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

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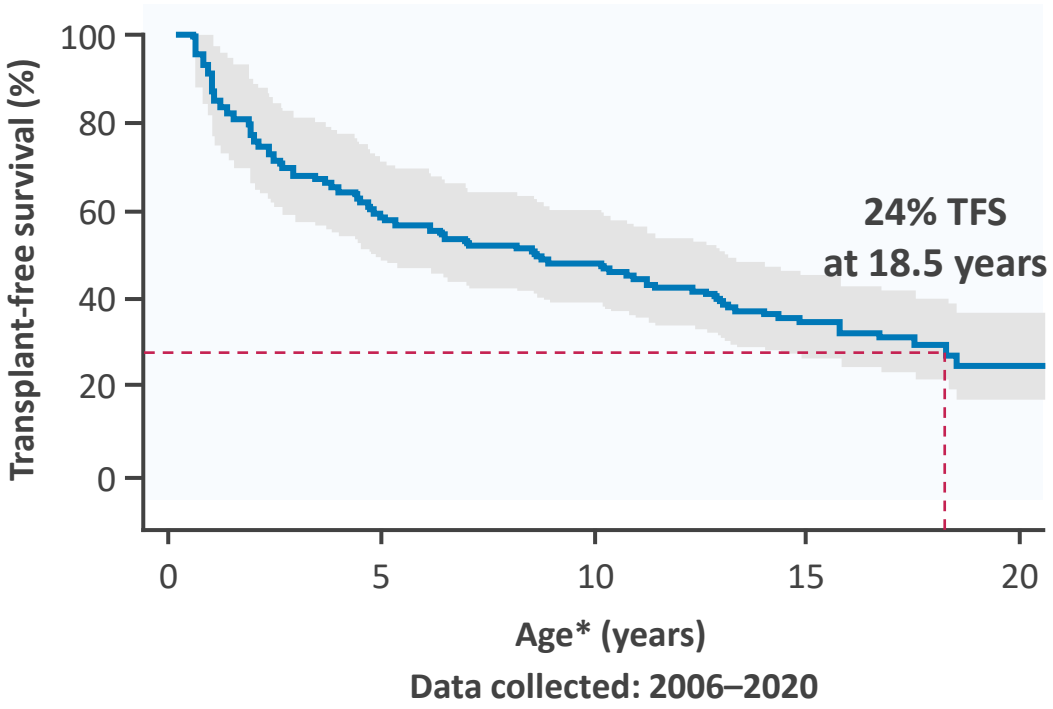
Alagille syndrome: Background

- Alagille syndrome (ALGS) is a debilitating, autosomal-dominant multi-systemic disorder characterised by intrahepatic bile duct paucity and caused by mutations in *JAGGED1* or *NOTCH2*[1,2]
- ALGS is a rare disease with an incidence of 1 in 30,000–50,000 live births[3]
- The key liver-related clinical features of ALGS are cholestasis, jaundice and severe pruritus, as well as a broad range of other clinical manifestations[4–7]
- Cholestatic pruritus and xanthomas represent a significant unaddressed clinical burden of disease, leading to greatly diminished quality of life[7]

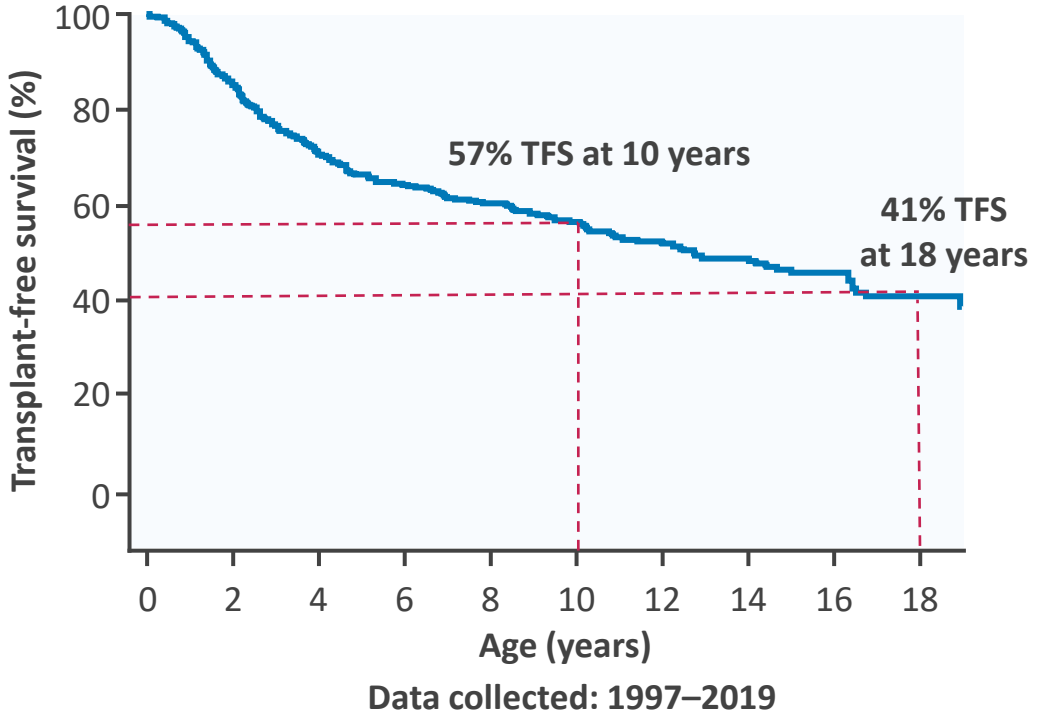
1. Saleh M, *et al*. *Appl Clin Genet* 2016;9:75–82; 2. NORD. Alagille syndrome. Available at: https://rarediseases.org/rare-diseases/alagille-syndrome/. Accessed June 2022;
3. Leonard LD, *et al. Eur J Hum Genet* 2014;22:435; 4. Kamath BM, *et al*. *J Pediatr Gastroenterol Nutr* 2018;67:148–156; 5. Turnpenny P & Ellard S. *Eur J Hum Genet* 2012;20:251–257;
6. Berniczei-Royko A, *et al*. *Med Sci Monit* 2014;20:476–480; 7. Kamath BM, *et al*. *Hepatol Communs* 2020;4:387–398.

Substantial risk for liver transplantation in patients with ALGS

ChiLDReN (North America network)[1] Transplant-free survival (TFS) in patients with ALGS (N = 293)



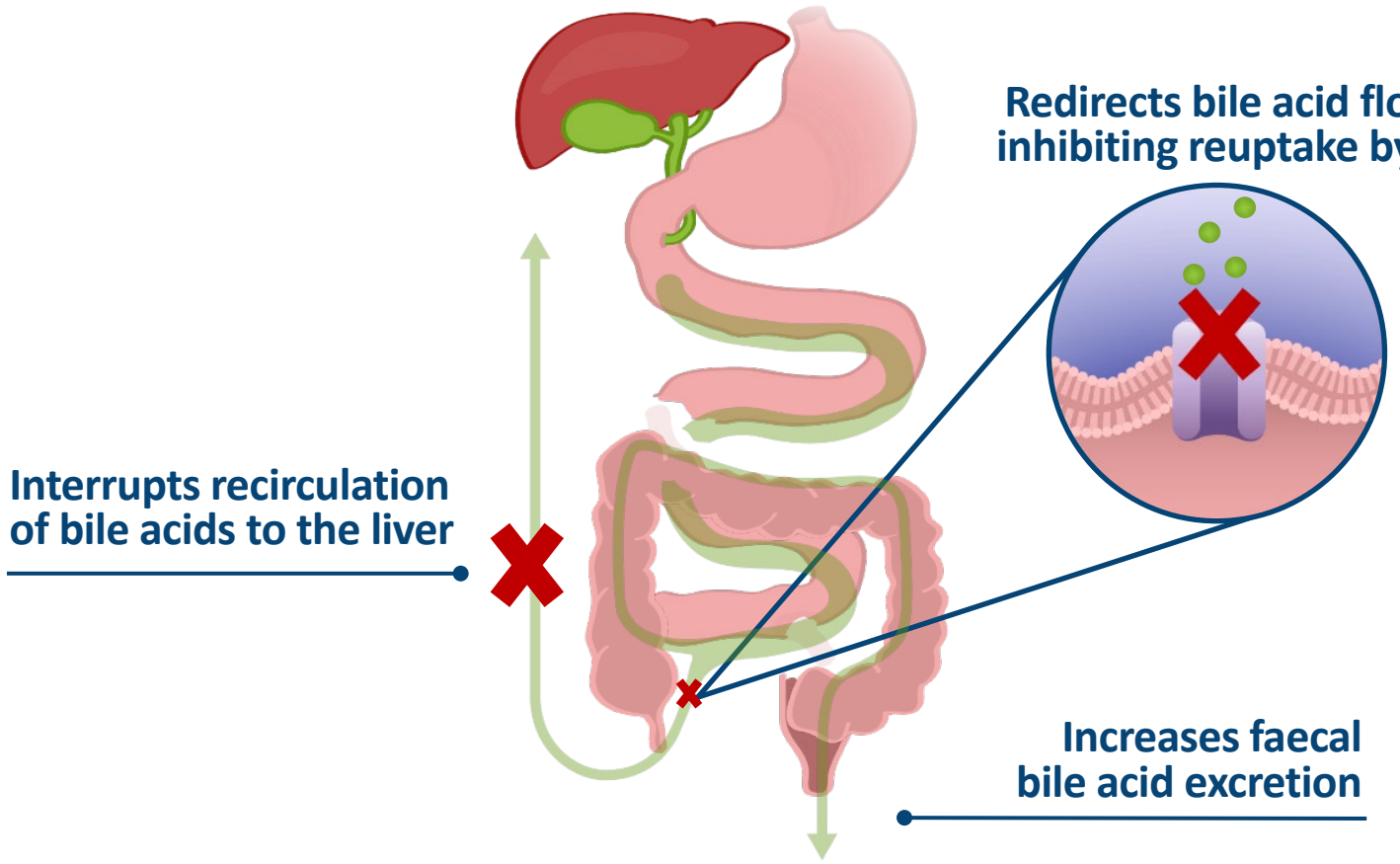
GALA[2] (Global) Transplant-free survival (TFS) in patients with ALGS presenting with neonatal cholestasis (N = 911)



Refractory pruritus and progression of end-stage liver disease are indications for liver transplantation in patients with ALGS[1–3]

*Left truncated at baseline age.
ALGS, Alagille syndrome; TFS, transplant-free survival.
1. Kamath BM, *et al. Hepatol Commun* 2020;4:387–398; 2. Vandriel S, *et al. J Hepatol* 2020;73:S554–S555 (and associated poster presentation); 3. Wang KS, *et al. Hepatology* 2017;65:1645–1654.

Maralixibat: IBAT inhibitor that interrupts enterohepatic circulation



Clinical effects of maralixibat in cholestasis:

- ✓ Improvements in pruritus (itch)
- ✓ Reductions in sBA
- ✓ Improved TFS
- ✓ Impact on markers of bile acid synthesis: 7α-C4

Maralixibat received FDA approval in 2021 for the treatment of cholestatic pruritus in patients with ALGS 1 year of age and older[1,2]

FDA, US Food and Drug Administration; IBAT, ileal bile acid transporter; sBA, serum bile acid.

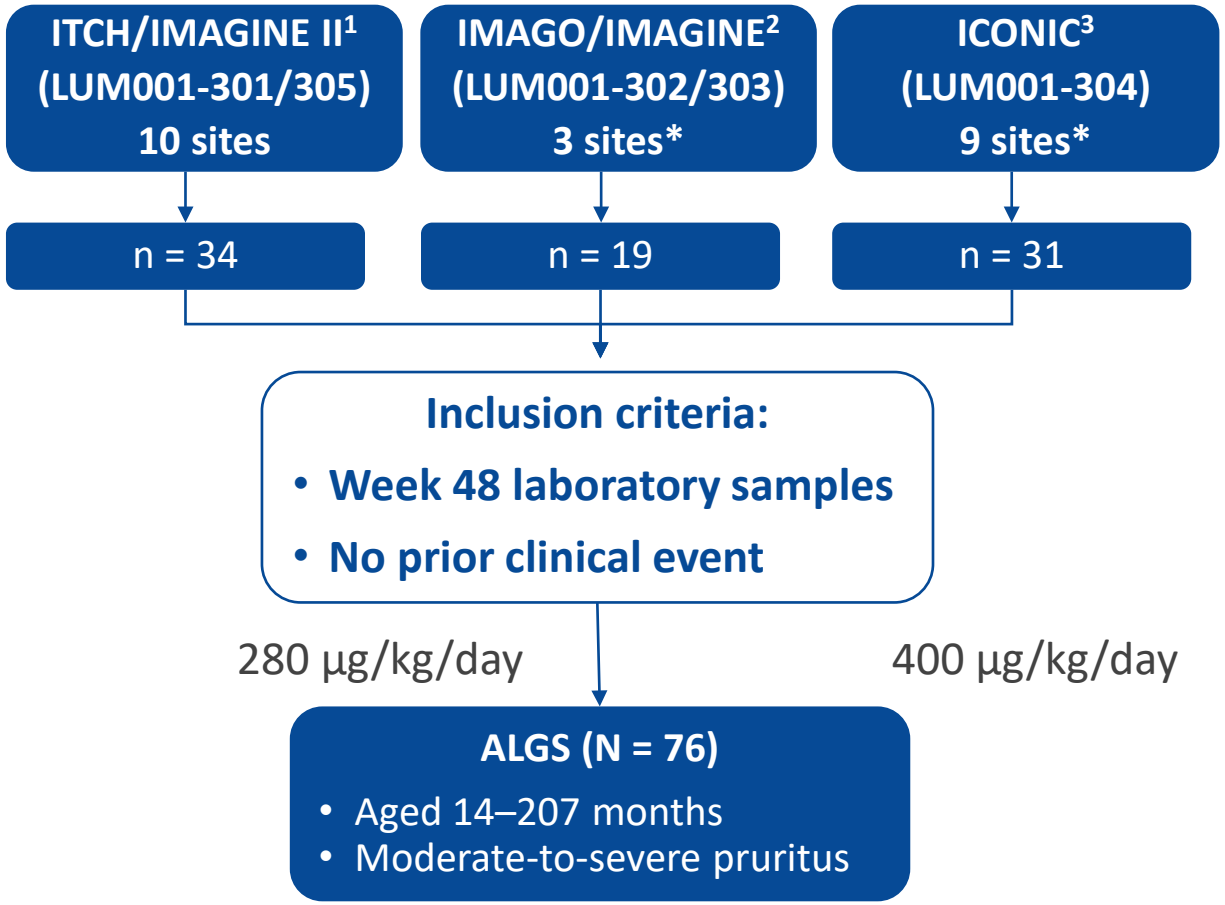
1. Gonzales E, *et al. Lancet* 2021;398:1581–1592; 2. Mirum Pharmaceuticals, Inc. LIVMARLI® (maralixibat) PI. 2021. Accessed online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214662s001lbl.pdf on April 20, 2022.

Study aim

To identify predictors of long-term event-free survival and transplant-free survival in patients with ALGS enrolled in three clinical trials of maralixibat,[1–3] an ileal bile acid transporter inhibitor, with up to 6 years of follow-up

1. ClinicalTrials.gov ID: NCT02047318. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT02047318 on February 28, 2022; 2. ClinicalTrials.gov ID: NCT02160782. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT02160782 on February 28, 2022; 3. ClinicalTrials.gov ID: NCT02117713. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT02117713 on February 28, 2022.

Methods: Study design



Endpoints of this analysis
• **Event-free survival: time to first clinically significant event** (e.g. liver transplant, surgical biliary diversion, hepatic decompensation [ascites requiring therapy and variceal bleeding], death)
• **Transplant-free survival: time to liver transplant or death, whichever came first**

*There was a common site in both IMAGO/IMAGINE and ICONIC trials. The total number of different sites for the N = 76 overall study population was 21.

1. ClinicalTrials.gov ID: NCT02117713. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT02117713 on February 28, 2022; 2. ClinicalTrials.gov ID: NCT02047318. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT02047318 on February 28, 2022; 3. ClinicalTrials.gov ID: NCT02160782. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT02160782 on February 28, 2022.

Methods: 43 variables included in the model

- The following variables were considered for inclusion in the model
  - Laboratory values (e.g. bilirubin, sBA, ALT)
  - Clinical values (e.g. ItchRO[Obs], weight, quality of life)
  - Demographics (e.g. age at enrolment)
  - Study characteristics (e.g. study number)
- Variables were considered at multiple timepoints, and as relative changes and absolute values
- Only variables that met a C-statistic threshold ≥0.7 were considered in the models

ALT, alanine transaminase; sBA, serum bile acids; C-statistic, concordance statistic; ItchRO(Obs), Itch-Reported Outcome(Observer).

Baseline characteristics in maralixibat-treated patients with ALGS

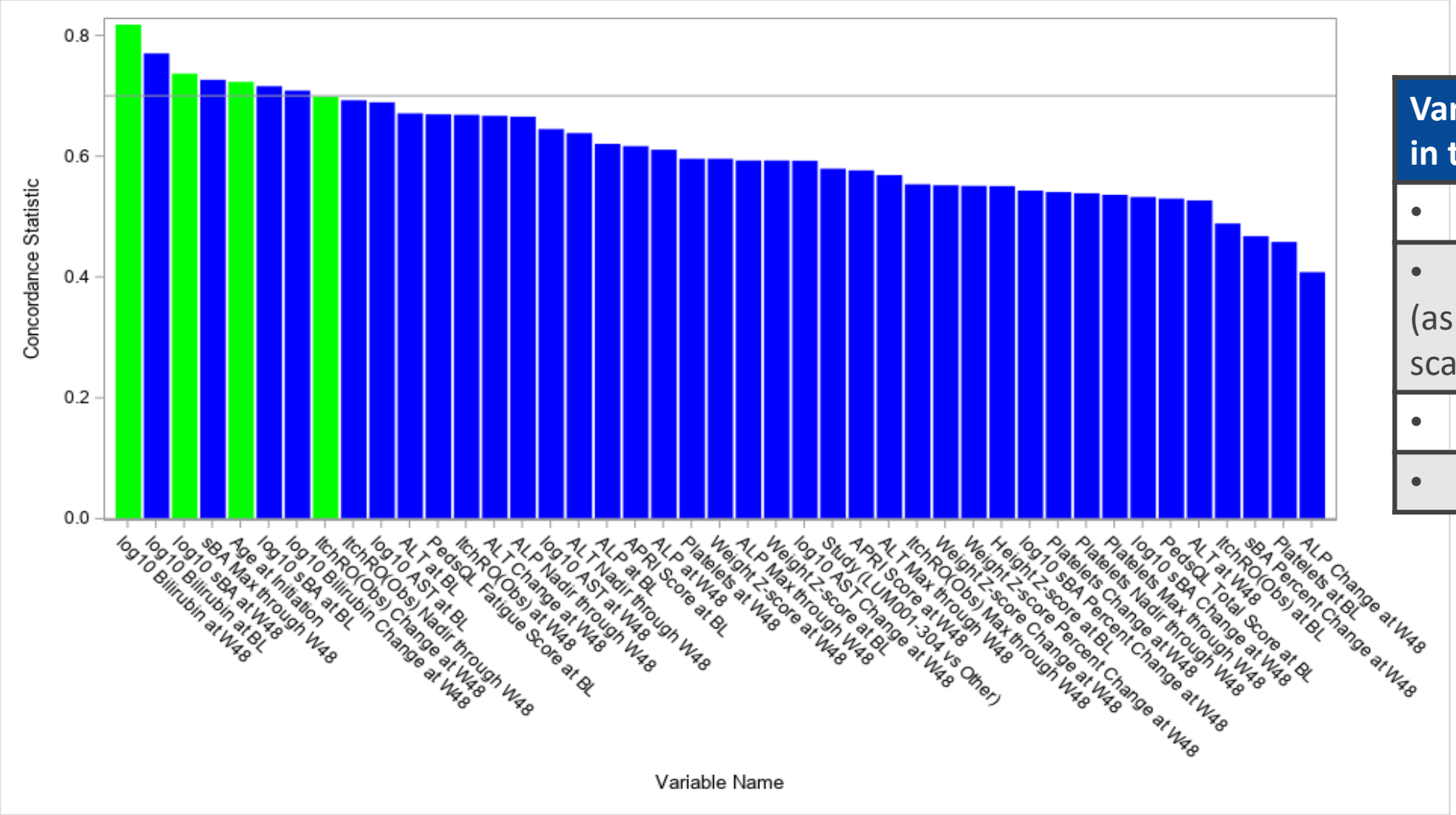
Patients (N = 76)	Median (IQR)
Age at first maralixibat dose, years	5.82 (2.76, 10.53)
Male, n (%)	45 (59)
Weight Z-score	–1.41 (–2.15, –0.67)
ItchRO(Obs) weekly morning average score	2.71 (2.14, 3.14)
Total sBA, µmol/L	184 (78, 361)
Total bilirubin, mg/dL	2.3 (0.9, 8.4)
Direct bilirubin, mg/dL	1.7 (0.6, 6.9)
Albumin, g/dL	4.6 (4.3, 4.7)
ALT, U/L	134 (95, 193)
AST, U/L	130 (96, 185)
GGT, U/L	392 (188, 751)
Total cholesterol, mg/dL	313 (247, 456)
INR	1.00 (1.00, 1.10)
Platelets, 10^9/L	293 (223, 383)

Median follow-up: 5.1 years (range 1.0–7.3)

AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; INR, international normalised ratio; IQR, interquartile range.

Descending plot of C-statistics calculated for each variable in the model

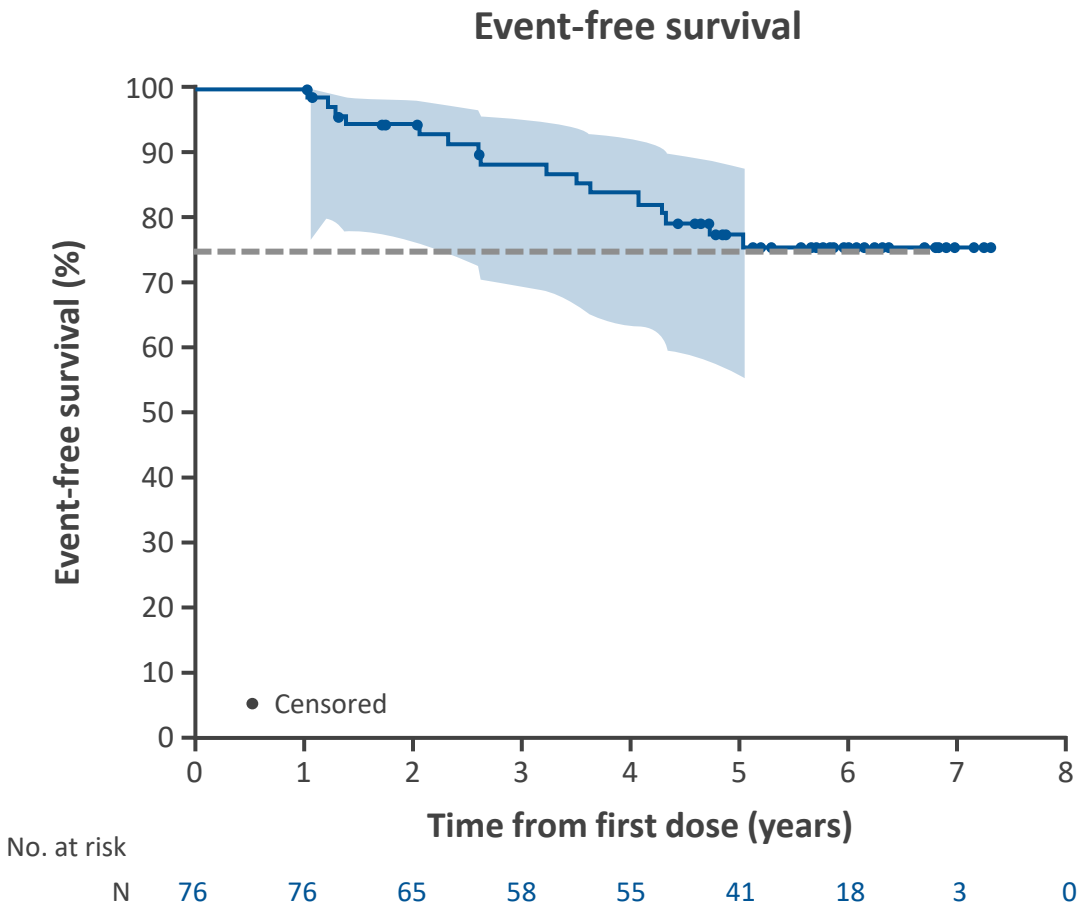
The four variables identified as predictors of event-free survival had high C-statistics over time, indicating that these cutoffs were stable predictors for 2–5 additional years after 48 weeks of maralixibat treatment

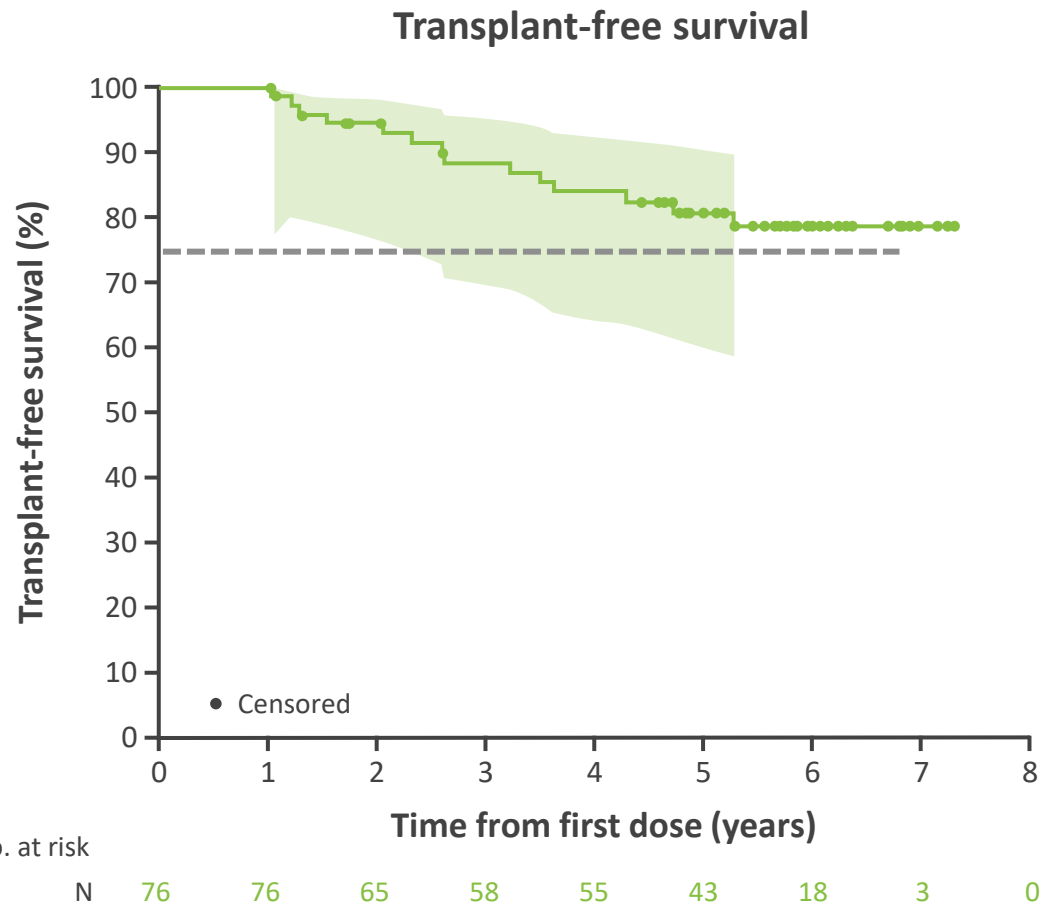


Variables selected for inclusion in the model (C-statistic >0.7):
• Bilirubin at 48 weeks
• Change in pruritus (as assessed by ItchRO[Obs] 0–4 scale)
• Total sBA at 48 weeks
• Age at enrolment

ALT, alanine transaminase; ALP, alkaline phosphatase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; BL, baseline PedsQL, Pediatric Quality of Life Inventory™ (PedsQL) 4.0 Generic Core Scales.

Most maralixibat-treated patients with ALGS remained event-free and transplant-free after 6 years

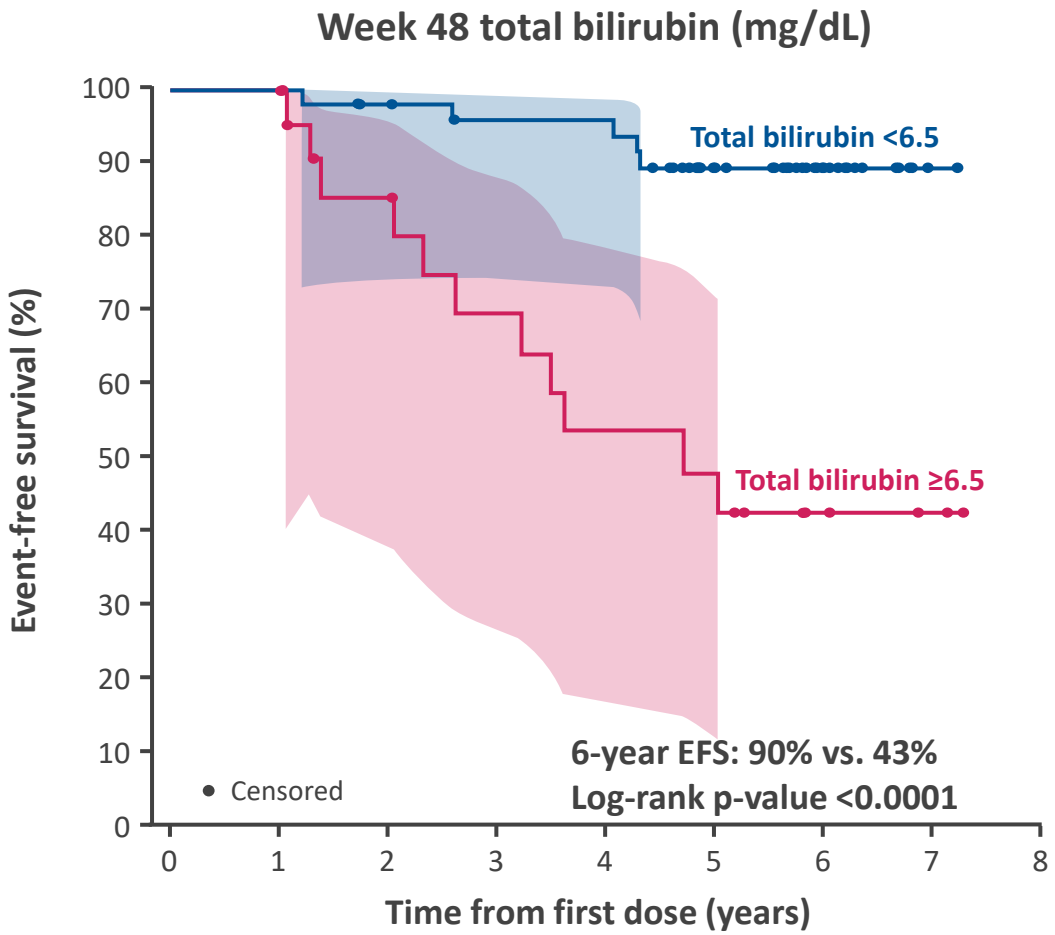




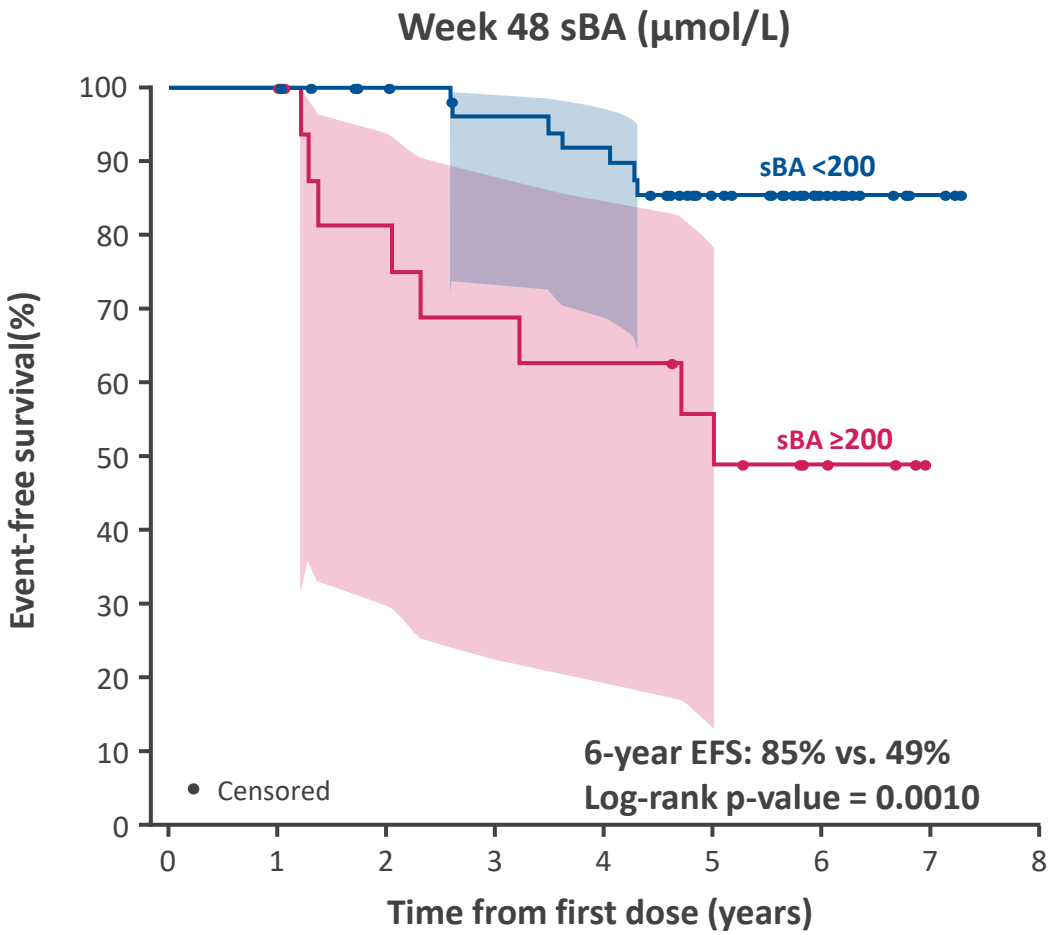
76% and 79% of maralixibat-treated patients with ALGS remained event-free and transplant-free, respectively, at 6 years after treatment initiation

Data values under each panel indicate the number of patients at risk for an event at each time point. Dashed line indicates 75% survival threshold.

Week 48 total bilirubin and sBA are significant predictors of event-free survival



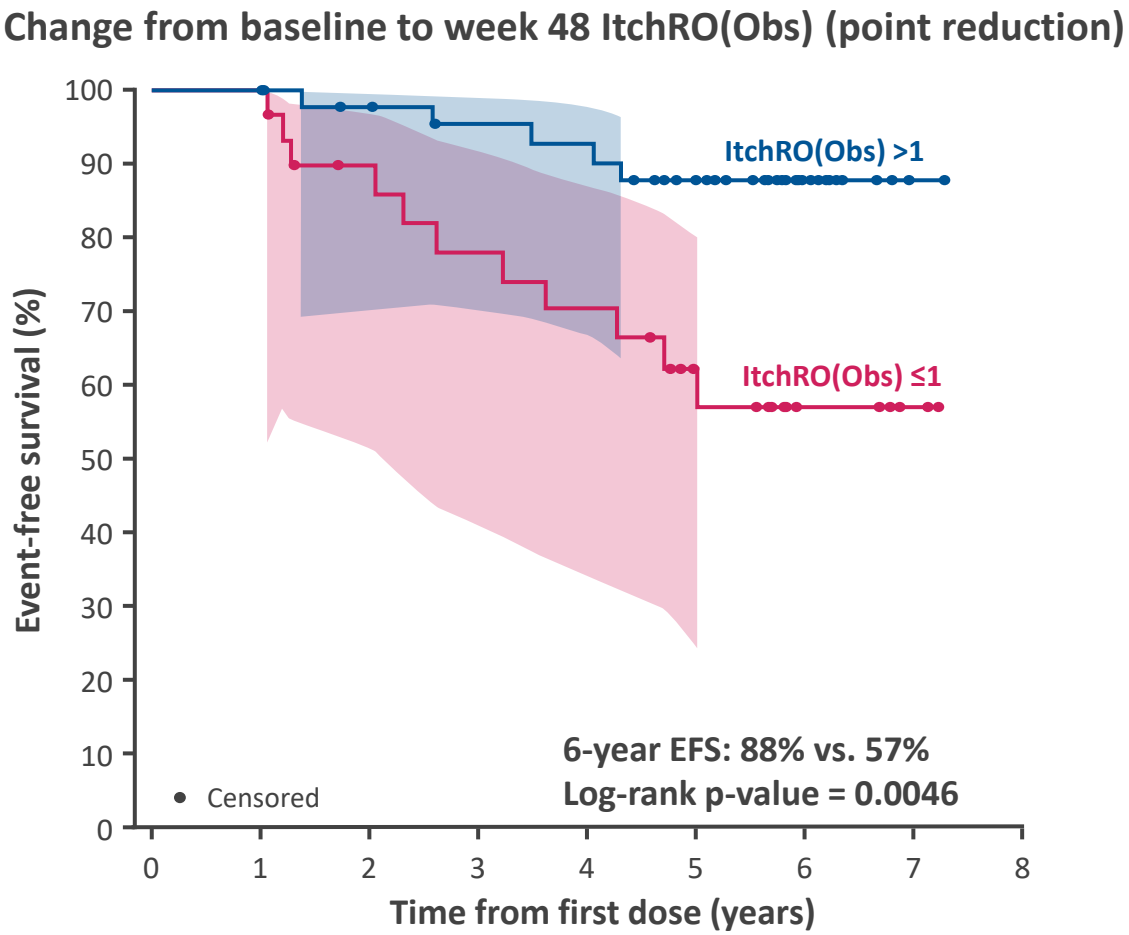
Total bilirubin <6.5 mg/dL	52	52	48	45	45	32	14	1	0
Total bilirubin ≥6.5 mg/dL	24	24	17	13	10	9	4	2	0



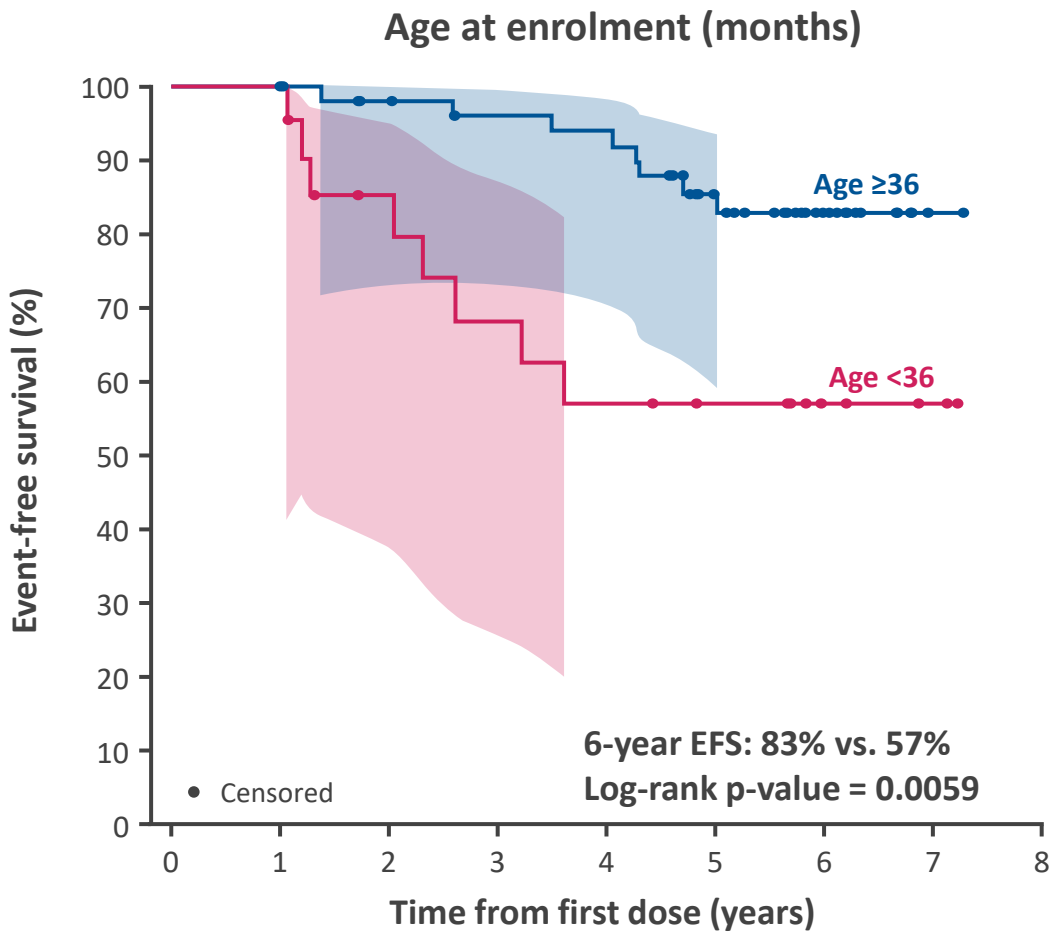
sBA <200 µmol/L	56	56	51	46	44	32	14	3	0
sBA ≥200 µmol/L	18	18	13	11	10	8	4	0	0

Data values under each panel indicate the number of patients at risk for an event at each time point.

Pruritus reduction and age at enrolment are significant predictors of event-free survival



ItchRO(Obs) >1 point reduction	46	46	42	38	37	29	13	1	0
ItchRO(Obs) ≤1 point reduction	30	30	23	20	18	12	5	2	0



Age ≥36 months	55	55	50	46	45	33	14	1	0
Age <36 months	21	21	15	12	10	8	4	2	0

Data values under each panel indicate the number of patients at risk for an event at each time point.

Distribution of predictors of EFS among the maralixibat-treated population

Week 48 total bilirubin (mg/dL)	Week 48 sBA (µmol/L)	Age at enrolment (months)	Change from baseline to week 48 ItchRO(Obs) (pt reduction)	Participants (N = 74)	6-year EFS (%)*	EFS variables (n)
<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		
<6.5	<200	<36	>1 pt reduction	5		
<6.5	≥200	≥36	>1 pt reduction	2		
≥6.5	≥200	≥36	>1 pt reduction	4	86	2
<6.5	<200	<36	≤1 pt reduction	3		
<6.5	≥200	≥36	≤1 pt reduction	1		
≥6.5	<200	<36	≤1 pt reduction	4	29	3
≥6.5	≥200	≥36	≤1 pt reduction	3		
<6.5	≥200	<36	≤1 pt reduction	1		
≥6.5	≥200	<36	≤1 pt reduction	7	33	4

n = 59 (79.7%)
6-year EFS: 88%

n = 15 (20.3%)
6-year EFS: 31%

Predicts for better EFS Predicts for worse EFS

Two or more predictors of better event-free survival (EFS) result in an increase in 6-year EFS from 31% to 88%

Proportion with events does not account for censoring and is not a survival probability.

Predictors of transplant-free survival in maralixibat-treated patients with ALGS

Variable	Better Transplant-free Survival	Worse Transplant-free Survival	p-value
Week 48 total bilirubin C-statistic: 0.85	**<6.5 mg/dL** n = 52 6-year TFS: 94%	**≥6.5 mg/dL** n = 24 6-year TFS: 42%	**<0.0001**
Week 48 sBA C-statistic: 0.79	**<200 µmol/L** n = 56 6-year TFS: 90%	**≥200 µmol/L** n = 18 6-year TFS: 49%	**0.0001**
Change from baseline to week 48 ItchRO(Obs) C-statistic: 0.77	**>1 pt reduction** n = 46 6-year TFS: 93%	**≤1 pt reduction** n = 30 6-year TFS: 57%	**0.0007**
Age at enrolment C-statistic: 0.74	**≥36 months** n = 55 6-year TFS: 87%	**<36 months** n = 21 6-year TFS: 57%	**0.0016**

Week 48 total bilirubin, week 48 sBA, change from baseline to week 48 in pruritus (ItchRO[Obs]), and age at enrolment were similarly predictive for event-free survival and transplant-free survival

C-statistic, Harrell's concordance statistic; TFS, transplant-free survival.

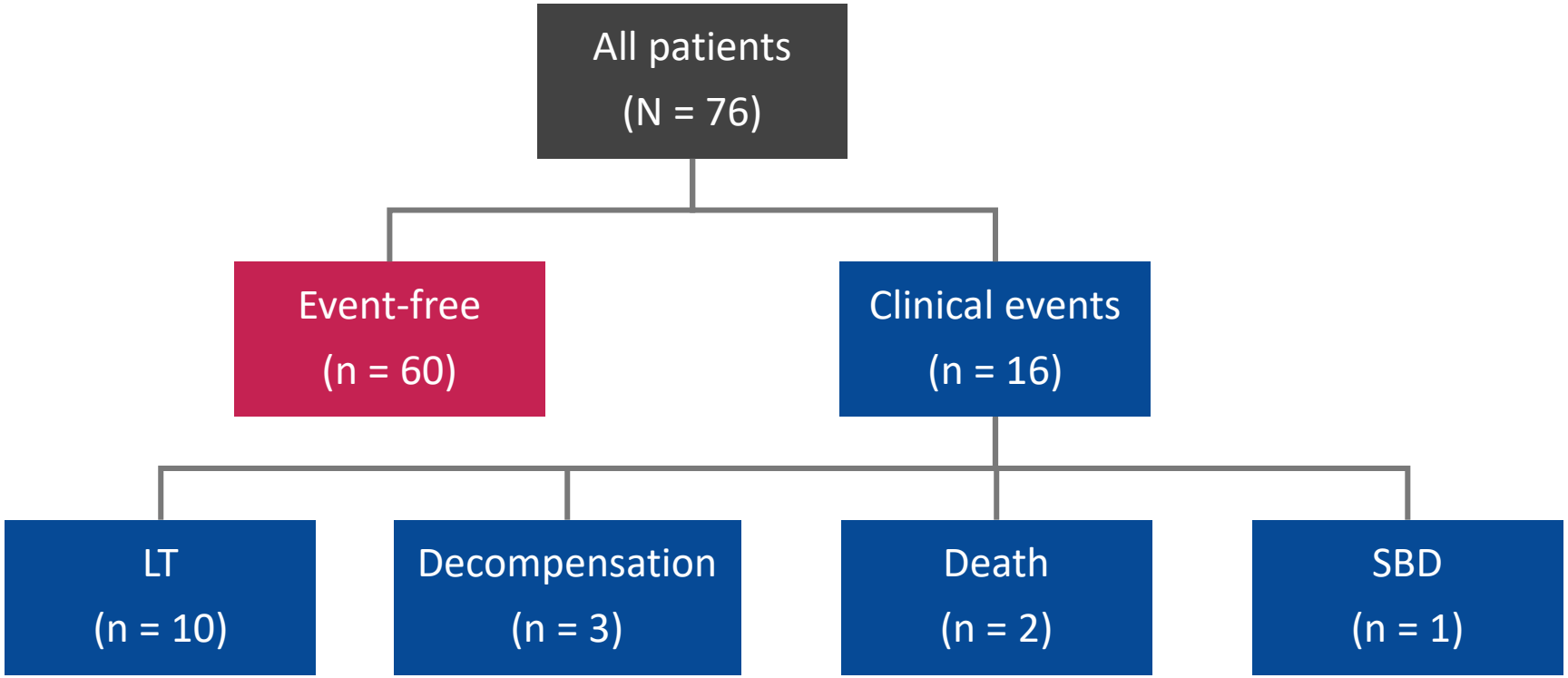
Summary and conclusions

- In patients with ALGS, predictors of long-term event-free survival with maralixibat treatment include:
  - Total bilirubin (at week 48), sBA (at week 48), pruritus reduction (from baseline to week 48), age at enrolment
- Most (>75%) maralixibat-treated patients with ALGS remained event-free and transplant-free after 6 years
- Improvement in pruritus is significantly associated with improved event-free survival and transplant-free survival
- These data identify potential prognostic markers that may better inform patient/provider discussions of clinical outcomes in patients with ALGS receiving maralixibat treatment

THANK YOU!

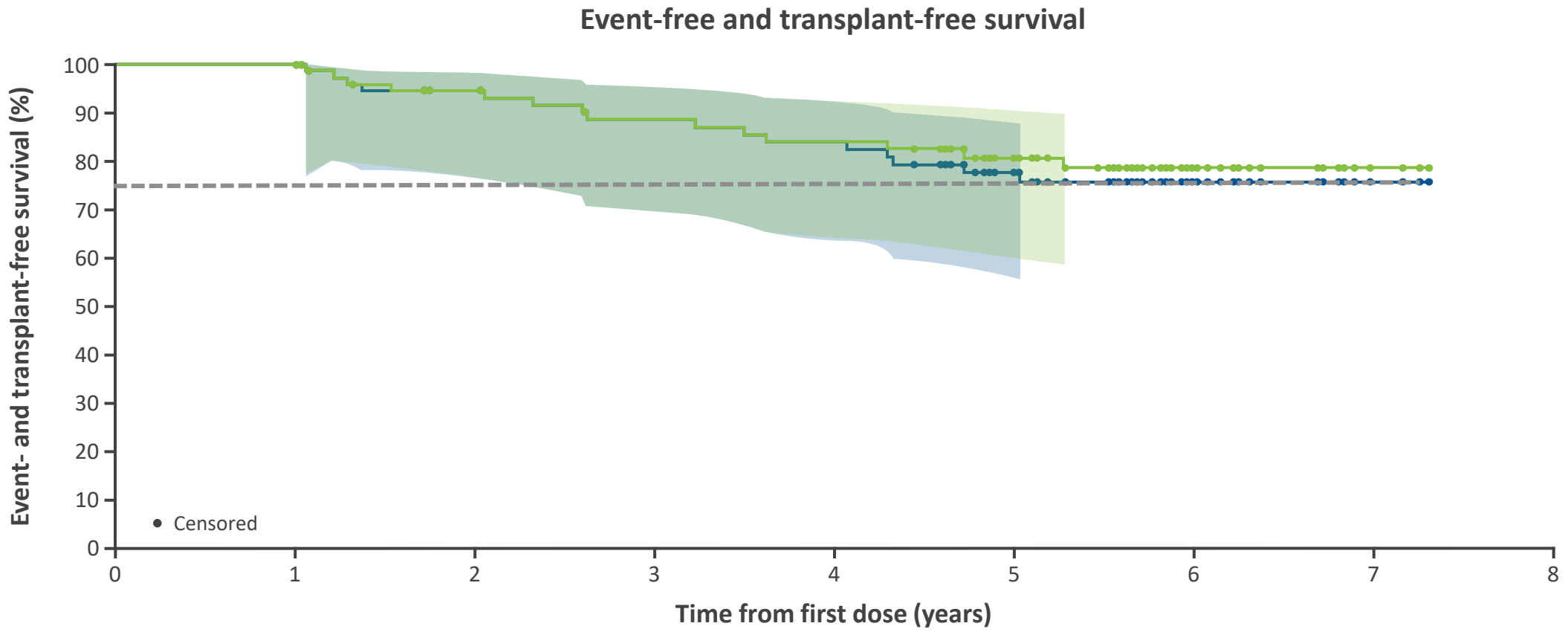
Back-up

Patient flow through the study



SBD, surgical biliary diversion; LT, liver transplantation.

Most maralixibat-treated ALGS patients remained event-free and transplant-free after 6 years



No. at risk

Event-free survival	76	76	65	58	55	41	18	3	0
Transplant-free survival	76	76	65	58	55	43	18	3	0

76% and 79% of maralixibat-treated patients with ALGS remained event-free and transplant-free, respectively, at 6 years after treatment initiation

Data values under each panel indicate the number of patients at risk for an event at each time point. Dashed line indicates 75% survival threshold.