inhibitor, is approved for the treatment of cholestatic pruritus in patients with ALGS ≥2 months of age in the EU and ≥3 months of age in the US.[3,4]
- Studies of ALGS have primarily focused on paediatric patients; however, 24% to 40.3% of patients with ALGS reach 18 years of age with their native liver and may require treatment for cholestasis and pruritus.[5,6]

Objective

- To report for the first time on the efficacy and safety of MRX in participants with ALGS aged ≥16 years transitioning to adult care and participants aged >16 years who initiate MRX treatment.

Methods

Figure 1. Study design



[a]All doses presented as MRX-free base. All patients received the daily dose appropriate for their weight, with an adult maximum dose of 28.5 mg/d.
[b]Before age 16 years is defined as the last data point prior to turning 16 years of age. After age 16 years is defined as the first data point after turning 16 years of age.

Results

Table 1. Key demographics and baseline characteristics (N=14)

Variable Mean (SE) Unless specified	Participants <16 y at MRX initiation (n=11)	Participants ≥16 y at MRX initiation (n=3)
Age, y	13.2 (0.4)	16.3 (0.3)
Sex, male, %	45.5	66.7
Pruritus, ItchRO(Obs)	2.5 (0.2)	3.1 (0.4)
Total sBA, µmol/L	130 (39)	82 (57)
Total bilirubin, µmol/L	36.4 (12.6)	27.9 (14.3)
Direct bilirubin, µmol/L	28.1 (11.5)	17.7 (10.0)
Height z score	-1.8 (0.5)	-1.0 (0.3)
Weight z score	-1.8 (0.3)	-1.1 (0.4)
ALT, U/L	174 (52)	106 (12)

- The median (min, max) duration of therapy for participants who initiated MRX at <16 years of age was 4.1 years (1.5, 5.9), with the oldest patient taking MRX at 21 years of age.
- Three participants began MRX at ≥16 years of age and were followed for a median of 3.8 years.

AEs decreased as patients got older

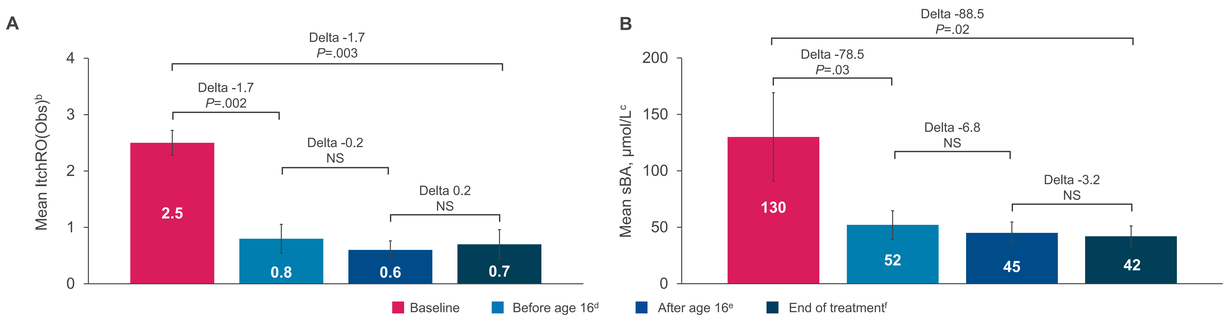
Table 2. Summary of TEAEs in full study cohort (N=14)

TEAE, n (%)	Participants aged <16 y at MRX initiation (n=11)[a]		Participants aged ≥16 y at MRX initiation (n=3)
	Before 16 y	After 16 y	
Any TEAEs	11 (100)	7 (63.6)	3 (100)
TEAEs ≥ grade 3	1 (9.1)	1 (9.1)	1 (33.3)
Treatment-related AEs	9 (81.8)	2 (18.2)	2 (66.7)
Treatment-related AEs ≥ grade 3[b]	0	0	1 (33.3)
SAEs	2 (18.2)	1 (9.1)	0
Treatment-related SAEs	0	0	0
AEs leading to study drug discontinuation	0	0	0
AEs leading to study discontinuation	0	0	0
AEs leading to death	0	0	0
Gastrointestinal TEAEs			
Diarrhoea	6 (54.5)	1 (9.1)	1 (33.3)
Abdominal pain	5 (45.5)	2 (18.2)	0

[a]Subjects were counted only once for each Preferred Term per period. Before age 16 years is defined as the last data point prior to turning 16 years of age. After age 16 years is defined as the first data point after turning 16 years of age.
[b]The treatment-related AE ≥ grade 3 was increased pruritus (grade 3) that was resolved without dose modification.

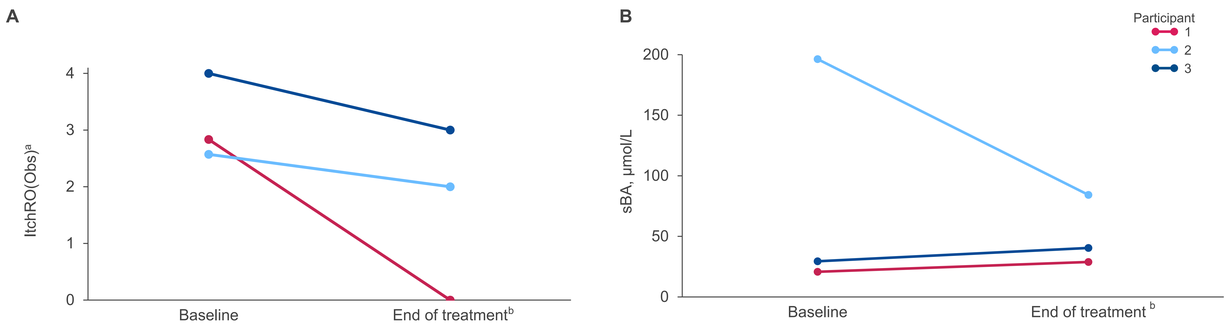
Patients receiving MRX had significant improvements in pruritus and sBA during childhood that were maintained into early adulthood

Figure 2. Change in ItchRO(Obs) (A) and sBA (B) for participants who initiated MRX treatment at <16 years of age (n=11)[a]



[a]Of 11 participants, 9 had ItchRO(Obs) scores available for all time points and were included in this analysis.
[b]ItchRO(Obs) is a 0-4 scale with ≥1-point reduction considered clinically meaningful. Mean ItchRO(Obs) was rounded to 1 decimal place. Error bars represent SE. Significance was determined using student *t* test.
[c]Mean sBA was rounded to the nearest whole number. Error bars represent SE.
[d]Average of last 2 records prior to age 16 years.
[e]Average of first 2 records after age 16 years.
[f]Average of final 2 records.

Figure 3. Change in ItchRO(Obs) (A) and sBA (B) for participants who initiated MRX treatment at ≥16 years of age (n=3)



[a]ItchRO(Obs) is a 0-4 scale with ≥1-point reduction considered clinically meaningful.
[b]Average of final 2 records.

Conclusions

- Participants receiving MRX in early adulthood showed significant improvements in pruritus and sBA upon treatment, which persisted throughout therapy.
- MRX was generally well tolerated and demonstrated a safety and tolerability profile consistent with data reported previously.
- The findings of this analysis provide critical data for patients who transition to adulthood while on MRX therapy.
- The observations presented here support the potential for MRX to have a positive impact on the management of adults with ALGS who survive with their native livers into adulthood.

Abbreviations

AE, adverse event; ALGS, Alagille syndrome; ALT, alanine aminotransferase; IBAT, ileal bile acid transporter; ItchRO(Obs), itch-reported outcome (observer); MRX, maralixibat; NS, not significant; SAE, serious adverse event; sBA, serum bile acid; TEAE, treatment-emergent adverse event.

Disclosures

G Hirschfield has nothing to disclose. D Mogul, M Baek, and P Vig are employees of and shareholders in Mirum Pharmaceuticals, Inc. BM Kamath is a consultant for Mirum Pharmaceuticals, Inc., Albireo, and Audentes and received grants from Mirum Pharmaceuticals, Inc., and Albireo.

Acknowledgments

The authors would like to thank the patients, and their families, involved in the maralixibat clinical development program to date. Maralixibat is owned by Mirum Pharmaceuticals, Inc. This analysis was funded by Mirum Pharmaceuticals, Inc. Medical writing support for the development of this poster was provided by PRECISIONscientia in Yardley, PA, USA, which was funded by Mirum Pharmaceuticals, Inc.

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Presented at European Association for the Study of the Liver (EASL) Congress; 21-24 June 2023; Vienna, Austria