Predictors of 6-year event-free survival in patients with Alagille syndrome treated with maralixibat, an IBAT inhibitor

Ronald J Sokol,[1] Emmanuel Gonzales,[2] Binita M Kamath,[3] Alastair Baker,[4] Pamela Vig,[5] Ed Tucker,[5] Will Garner,[5] Bettina E Hansen,[6] Emmanuel Jacquemin,[2] Richard J Thompson[7]

[1]Pediatric Gastroenterology, Hepatology and Nutrition and the Digestive Health Institute, Children's Hospital Colorado and University of Colorado School of Medicine, Aurora, CO, USA; [2]Hépatologie Pédiatrique, Hôpital Bicêtre, AP-HP, Université Paris-Saclay, Le Kremlin-Bicêtre, Paris, France; [3]Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children and the University of Toronto, Toronto, ON, Canada; [4]Paediatric Liver Centre, King's College Hospital, London, UK; [5]Mirum Pharmaceuticals, Inc., Foster City, CA, USA; [6]Toronto General Hospital and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada; [7]Institute of Liver Studies, King's College London, London, UK

LP16

Introduction

- Refractory pruritus and progression of end-stage liver disease are indications for liver transplantation (LT) in patients with Alagille syndrome (ALGS).[1–3]
- It is reported that only 41% of patients have native liver survival by 18.5 years of age.[2]
- Maralixibat is a novel, oral, minimally absorbed ileal bile acid transporter inhibitor (IBATi) which has shown significant and durable improvements in cholestatic pruritus and serum bile acid (sBA) levels with up to 6 years of treatment.[4–7]
- Maralixibat (LIVMARLI™) has recently been approved in the US for the treatment of cholestatic pruritus in patients with ALGS ≥1 year of age.[6]

Aim

- To examine predictors of long-term event-free survival (EFS), including transplant-free survival (TFS), in patients with ALGS enrolled in three clinical trials of maralixibat,[8–10] with up to 6 years of follow-up.

Methods

Patient selection

- Patients (N=76) with ALGS aged 1–207 months with moderate-to-severe pruritus were included in this analysis.
- Maralixibat-treated patients with ALGS from three long-term clinical trials[8–10] were followed for development of first clinically significant event (LT, surgical biliary diversion, hepatic decompensation [ascites requiring therapy and variceal bleeding], or death) for up to six years.
- TFS (LT and death only) was also assessed.
- Patients who were on maralixibat 48 weeks from the first dose and had lab results at 48 weeks were included in this analysis.

Statistical analysis

- Variables considered in the model included: liver biochemistries, platelets, pruritus (as assessed by Itch-Reported Outcome [Observer] [ItchRO(Obs)] 0–4 scale), total sBA, and age at initiation.
  - These were explored at baseline, week 48, and change from baseline to week 48.
- Goodness of fit was assessed using Harrell's concordance statistic (C-statistic).
- Variables with a value ≥0.7 (indicating a good model) were selected for further analysis.
- Cutoffs for each variable were determined via a grid search across the range of values.
- Statistical comparisons between the cutoff groups were calculated using a log-rank test.

Results

Patient population

- This analysis included 76 maralixibat-treated patients, with a median follow-up of 266 weeks (range: 53–380). Patient baseline characteristics are shown in **Table 1**.

Table 1. Baseline characteristics in maralixibat-treated patients with ALGS.

Patients (N = 76)	Median (IQR)
Age (months)	70 (33–126)
Male, n (%)	45 (59)
Total bilirubin (mg/dL)	2.3 (0.9–8.4)
sBA (µmol/L)	184 (78–361)
ItchRO(Obs) score	2.7 (2.1–3.1)
ALT (U/L)	134 (95–193)
GGT (U/L)	392 (188–751)

ALT, alanine transaminase; GGT, gamma-glutamyl transferase; ItchRO(Obs), itch-reported outcome (observer); IQR, interquartile range; sBA, serum bile acid.

Predictors of EFS

- Sixty out of 76 patients remained event-free at the time of analysis.
  - Sixteen patients experienced clinical events: LT (n = 10), decompensation (n = 3), death (n = 2), and surgical biliary diversion (n = 1).
- Variables that were predictive of EFS included: week 48 total bilirubin, week 48 sBA, change from baseline to week 48 in pruritus (ItchRO[Obs]), and age at initiation of maralixibat (**Table 2; Figure 1**).

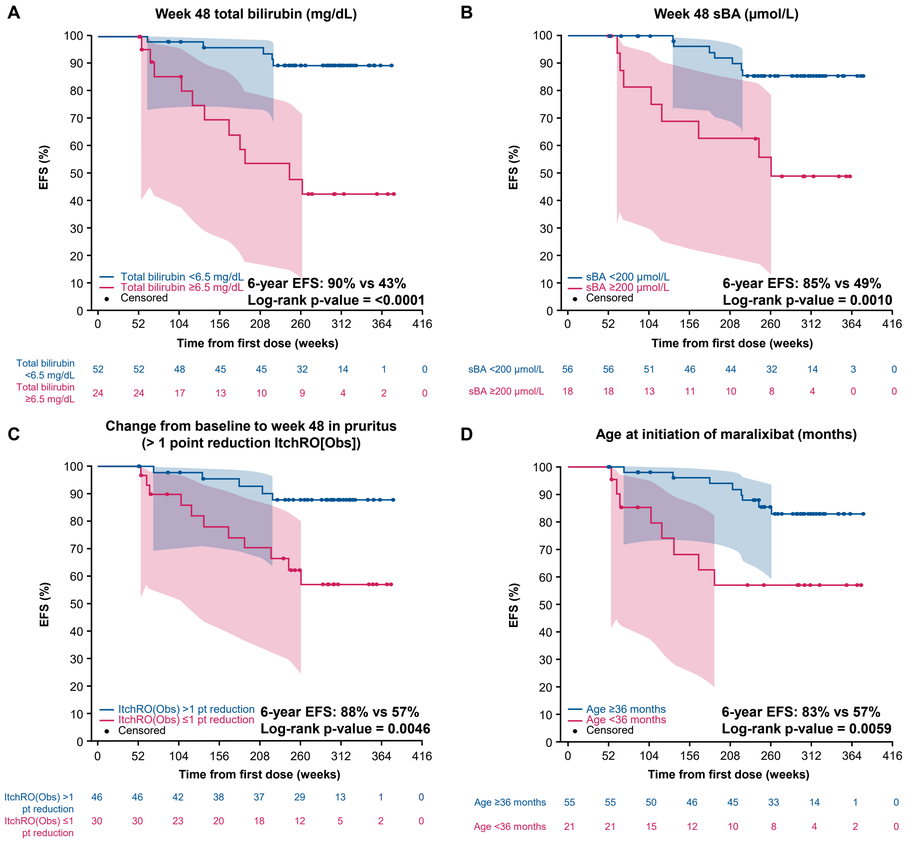
Table 2. Predictors of EFS and TFS in maralixibat-treated patients with ALGS.

Variable	Better EFS/TFS	Worse EFS/TFS	p-value
Week 48 total bilirubin	<6.5 mg/dL	≥6.5 mg/dL	
	n = 52	n = 24	
C-statistic: 0.82	6-year EFS: 90%	6-year EFS: 43%	<0.0001
C-statistic: 0.85	6-year TFS: 94%	6-year TFS: 42%	<0.0001
Week 48 sBA	<200 µmol/L	≥200 µmol/L	
	n = 56	n = 18	
C-statistic: 0.74	6-year EFS: 85%	6-year EFS: 49%	0.0010
C-statistic: 0.79	6-year TFS: 90%	6-year TFS: 49%	0.0001
Change from baseline to week 48 ItchRO(Obs)	>1 pt reduction	≤1 pt reduction	
	n = 46	n = 30	
C-statistic: 0.70	6-year EFS: 88%	6-year EFS: 57%	0.0046
C-statistic: 0.77	6-year TFS: 93%	6-year TFS: 57%	0.0007
Age at initiation of maralixibat	≥36 months	<36 months	
	n = 55	n = 21	
C-statistic: 0.72	6-year EFS: 83%	6-year EFS: 57%	0.0059
C-statistic: 0.74	6-year TFS: 87%	6-year TFS: 57%	0.0016

ALGS, Alagille syndrome; C-statistic, Harrell's concordance statistic; EFS, event-free survival; ItchRO(Obs), itch-reported outcome (observer); pt, point; sBA, serum bile acid; TFS, transplant-free survival.

- The four variables identified as predictors of EFS had high C-statistics over time, indicating that these cutoffs were stable predictors for 2–5 additional years after 48 weeks of maralixibat treatment.
- These four variables and cutoffs were similarly predictive for TFS.

Figure 1. Kaplan–Meier plots of EFS according to the following variables: **(A)** week 48 total bilirubin, **(B)** week 48 sBA, **(C)** change from baseline to week 48 ItchRO(Obs), and **(D)** age at initiation of maralixibat.



Data values under each panel indicate the number of patients at each time point.
EFS, event-free survival; ItchRO(Obs), itch-reported outcome (observer); pt, point; sBA, serum bile acid.

Distribution of predictors of EFS among the maralixibat-treated population

- Fifty-nine (79.7%) patients had ≤2 predictors of worse EFS at the end of 48 weeks of maralixibat treatment (**Table 3**). The rate of 6-year EFS was 88% in this group.
- Fifteen (20.3%) patients had ≥3 predictors of worse EFS. The rate of 6-year EFS was 31% in this group.

Table 3. Distribution of participants across worse (red) and better (green) EFS predictor variables.

Week 48 total bilirubin (mg/dL)	Week 48 sBA (µmol/L)	Age at initiation of maralixibat (months)	Week 48 Change from BL ItchRO(Obs)	Participants (N = 74)	6-year EFS (%)	Number of EFS variables
<6.5	<200	≥36	>1 pt reduction	30	89	0
<6.5	<200	≥36	≤1 pt reduction	9	89	1
≥6.5	<200	≥36	>1 pt reduction	5	89	1
<6.5	<200	<36	>1 pt reduction	5	89	1
<6.5	≥200	≥36	>1 pt reduction	2	89	1
≥6.5	≥200	≥36	>1 pt reduction	4	86	2
<6.5	<200	<36	≤1 pt reduction	3	86	2
<6.5	≥200	≥36	≤1 pt reduction	1	86	2
≥6.5	<200	<36	≤1 pt reduction	4	29	3
≥6.5	≥200	≥36	≤1 pt reduction	3	29	3
<6.5	≥200	<36	≤1 pt reduction	1	29	3
≥6.5	≥200	<36	≤1pt reduction	7	33	4

ALGS, Alagille syndrome; BL, baseline; EFS, event-free survival; ItchRO, itch-reported outcome; pt, point; sBA, serum bile acid.

Conclusions

- **In patients with ALGS, predictors of EFS with maralixibat treatment include: total bilirubin and sBA (both at week 48); pruritus reduction (from baseline to week 48); and age at initiation of maralixibat.**
- **As pruritus is often an indication for LT in patients with ALGS, these data demonstrate that improvements in pruritus with maralixibat are significantly associated with improved EFS and TFS.**
- **These data identify potential prognostic markers that may better inform patient/provider discussions of clinical outcomes in patients receiving maralixibat treatment.**

Contact information
Ronald J Sokol, ronald.sokol@childrenscolorado.org

Presented at the American Association for the Study of Liver Diseases (AASLD) The Liver Meeting™ Digital Experience (TLMdX; Virtual); USA; November 12–15, 2021.

References
1. Kamath BM, Stein P, Houwen RHJ, *et al*. Potential of ileal bile acid transporter inhibition as a therapeutic target in Alagille syndrome and progressive familial intrahepatic cholestasis. *Liver Int* 2020;40:1812–1822.
2. Vandriel S, Lilling L, She H, *et al*. Clinical features and natural history of 1154 Alagille syndrome patients: results from the international multicenter GALA study group. *J Hepatol* 2020;73:S554–S555 (and associated poster presentation).
3. Wang KS, Tiao G, Bass LM, *et al*. Analysis of surgical interruption of the enterohepatic circulation as a treatment for pediatric cholestasis. *Hepatology* 2017;65:1645–1654.
4. Shneider BL, Spino C, Kamath BM, et al. Placebo-controlled randomized trial of an intestinal bile salt transport inhibitor for pruritus in Alagille syndrome. *Hepatol Commun* 2018;2:1184–1198.
5. Malatack JJ & Doyle D. A drug regimen for progressive familial cholestasis type 2. *Pediatrics* 2018;141:e20163877.
6. Mirum Pharmaceuticals, Inc. LIVMARLI™ (maralixibat) Prescribing Information. 2021. Accessed online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214662s000lbl.pdf on October 21, 2021.
7. Gonzales E, Hardikar W, Stormon M, *et al*. Maralixibat treatment significantly reduces pruritus and serum bile acids in patients with Alagille syndrome: results from a randomized Phase II study with 4 years of follow-up. *Lancet* 2021; In press.
8. ClinicalTrials.gov ID: NCT02047318. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT02047318 on October 21, 2021.
9. ClinicalTrials.gov ID: NCT02160782. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT02160782 on October 21, 2021.
10. ClinicalTrials.gov ID: NCT02117713. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT02117713 on October 21, 2021.

Acknowledgments
The authors would like to thank the clinical trial participants, their families, and investigators for their participation in the maralixibat clinical studies 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 Steven Duckett, MSc, of Health Interactions, and funded by Mirum Pharmaceuticals, Inc.

Disclosures
P Vig, E Tucker, and W Garner are full-time employees of and shareholders in Mirum Pharmaceuticals, Inc.
R J Sokol is a consultant for Albireo Pharma, Inc., and has served on an advisory committee for Mirum Pharmaceuticals, Inc., and Retrophin, Inc.
E Gonzales is a consultant for Mirum Pharmaceuticals, Inc., Albireo Pharma, Inc., and Laboratoires CTRS, Inc.
B M Kamath has received unrestricted educational grants from Mirum Pharmaceuticals, Inc., and Albireo Pharma, Inc., and is a consultant for Mirum Pharmaceuticals, Inc., Albireo Pharma, Inc., Audentes Therapeutics, Inc., and Third Rock Ventures.
A Baker has nothing to disclose.
B E Hansen has received grant support from and is a consultant for Albireo Pharma, Inc., Calliditas, Ltd, Chemomab Therapeutics, Ltd, Mirum Pharmaceuticals, Inc., Genfit, Inc., Cymabay Therapeutics, Inc., Intercept Pharmaceuticals, Inc.
E Jacquemin has received consultancy fees from Laboratoires CTRS and Vivet Therapeutics.
R J Thompson is a consultant for Mirum Pharmaceuticals, Inc., Albireo Pharma, Inc., Generation Bio, Co., Qing Bile Therapeutics, Inc., Horizon Pharma, Plc., Alnylam, Inc., Sana Biotechnology, Inc., EVOX Therapeutics, Ltd, and is a shareholder in Qing Bile Therapeutics, Inc., and Generation Bio, Co.