The Annual Alex Mowat Prize Nominee

INDIGO Study

Serum bile acid control in long-term maralixibat-treated patients is associated with native liver survival in children with progressive familial intrahepatic cholestasis due to bile salt export pump deficiency

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Author Disclosures

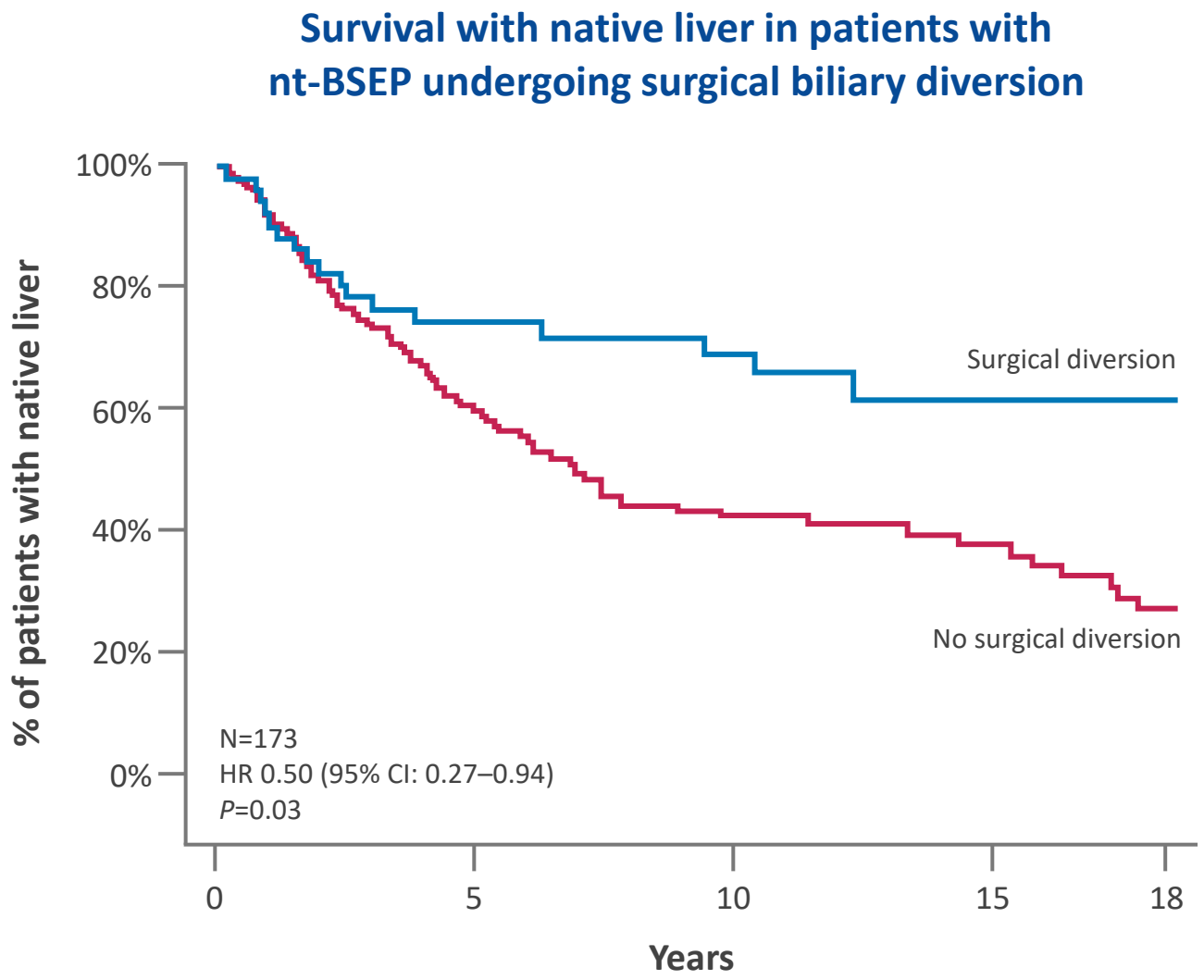
- R. Thompson discloses the following financial relationships with commercial interest;
  - **Consultancy**: Mirum Pharmaceuticals, Inc., Albireo Pharma, Inc., GenerationBio, Qing Bile Therapeutics, Horizon Pharma, Alnylam Pharmaceuticals, Sana Biotechnology, Inc., EVOX Therapeutics Ltd.
  - **Share options:** Qing Bile Therapeutics, GenerationBio, Rectify Therapeautics
- The co-authors disclose the following financial relationships with commercial interest;
  - D. Kelly is an advisor for Intercept Pharmaceuticals, Mirum Pharmaceuticals, Inc., Albireo Pharma, Inc., Astellas Pharma, Inc.; S. Rajwal is a full-time employee of the NHS Trust; T. Jaecklin is a full-time employee of Mirum Pharmaceuticals, Inc.; A J. Wardle and P. Vig are full-time employees and shareholders of Mirum Pharmaceuticals, Inc.; A. Miethke is a full-time employee of Cincinnati Children's Hospital Medical Center, a consultant for Mirum Pharmaceuticals Inc. and Metacrine, Inc., and has received grants from the National Institute of Health; R. H. Squires is a consultant for Mirum Pharmaceuticals, Inc., and has royalties in and contributes to Up-To-Date; K. M. Loomes is a consultant for Mirum Pharmaceuticals, Inc., Albireo Pharma, Inc. and Travere Therapeutics; N. Soufi has received grants from Albireo Pharma and Inc. Mirum Pharmaceuticals, Inc.

Background and Treatment Landscape for BSEP Deficiency

- Also called Progressive Familial Intrahepatic Cholestasis Type 2 (PFIC2)
  - Rare genetic defect of ABCB11 gene
  - Cholestasis and end-stage liver disease, severe pruritus, lipid-soluble vitamin deficiency, growth deficit
- No approved pharmacological treatments for BSEP deficiency
- Current treatments include surgical biliary diversion and liver transplantation
- Interruption of the enterohepatic circulation with surgical biliary diversion has shown native liver survival if serum bile acids are controlled post-surgery[1]

1. Van Wessel DBE, *et al. J Hepatol* 2020; **73:**84–93.

Native Liver Survival ± Surgical Biliary Diversion (NAPPED)



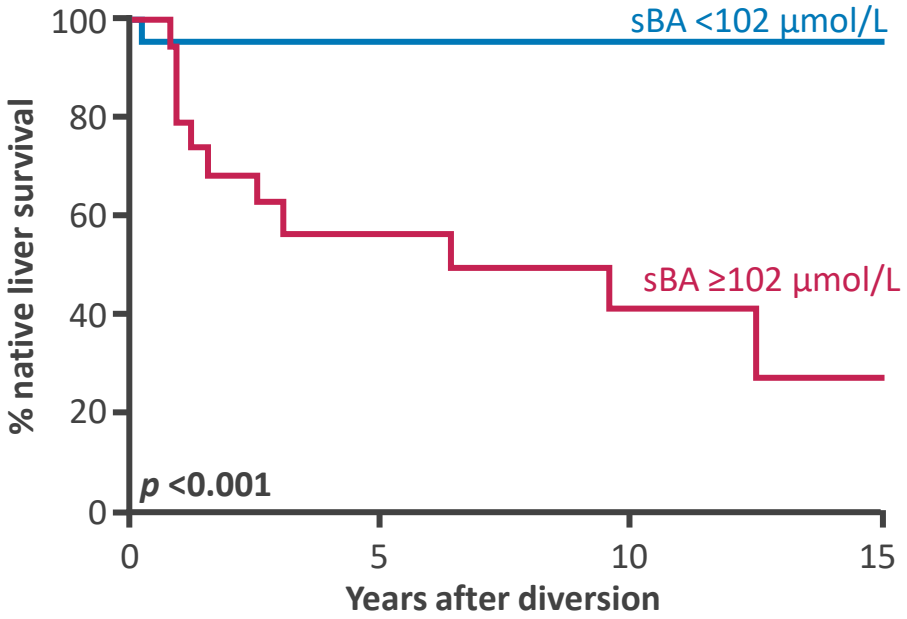
Nt, non-truncated.

1. Van Wessel DBE, *et al. J Hepatol* 2020; **73:**84–93.

Serum Bile Acid reduction: Predictive of Long-Term Native Liver Survival

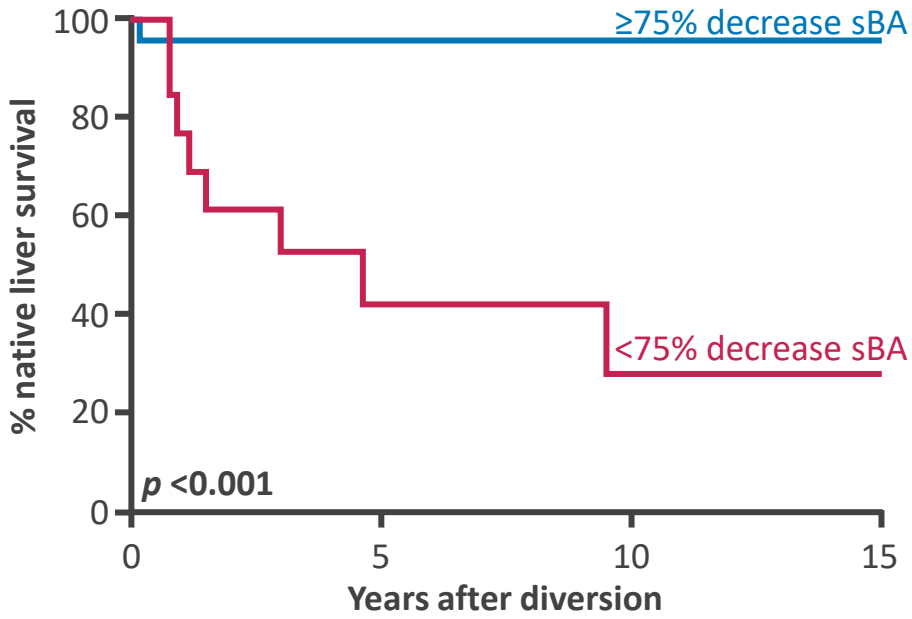
Serum bile acid control after surgical biliary diversion is associated with native liver survival to 15 years (NAPPED)

NLS after SBD in patients with sBA < or ≥102 mmol/L



No. at risk				
sBA <102 µmol/L	27	23	16	9
sBA ≥102 µmol/L	20	8	5	1

NLS after SBD in patients with a relative decrease in sBA of < or ≥75%

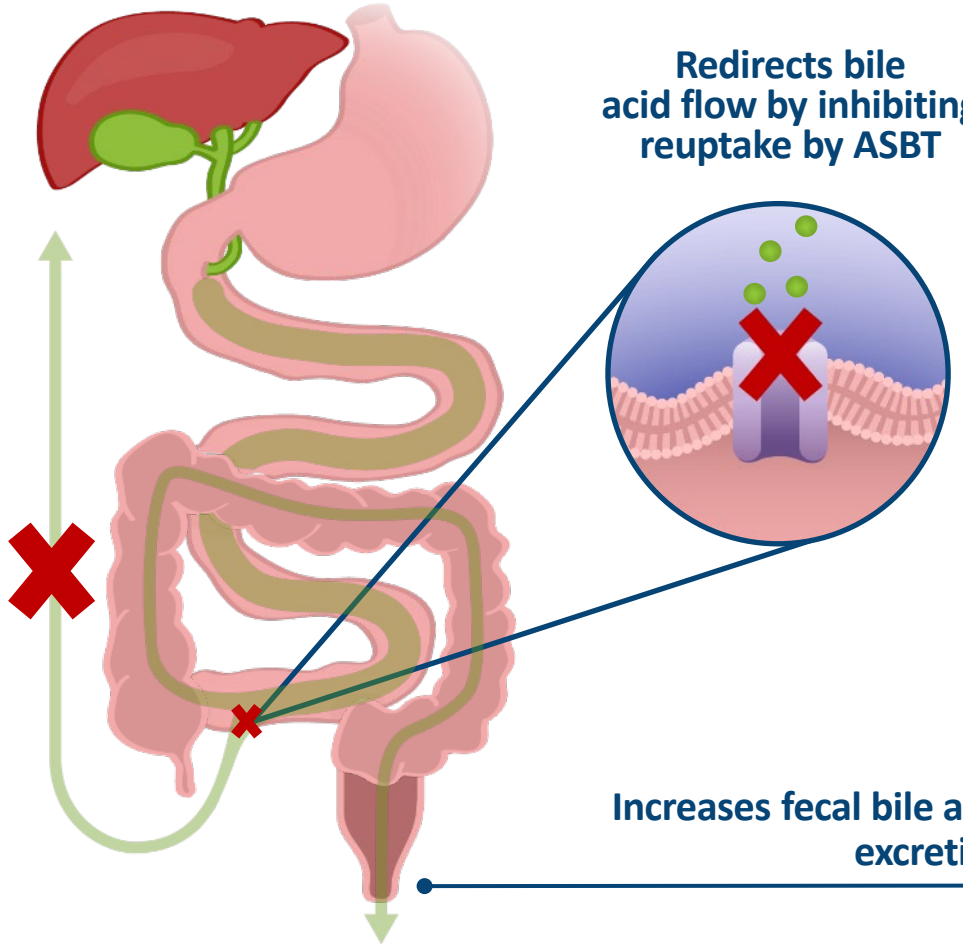


No. at risk				
<75% decrease sBA	14	4	2	1
≥75% decrease sBA	24	21	14	8

NLS, native liver survival; sBA, serum bile acid; SBD, surgical biliary diversion.

1. Van Wessel DBE, *et al. J Hepatol* 2020; **73:**84–93.

Maralixibat: ASBT Inhibitor which Interrupts Enterohepatic Circulation



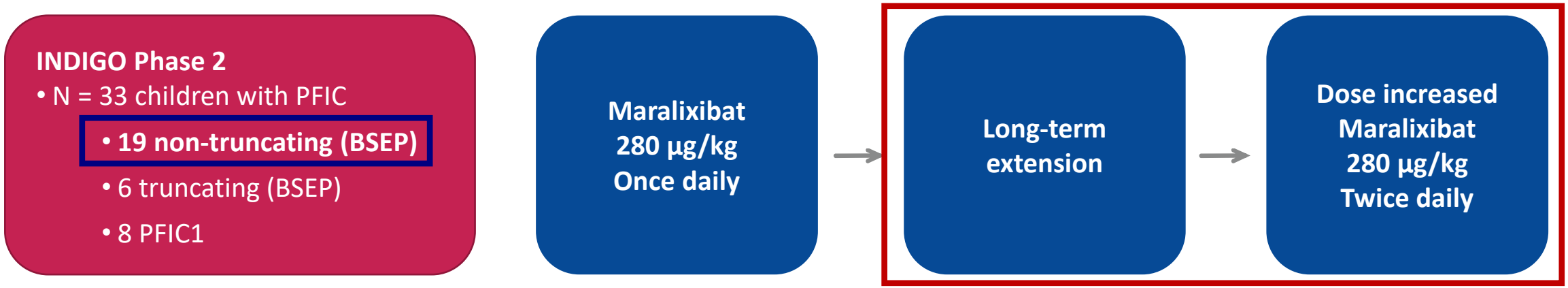
Clinical effects seen in cholestasis

ASBTi clinical studies show:

- ✓ **Reductions in pruritus**
- ✓ **Reduction in sBA**
- ✓ **Impact on markers of bile acid synthesis: cholesterol, C4, FGF19**

ASBT, apical sodium-dependent bile acid transporter; sBA, serum bile acid.

INDIGO: Open-label Phase 2 Study of Maralixibat in PFIC



Study endpoints: serum bile acids, pruritus, QoL, growth, safety and tolerability

Aim: Investigate long-term effects of pharmacological interruption of enterohepatic circulation in BSEP deficiency

Methods: Long-term analysis of response from maralixibat Phase 2 INDIGO trial in children with BSEP deficiency after >5 years

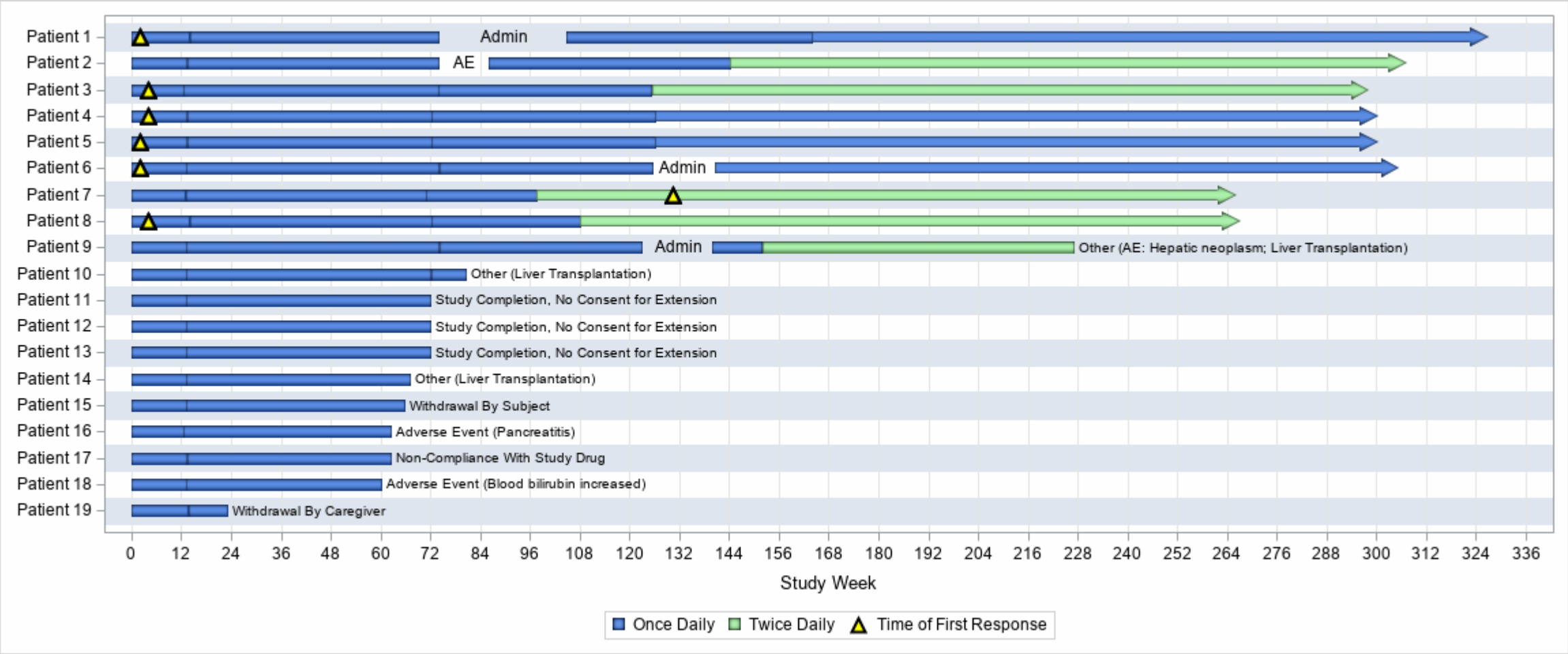
INDIGO: Patient Characteristics and Demographics
Overall Non-truncating BSEP Deficiency

Overall baseline demographics

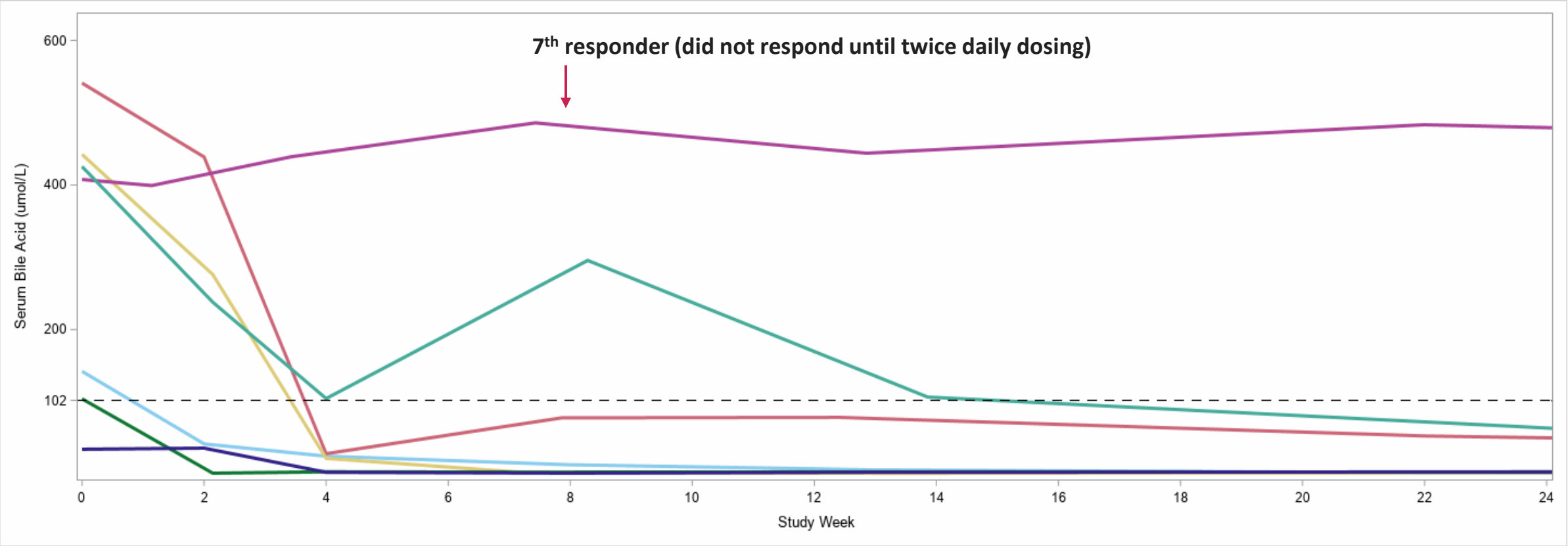
non-truncating BSEP	n = 19
Median age (range), year	3 (1–13)
Boys, n (%)	6 (32)
White, n (%)	18 (95)
Serum bile acid (range) µmol/L	373.4 (34.3, 601.4)
ALT (range) U/L	116 (13, 379)
Total bilirubin (range) mg/dL	1.8 (0.1, 6.5)
Z-score mean (SD)	
Height	-1.07 (1.00)
Weight	-0.40 (0.77)
ItchRO(Obs) (range) 0-4 scale	2.14 (0.14, 3.29)

INDIGO: Patient Disposition
Subjects Ongoing with >5 years of Maralixibat Treatment

Seven sBA responders (75% reduction or <102µmol/L, per NAPPED); 1 non-responder remains on study

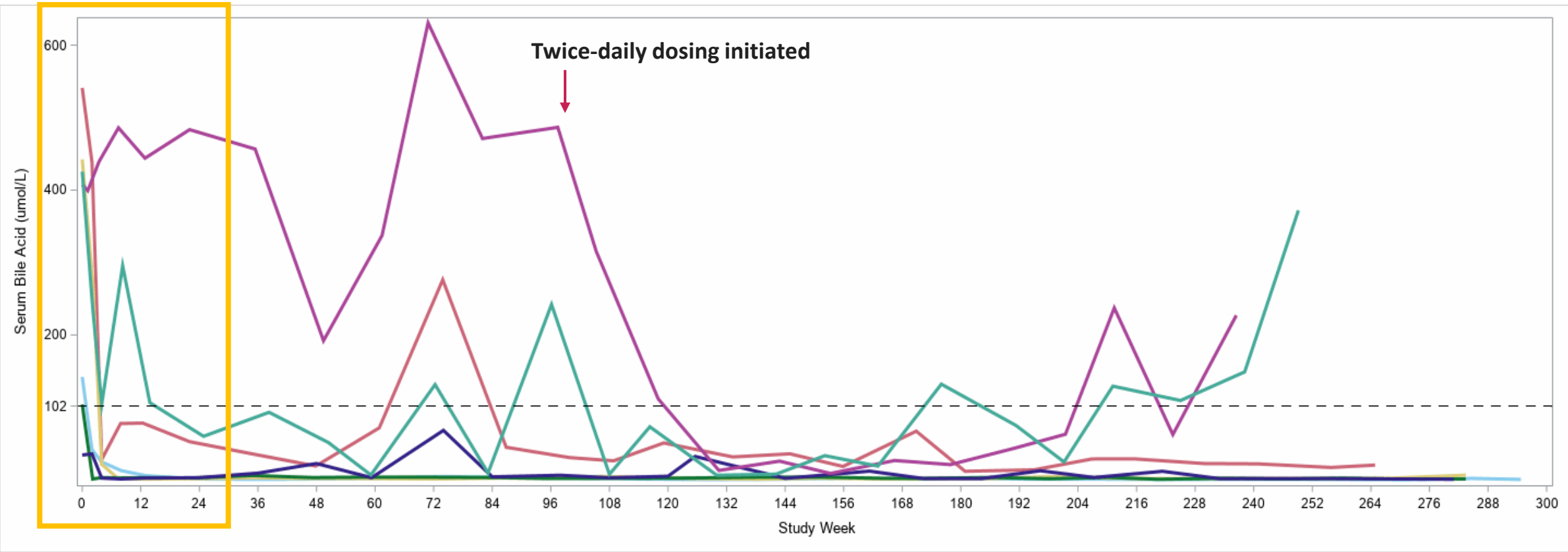


INDIGO: sBA Response on Maralixibat is Observed Early for Responders



Early sBA response observed at 280µg/kg/day for 6 subjects; between 2–4 weeks on maralixibat

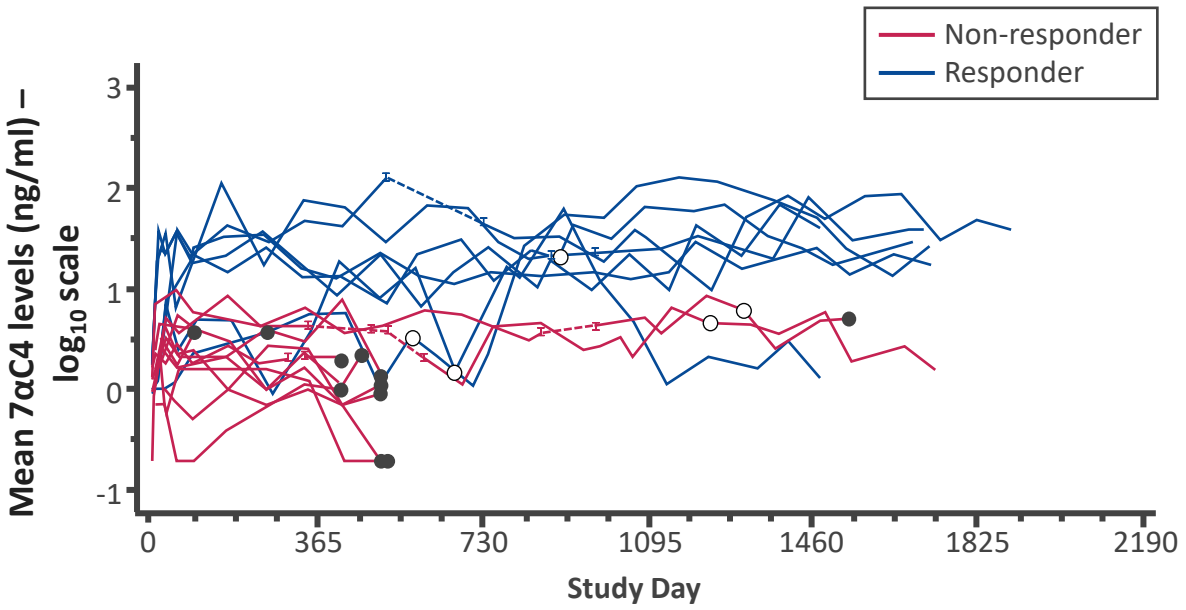
INDIGO: Maralixibat sBA Response is Maintained Long-Term



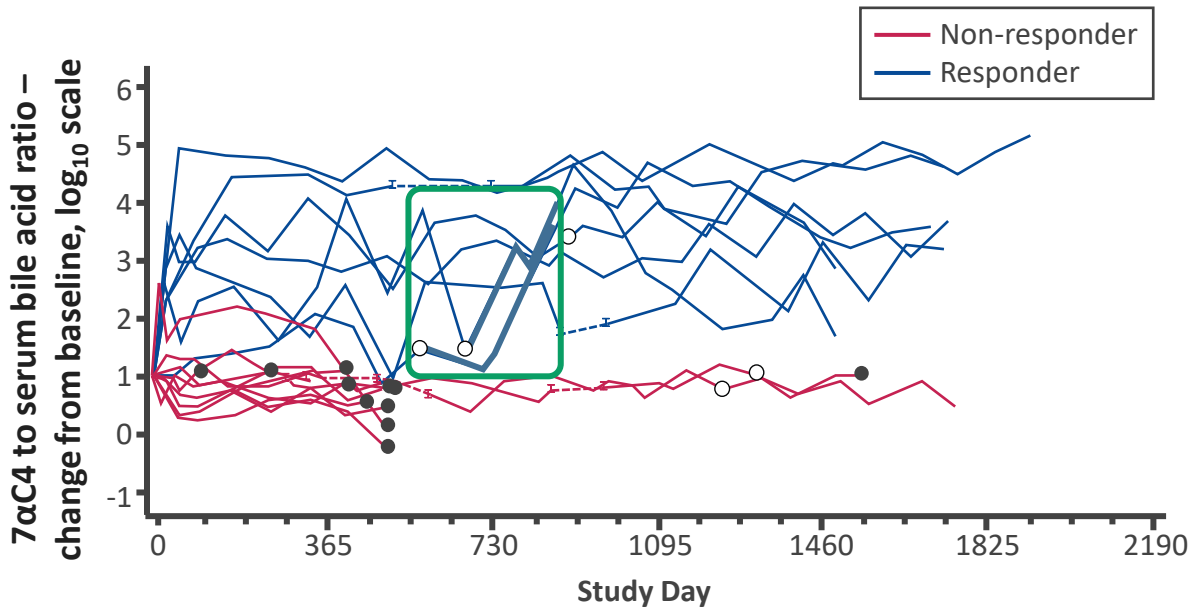
- No clinical events have been observed
- 2 patients have come off the transplant waiting list
- 7th sBA responder observed after twice-daily dosing at week 97

INDIGO: Changes in 7αC4 Levels and 7αC4/BA Ratio from Baseline Over 5 Years of Maralixibat Treatment

7αC4 levels

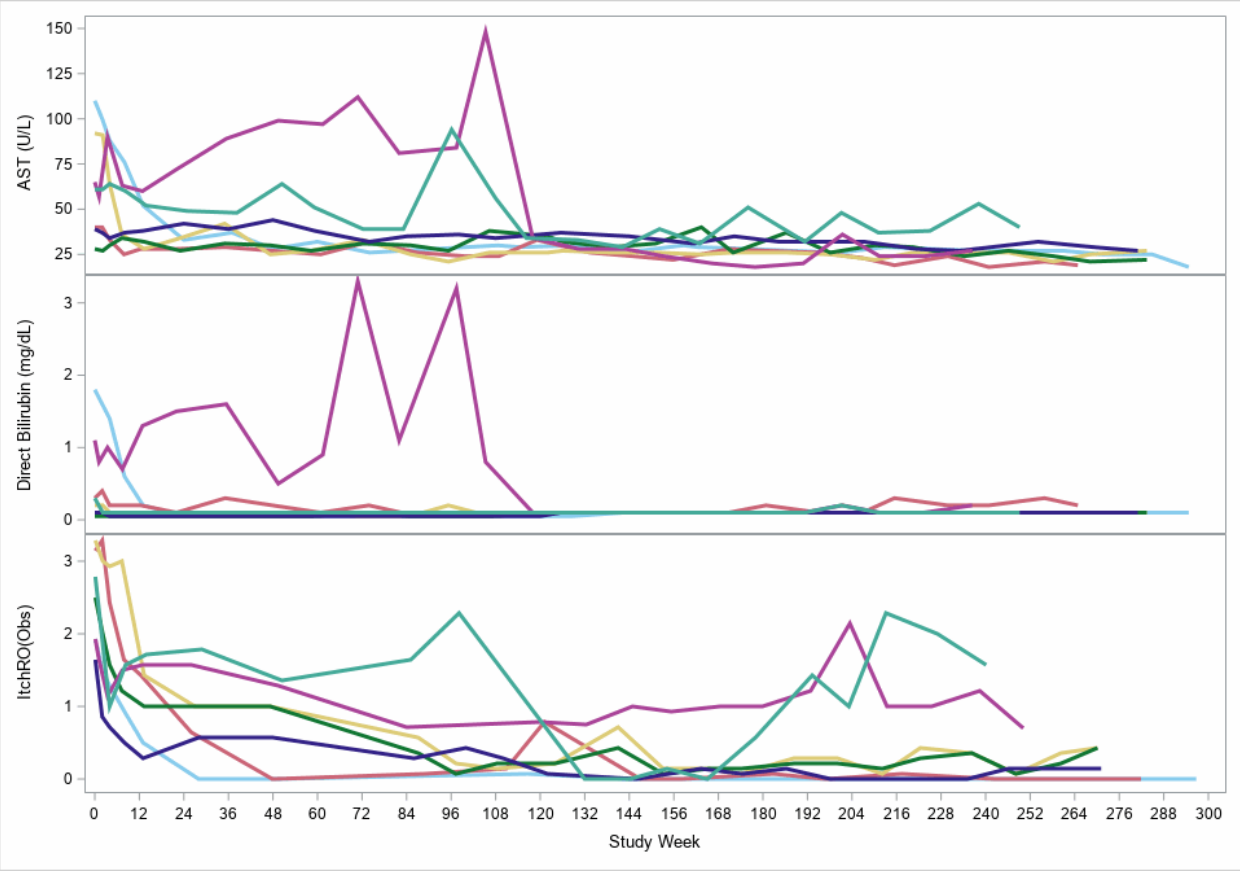


7αC4/BA ratio



INDIGO: Improved Liver Enzymes, Pruritus, Growth and QoL

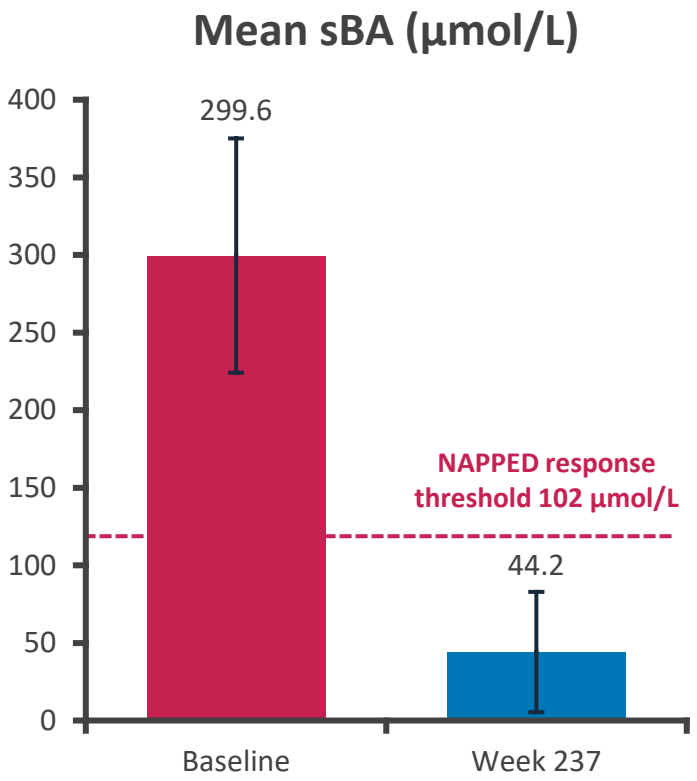
sBA responders remain on maralixibat >5 years with improvements across multiple parameters

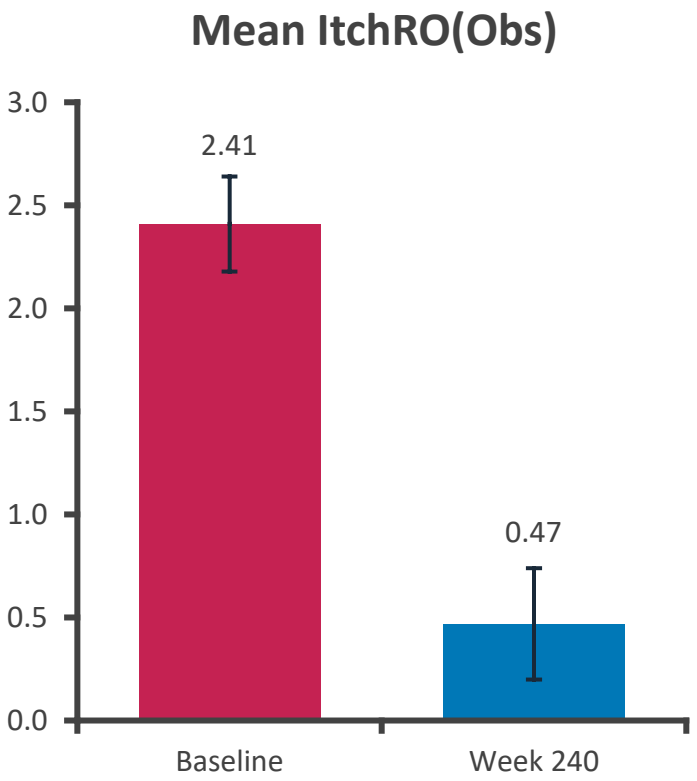


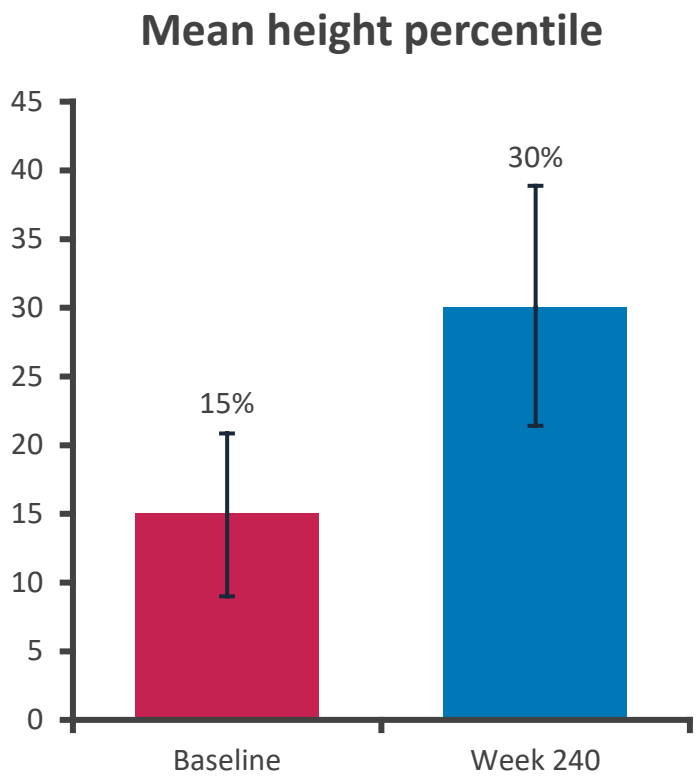
Week 240 (n=7)	Mean Value	Mean Change	P-value*
sBA (SE) µmol/L	57.8 (92.1)	-241.8 (68.1)	0.016
ALT (SE) U/L	23.7	-34.1 (15.7)	0.08
AST (SE) U/L	28.9	-33.3 (11.6)	0.016
Bilirubin (SE) mg/dL	0.7	-0.1 (0.3)	0.78
Direct Bili (SE) mg/dL	0.1	-0.4 (0.2)	0.06
ItchRO(Obs) (score 0–4)	0.5	-2.0 (0.3)	0.016
Height z-score	-0.6	0.6 (0.1)	0.016
Peds QoL	85.3	23.6 (6.9)	0.047

*P-value from Wilcoxon signed-rank test

INDIGO: Absolute Values for sBA Response, Pruritus and Growth



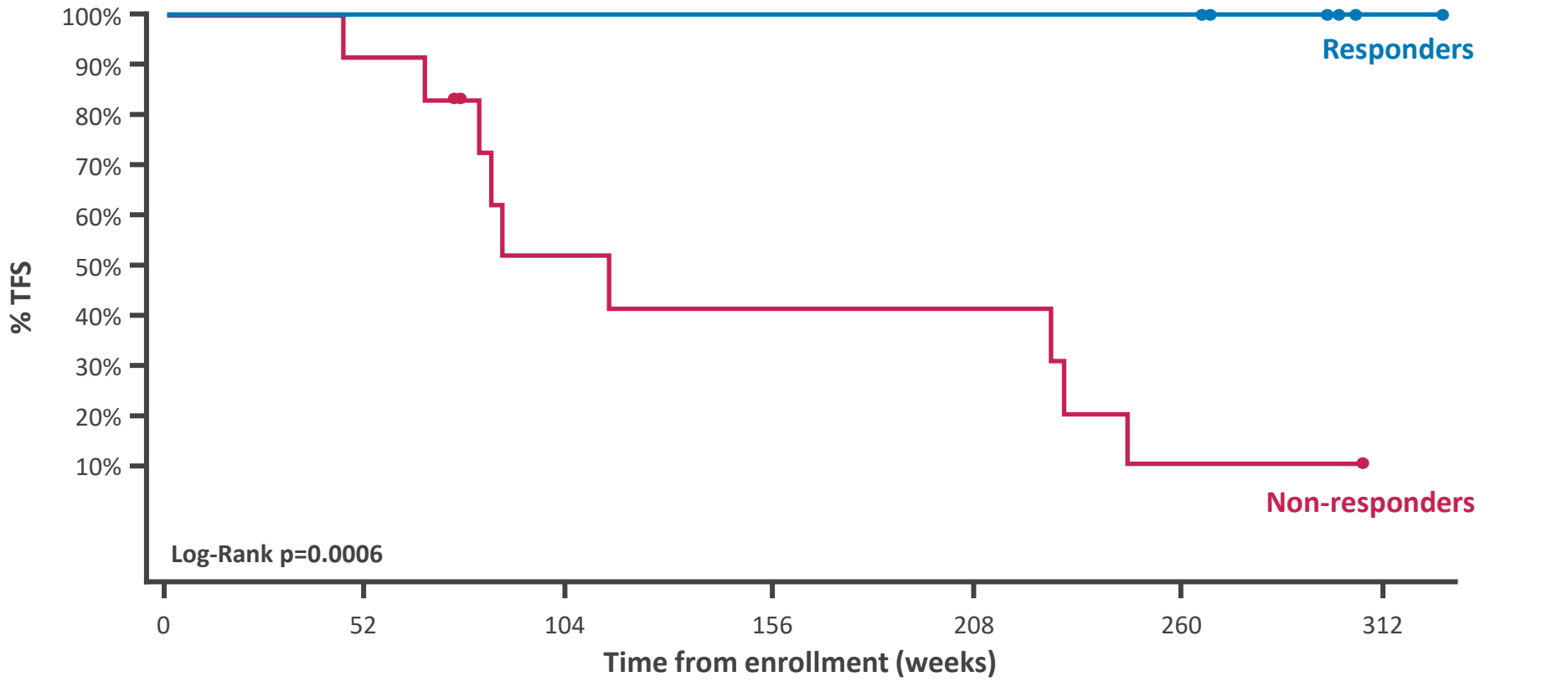




All data from n = 7 responders.

INDIGO: sBA Control in Long-Term Maralixibat-Treated Patients is Associated with Native Liver Survival

100% maralixibat sBA responders remain transplant-free after >5 years of treatment



No. at risk							
Responders	7	7	7	7	7	7	1
Non-responders	12	11	5	4	4	1	0

INDIGO: Treatment-Emergent Adverse Events (TEAEs) in All Patients (N = 19)

TEAEs	Participants, n (%)
Any TEAE	19 (100.0)
Potentially maralixibat-related	15 (78.9)
Leading to discontinuation*	3 (15.8)
Leading to death	0
Any serious TEAE	7 (36.8)
Potentially maralixibat-related[a]	2 (10.5)

Most frequently reported TEAEs	Participants, n (%)
Nasopharyngitis	12 (63.2)
Vomiting	12 (63.2)
Cough	11 (57.9)
Diarrhea	11 (57.9)
Pyrexia	11 (57.9)
Abdominal pain	9 (47.4)
Oropharyngeal pain	8 (42.1)
Pruritus	8 (42.1)

* Pancreatitis, blood bilirubin increased

Summary and Conclusions

- 5-year native liver survival is observed in maralixibat sBA responders; findings consistent with NAPPED results[1]
- These patients also experience:
  - Improvements in ALT, AST and bilirubin
  - Improved growth
  - Controlled pruritus
  - Improved quality of life (PedsQoL)
- sBA responders had a greater 7αC4/BA ratio than non-responders
- Native liver survival observed in maralixibat sBA responders is consistent with NAPPED results[1]
- Maralixibat interrupts the enterohepatic circulation by inhibiting ASBT and may offer an alternative pharmacological treatment option to surgical biliary diversion or liver transplant in some patients
- Maralixibat is generally well-tolerated; most common AEs transient mild to moderate diarrhea and abdominal pain. No GI-related discontinuations

1. Van Wessel DBE, *et al. J Hepatol* 2020; **73:**84–93.

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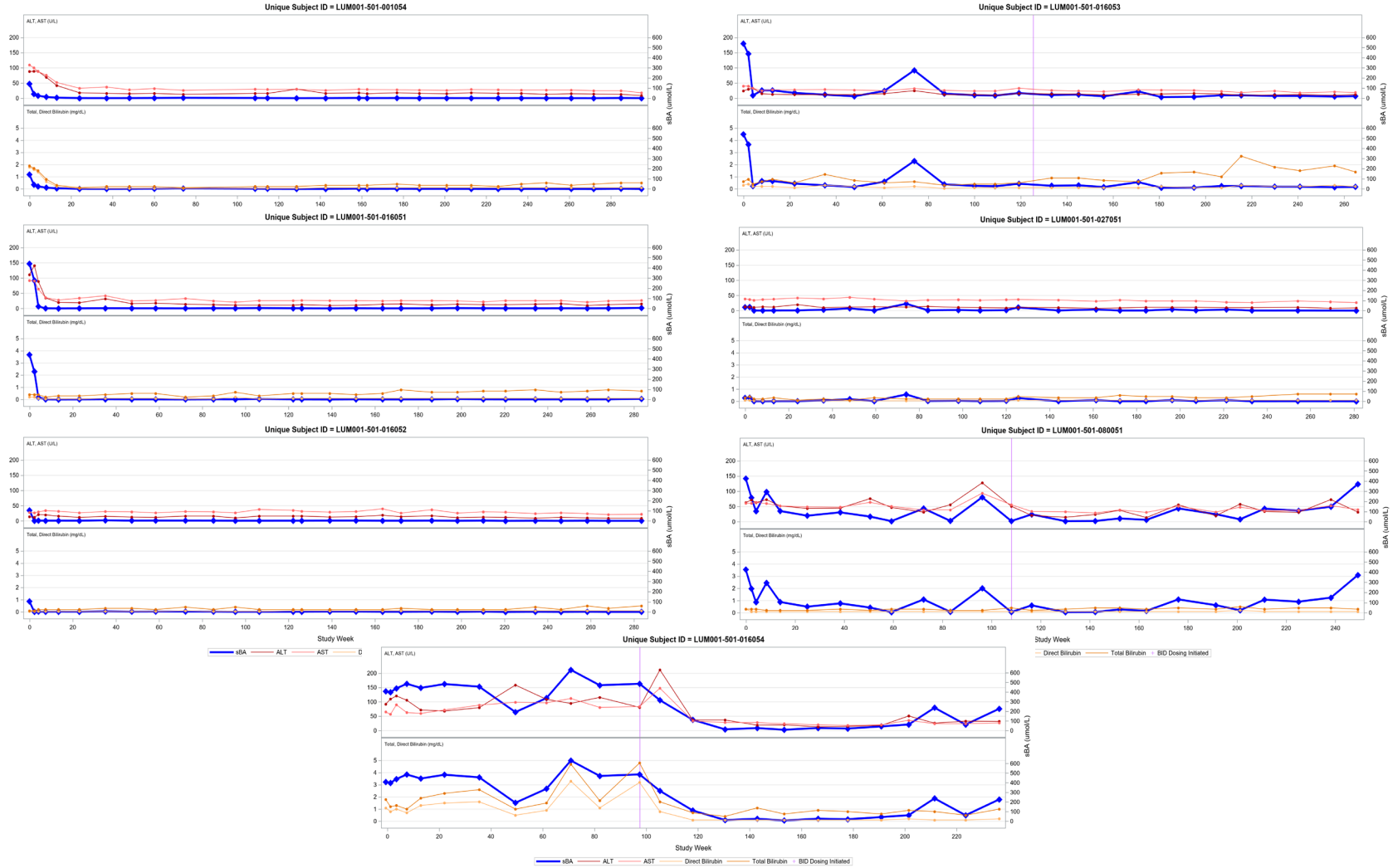
Back-up

Maralixibat sBA responders experience ALT , AST and bilirubin reductions



Key entry criteria and efficacy endpoints

Key exclusion criteria

- PEBD or ileal exclusion
- Liver transplant
- Decompensated cirrhosis

Key efficacy endpoints

- Height and weight
- Cholestasis biomarkers
  - sBA (primary efficacy measure)
  - ALT, AST, bilirubin, C4
- Pruritus assessments
  - ItchRO(Obs) score (caregiver-rated pruritus; 0 = none, 4 = severe)
  - CSS score (investigator-rated, 0–4)
- HRQoL assessment
  - PedsQL total score (parent-rated, 0–100)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSS, clinician scratch scale; HRQoL, health-related quality of life; ItchRO(Obs), Itch-Reported Outcome (Observer); PedsQL, Pediatric Quality of Life Inventory

Patient characteristics, demographics and disposition of maralixibat responders

Baseline characteristics of ongoing responders (n=7)

non-truncating BSEP, Ongoing Responders	n = 7
Median age (range), year	4 (1–10)
Boys, n (%)	3 (43)
White, n (%)	6 (86)
Serum bile acid (range) µmol/L	299.6 (34.3, 541.1)
ALT (range) U/L	58 (13, 111)
Total bilirubin (range) mg/dL	0.8 (0.1, 1.9)
Z-score mean (SD)	
Height	-1.22 (0.64)
Weight	-0.52 (0.86)
ItchRO(Obs) (range) 0-4 scale	2.46 (1.64, 3.29)

INDIGO: sBA Responses to Maralixibat in Patients with nt-BSEP

Non-truncating BSEP mutations