The Relationship Between Serum Bile Acids and Event-Free Survival Following the Use of Maralixibat for Progressive Familial Intrahepatic Cholestasis (PFIC): Data From the MARCH/MARCH-ON Trials

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Presenter Disclosure: Richard J. Thompson

	No, Nothing to Disclose
x	Yes, Please Specify:

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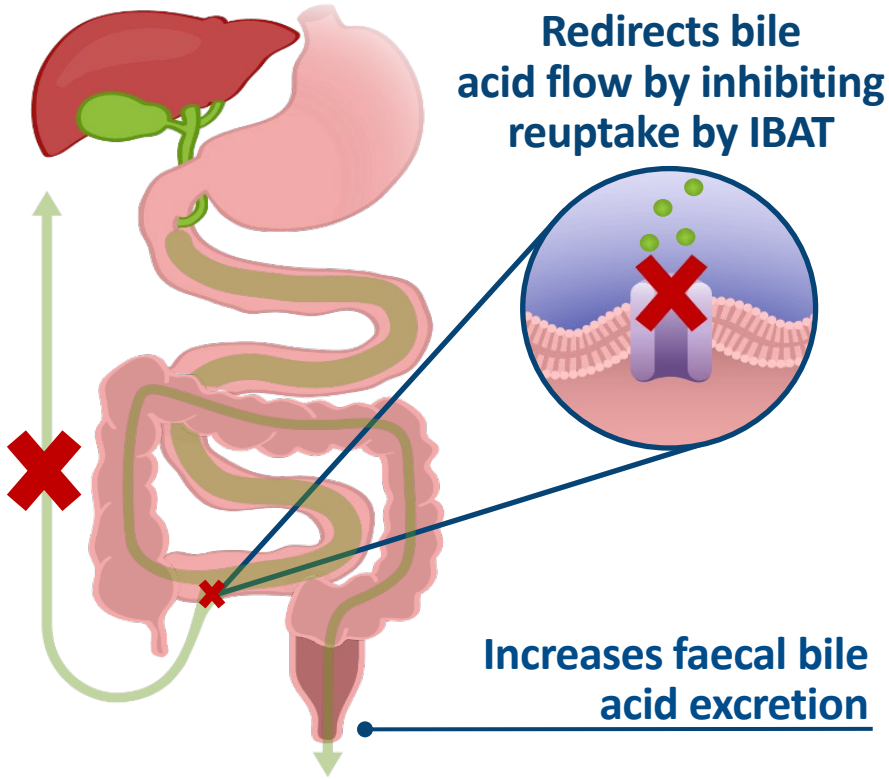
Progressive Familial Intrahepatic Cholestasis

- Genetic disorders resulting in disrupted bile composition and chronic cholestasis[1]
- Debilitating pruritus, impaired growth, reduced QoL, and progressive liver disease, with many children undergoing liver transplantation[2-5]
- PFIC types include deficiencies of[1-3]:
  - Bile salt export pump (BSEP)
  - Familial intrahepatic cholestasis-associated protein type 1 (FIC1)
  - Multidrug-resistance 3 protein (MDR3)
  - Tight junction protein 2 (TJP2)
  - Myosin VB (MYO5B)
- Current treatments include off-label antipruritic treatments, surgical biliary diversion, liver transplantation, and IBAT inhibitors approved for the treatment of cholestatic pruritus in PFIC[6-8,a,b]
  - sBA control (reduction of sBA to < 102 µmol/L or ≥ 75% reduction) after surgical biliary diversion is associated with native liver survival to 15 years (NAPPED)[2]

EU, European Union; IBAT, ileal bile acid transporter; NAPPED, NAtural course and Prognosis of PFIC and Effect of biliary Diversion; PFIC, progressive familial intrahepatic cholestasis; QoL, quality of life; sBA, serum bile acid.
[a]Maralixibat is an IBAT inhibitor approved for the treatment of PFIC in patients 3 months of age and older in the EU.[7]
[b]Odevixibat is an IBAT inhibitor approved for the treatment of PFIC in patients 6 months of age and older in the EU.[8]

1. Jacquemin E. *Clin Res Hepatol Gastroenterol*. 2012;36:S26-S35. **2.** van Wessel D, et al. *J Hepatol*. 2020;73:84-93. **3.** Kamath BM, et al. *Liver Int*. 2020;40:1812-1822. **4.** Kamath BM, et al. *Patient*. 2018;11:69-82. **5.** Loomes MK, et al. *Hepatol Commun*. 2022;6:2379-2390. **6.** Davit-Spraul A, et al. *Orphanet J Rare Dis*. 2009;**4**:**1**. **7.** LIVMARLI® (maralixibat) [summary of product characteristics]. Amsterdam, Netherlands; Mirum Pharmaceuticals International B.V. Dec 2024. **8.** BYLVAY® (odevixibat) [summary of product characteristics]. Göteborg, Sweden; Albireo AB.; July 2021.

Maralixibat: IBAT Inhibitor That Interrupts Enterohepatic Circulation



Clinical effects of maralixibat in PFIC and Alagille syndrome

- ✓ Improvements in pruritus[1-4]
- ✓ Reduction in peripheral sBA[1-4]
- ✓ Improved transplant-free survival[1,2]

Maralixibat is approved for the treatment of PFIC in patients ≥3 months of age in the EU[4]

IBAT, ileal bile acid transporter; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.

1. Gonzales E, et al. *Lancet*. 2021;398:1581-1592. **2.** Sokol RJ, et al. *Hepatology*. 2023;78:1698-1710. **3.** Miethke AG, et al. *Lancet Gastroenterol Hepatol*. 2024;9:620-631. **4.** LIVMARLI® (maralixibat) [summary of product characteristics]. Amsterdam, Netherlands; Mirum Pharmaceuticals International B.V. Dec 2024.

Study Overview

- Improved EFS has been previously demonstrated following treatment with maralixibat in patients with Alagille syndrome[1]
  - Improvement in EFS was associated with reductions in sBA levels[2]
- MARCH (NCT03905330) was a phase 3, randomised, double-blind, placebo-controlled, 26-week trial investigating the efficacy and safety of maralixibat in participants with PFIC across the broadest range of PFIC types studied to date[3,4]
  - In MARCH, participants who received maralixibat achieved statistically significant improvements in pruritus, levels of sBAs and bilirubin, and growth[3]
  - Significant and sustained responses were observed with up to 2 years of maralixibat treatment in MARCH-ON (NCT04185363), an open-label extension study for participants who completed the MARCH study[5,6]

Objective: To report on the impact of sBA reduction on EFS in participants with PFIC who received maralixibat in MARCH/MARCH-ON

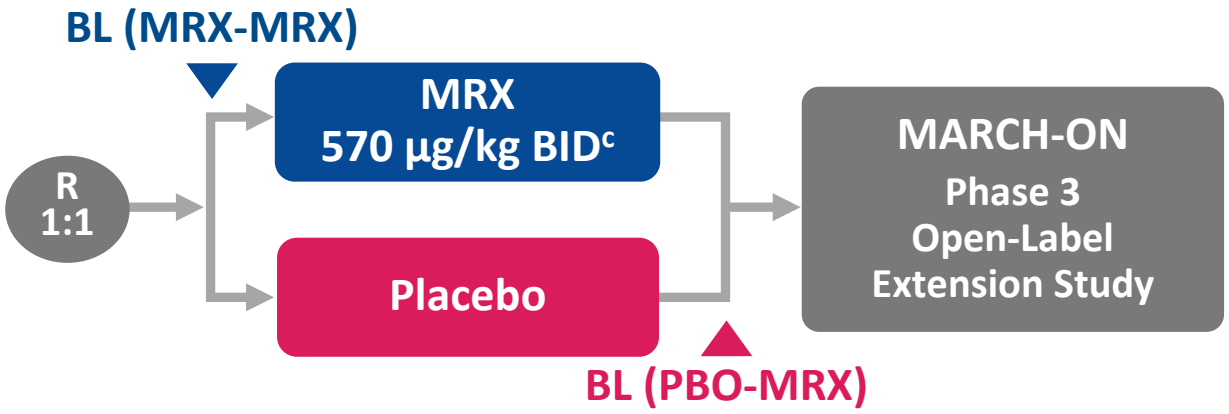
EFS, event-free survival; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.

1. Hansen BE, et al. *Hepatology*. 2024;79:1279-1292. **2.** Sokol RJ, et al. *Hepatology*. 2023;78:1698-1710. **3.** Miethke AG, et al. *Lancet Gastroenterol Hepatol.* 2024;9:620-631. **4.** ClinicalTrials.gov identifier: NCT03905330. Updated December 11, 2023. Accessed March 26, 2025. https://www.clinicaltrials.gov/study/NCT03905330. **5.** Miethke AG, et al. Presented at AASLD 2023. **6.** ClinicalTrials.gov identifier: NCT04185363. Updated February 14, 2025. Accessed March 26, 2025. https://www.clinicaltrials.gov/study/NCT04185363.

Methods

MARCH Phase 3 Study Design

Key Entry Criteria
- Diagnosis of PFIC
- Age ≥ 12 months and < 18 years at Baseline
- Persistent, moderate to severe pruritus[a]
- sBA ≥ 3 × ULN[b]



Key Endpoints and Assessments
- Pruritus[d]
- sBA
- Bilirubin
- Growth Z-scores
- Incidence of TEAEs

EFS was defined as the absence of manifestations of first events. First events were defined as liver transplant, decompensation, SBD, or death[1]

- First events were identified for participants with different PFIC types who received maralixibat in MARCH or MARCH-ON
- Two-year EFS was calculated for the overall cohort and further stratified by sBA response at Week 26 (averaged over last 12 weeks) for BSEP and FIC1 cohorts, using thresholds developed by the NAPPED Consortium (BSEP: > 75% reduction from Baseline or concentrations < 102 µmol/L; FIC1: concentrations < 65 µmol/L)[2,3]
- Data were administratively censored in June 2023

[a]ItchRO(Obs) score ≥ 1.5; [b]Criteria for primary BSEP cohort only; [c]Maralixibat 570 µg/kg is equivalent to 600 µg/kg maralixibat chloride; [d]ItchRO(Obs) is a 0 to 4 scale, where 0 = no itch, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.[4] A ≥ 1-point reduction in ItchRO(Obs) is considered clinically meaningful.
BL, baseline; BSEP, bile salt export pump; EFS, event-free survival; FIC1, Familial Intrahepatic Cholestasis 1; MRX, maralixibat; NAPPED, NAtural course and Prognosis of PFIC and Effect of biliary Diversion; PBO, placebo; PFIC, progressive familial intrahepatic cholestasis; R, randomised; sBA, serum bile acid; SBD, surgical biliary diversion; TEAE, treatment-emergent adverse events; ULN, upper limit of normal.
1. Hansen BE, et al. *Hepatology*. 2024;79:1279-1292. **2.** van Wessel DBE, et al. *Hepatology*. 2021;74:892-906. **3.** van Wessel DBE, et al. *J Hepatol.* 2020;73:84-93. **4.** Kamath BM, et al. *Hepatol Commun.* 2020;4:1012-1018.

Key Demographics and Baseline Characteristics

Parameter[a]	BSEP Cohort[b]		FIC1 Cohort[b]		All-PFIC + No Variants Cohort[c] (N = 72)
	sBA Responder (n = 12)	sBA Nonresponder (n = 15)	sBA Responder (n = 3)	sBA Nonresponder (n = 9)	
Age, years	6 (3, 11)	3 (2, 7)	6 (2, 7)	2 (1, 3)	4 (2, 8)
Sex, male, %	33	33	67	78	44
Pruritus, ItchRO(Obs) score	2.7 (1.5, 3.9)	2.0 (1.5, 3.6)	3.3 (2.8, 4.0)	2.9 (2.4, 3.5)	2.9 (1.9, 3.6)
CSS score	2 (2, 3)	2 (2, 3)	3 (2, 3)	2 (2, 3)	3 (2, 3)
sBA, µmol/L	247 (53, 386)	399 (283, 455)	132 (4, 356)	212 (199, 288)	217 (112, 354)
Total bilirubin, µmol/L	25.7 (8.1, 65.0)	47.9 (14.5, 77.8)	66.7 (42.8, 77.0)	103.5 (88.1, 199.2)	44.5 (18.8, 85.5)
Direct bilirubin, µmol/L	16.7 (3.8, 41.0)	35.1 (8.6, 59.9)	44.5 (35.1, 50.4)	114.6 (63.3, 141.1)	34.2 (12.0, 61.6)
Height Z-score	-1.8 (-3.0, -1.3)	-2.0 (-3.5, -1.2)	-1.6 (-3.7, -1.0)	-3.2 (-3.8, -2.9)	-1.2 (-2.0, -0.6)
Weight Z-score	-1.0 (-1.6, 0.0)	-1.2 (-1.8, -0.5)	-1.8 (-3.3, -0.7)	-1.7 (-3.7, -1.1)	-1.9 (-2.9, -1.2)

The median (Q1, Q3) follow-up time was 94 (68, 110) weeks

[a]All data are median (Q1, Q3) unless otherwise indicated; [b]Two BSEP participants and one FIC1 participant had missing baseline sBA data and thus could not be classified; [c]All-PFIC included BSEP, FIC1, MDR3, MYO5B, and TJP2. Did not include heterozygous, surgery, or t-BSEP participants.
BSEP, bile salt export pump; CSS, Clinical Scratch Scale; FIC1, familial intrahepatic cholestasis-associated protein 1; ItchRO(Obs), Itch-Reported Outcome (Observer); MDR3, multidrug resistance protein 3; MYO5B, myosin Vb; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid; t, truncated; TJP2, tight junction protein 2.

EFS and Events Observed in the BSEP and FIC1 Cohorts by sBA Response

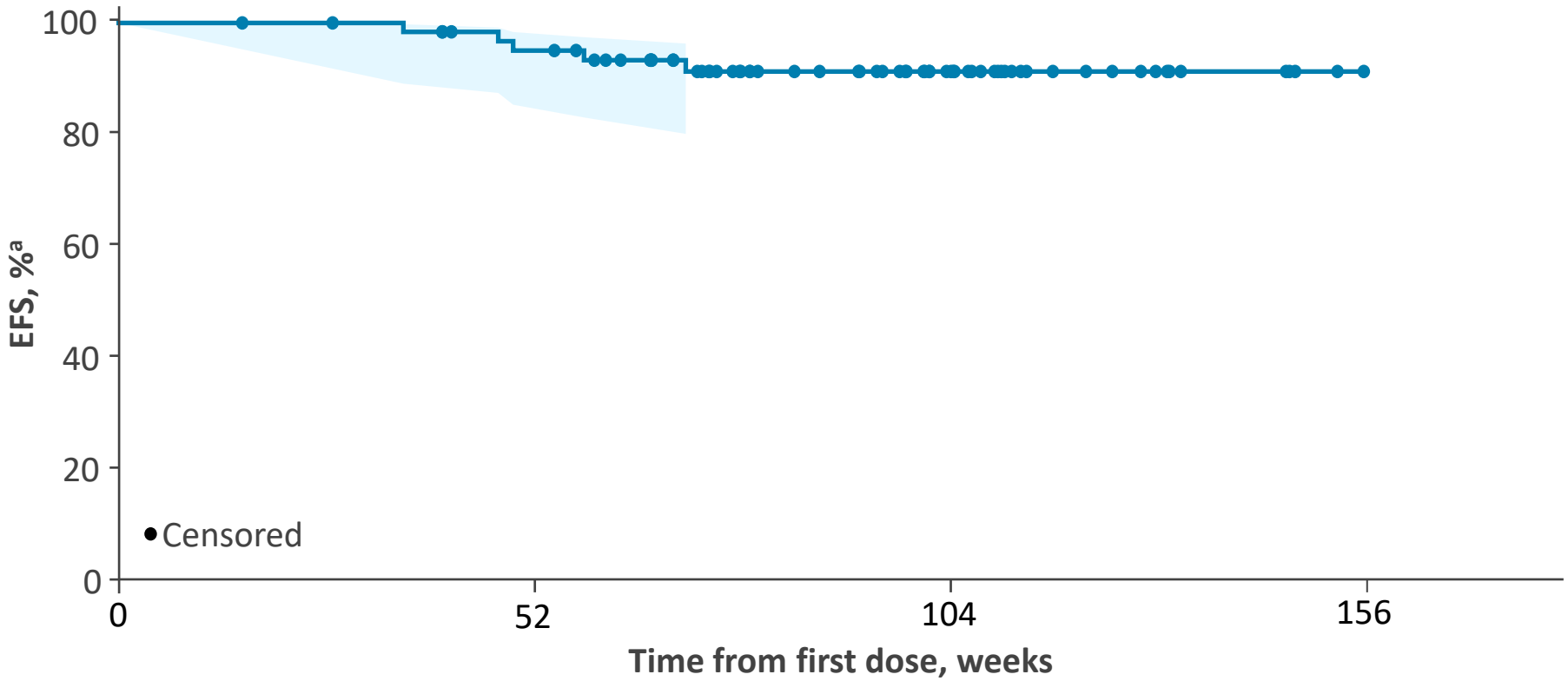
Parameter[a]	BSEP (n = 27)		FIC1 (n = 12)	
	sBA Responder (n = 12; 44%)	sBA Nonresponder (n = 15; 56%)[b]	sBA Responder (n = 3; 25%)	sBA Nonresponder (n = 9; 75%)[c]
EFS, %	100	84	100	78
Any event	0	2	0	2
Transplant	0	1	0	0
Decompensation	0	1	0	0
SBD	0	0	0	1
Death	0	0	0	1

- One participant in the MDR3 cohort with sBA reduction of 44% required a transplant

sBA responders had an EFS of 100% and sBA nonresponders had an EFS of 81% in the combined BSEP + FIC1 cohort

[a]sBA response was defined as > 75% reduction from baseline or concentrations < 102 µmol/L in the BSEP cohort and concentrations < 65 µmol/L in the FIC1 cohort;[1,2] [b]The 2 participants who had events had sBA reductions of 19% and 26%, respectively; [c]The 2 participants who had events had sBA reductions of 18% and 16%, respectively.
BSEP, bile salt export pump; EFS, event-free survival; FIC1, familial intrahepatic cholestasis-associated protein 1; MDR3, multidrug resistance protein 3; sBA, serum bile acid; SBD, surgical biliary diversion.
1. van Wessel DBE, et al. *Hepatology.* 2021;74:892-906. **2.** van Wessel DBE, et al. *J Hepatol.* 2020;73:84-93.

Kaplan-Meier Estimates of EFS in the All-PFIC + No Variants Cohort (N = 72)



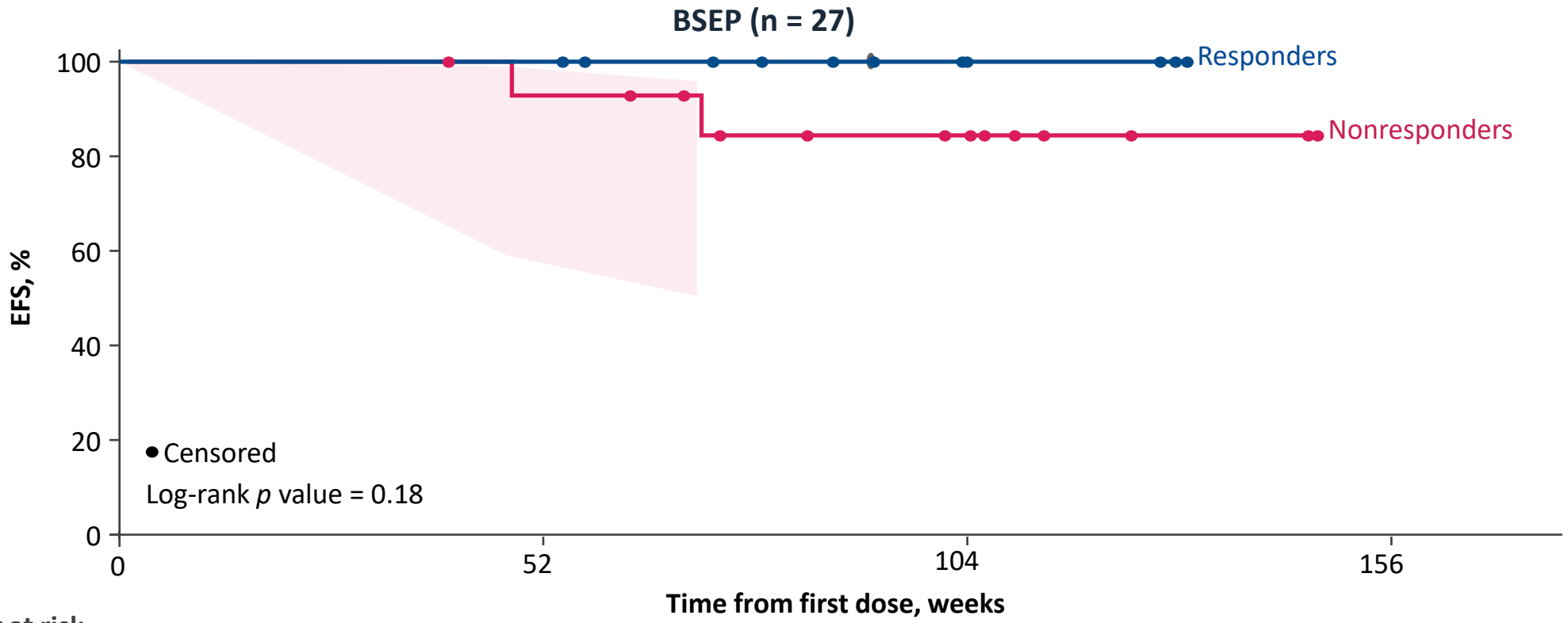
Number at risk				
All-PFIC + No Variants	72	64	25	0

92% EFS for Maralixibat-treated Participants in the All-PFIC + No Variants Cohort

EFS, event-free survival; PFIC, progressive familial intrahepatic cholestasis.

Higher EFS Was Observed Among sBA Responders Compared With Nonresponders in the BSEP Cohort

Kaplan-Meier Estimates of EFS in the BSEP Cohort by sBA Response[a]



Number at risk

Responders	12	12	3	0
Nonresponders	15	13	7	0

[a]sBA response was defined as > 75% reduction from baseline or concentrations < 102 µmol/L in the BSEP cohort and concentrations < 65 µmol/L in the FIC1 cohort.[1,2]
BSEP, bile salt export pump; EFS, event-free survival; sBA, serum bile acid.

1. van Wessel DBE, et al. *Hepatology.* 2021;74:892-906. **2.** van Wessel DBE, et al. *J Hepatol.* 2020;73:84-93.

Conclusions

- Results from this analysis demonstrate a high overall EFS in participants with PFIC who received maralixibat in MARCH/MARCH-ON clinical trials
- Consistent with NAPPED sBA response thresholds associated with EFS, participants who achieved reduction in sBA levels below the threshold (responders) did not have clinically meaningful events, whereas some individuals who had lower reductions in sBA (nonresponders) experienced events
- These data support the importance of sBA reduction in PFIC and the potential of maralixibat to facilitate this biochemical change and improve EFS in patients with PFIC
- While these results are promising, additional time is needed to assess longer-term outcomes

EFS, event-free survival; NAPPED, NAtural course and Prognosis of PFIC and Effect of biliary Diversion; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.

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Disclosures

- LDA is a consultant and advisor for Mirum Pharmaceuticals, Inc., Albireo, Selecta, Vivet Pharmaceuticals, Tome, Spark, Genespire, and Alexion.
- SPH is a hepatic safety adjudication committee (HSAC) member at Albireo and has received a research grant from Mirum Pharmaceuticals, Inc.
- DBM, TN, WG, and PV are employees of and shareholders in Mirum Pharmaceuticals, Inc.
- AGM is a consultant and has a sponsored research agreement for Mirum Pharmaceuticals, Inc.

Thank You!