

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

INDIGO Study

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Author Disclosures

I disclose the following financial relationships with commercial interest

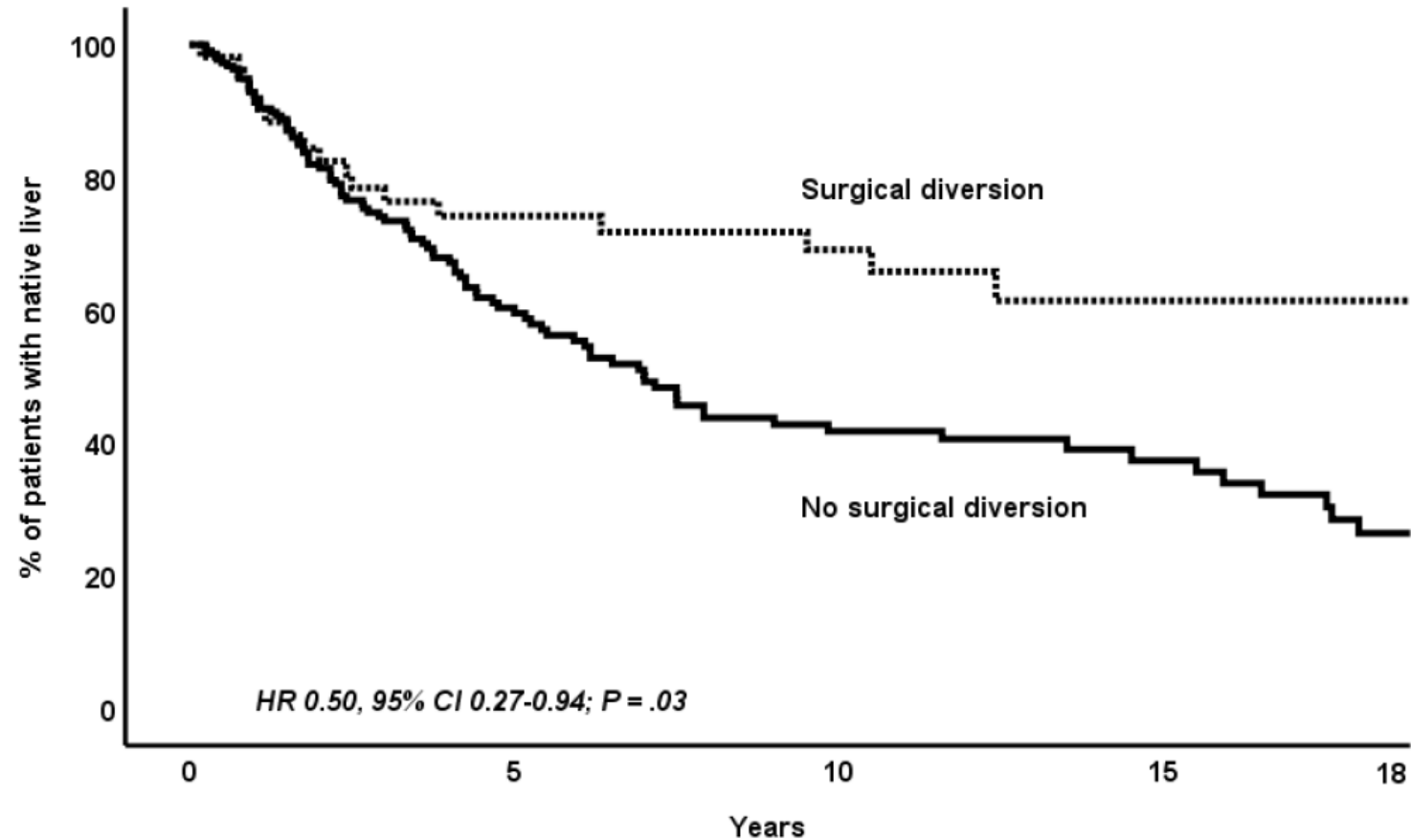
Consultancy: Mirum, Albireo Pharma, GenerationBio, Qing Bile Therapeutics, Horizon Pharma, Alnylam, Sana Biotechnology, EVOX Therapeutics

Share options: Qing Bile Therapeutics, GenerationBio

Background and Treatment Landscape for BSEP Deficiency

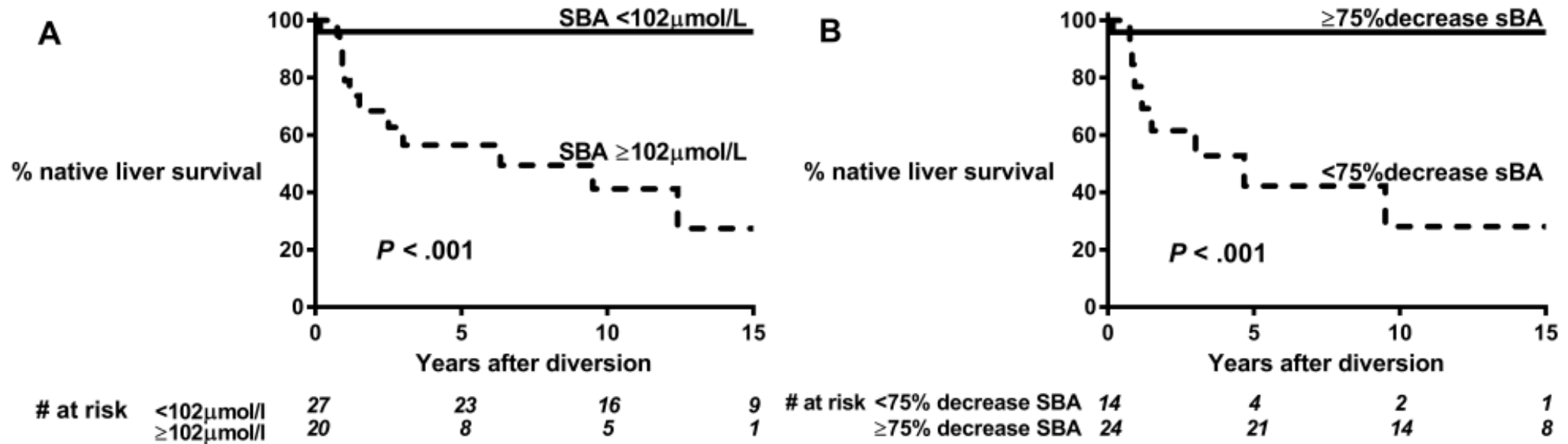
- Also called Progressive familial intrahepatic cholestasis Type 2 (PFIC2)
 - Rare genetic defect of ABCB11 gene
 - Cholestasis and end stage liver disease, severe pruritus, lipid-soluble vitamin deficiency, growth deficit
- No approved pharmacological treatments for BSEP deficiency
- Current treatments 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-surgery¹

Native Liver Survival +/- Surgical Biliary Diversion (NAPPED)

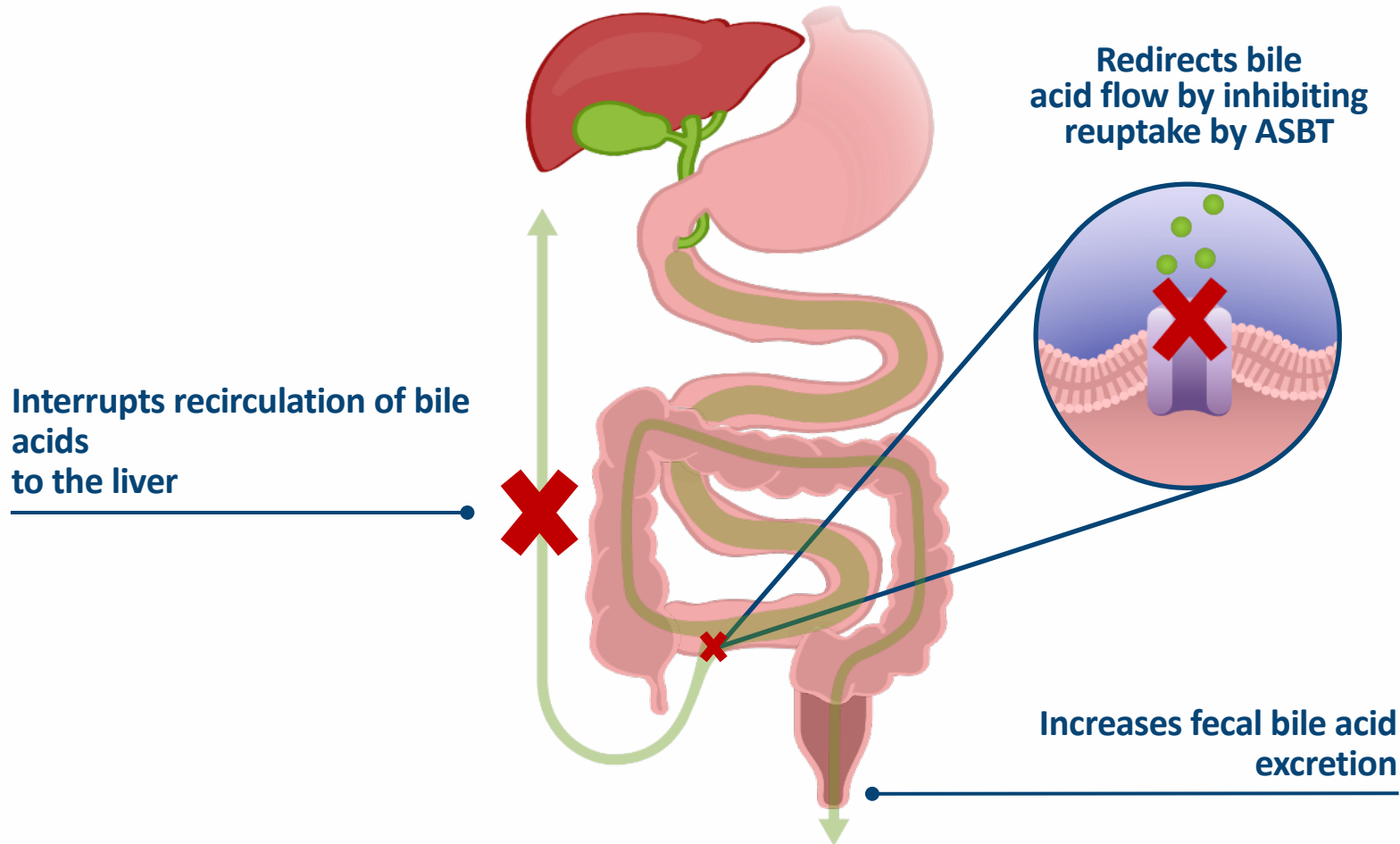


Serum Bile Acid reduction: Predictive of Long-Term Native Liver Survival

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



Maralixibat: ASBT Inhibitor which Interrupts Enterohepatic Circulation

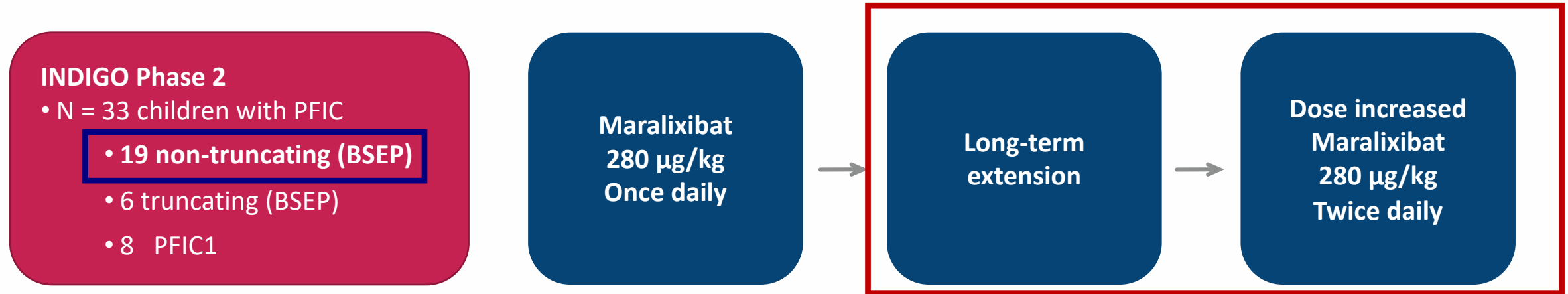


Clinical effects seen in cholestasis

ASBTi clinical studies show:

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

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

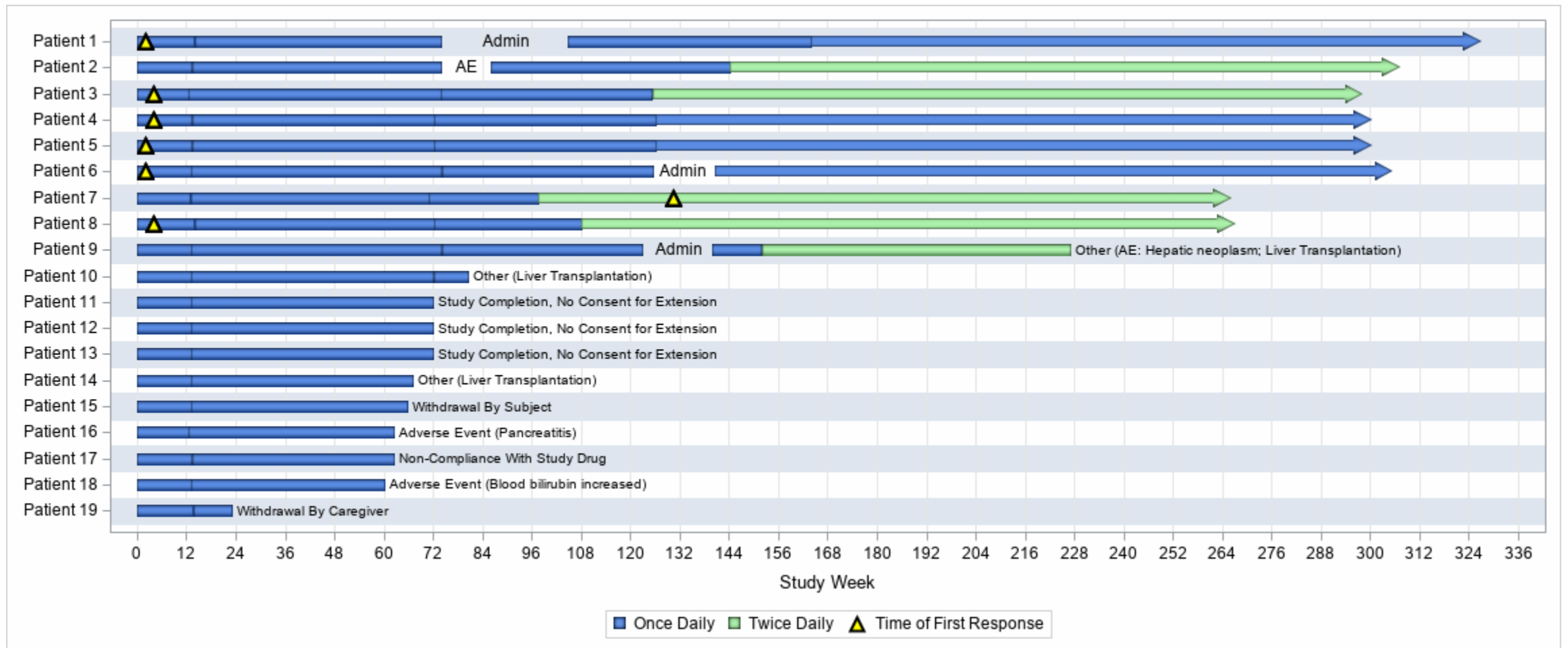
Overall baseline demographics

non-truncating BSEP	n = 19
Median age (range), year	3 (1–13)
Boys, n (%)	6 (32)
White, n (%)	18 (95)
Serum bile acid (range) $\mu\text{mol/L}$	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)

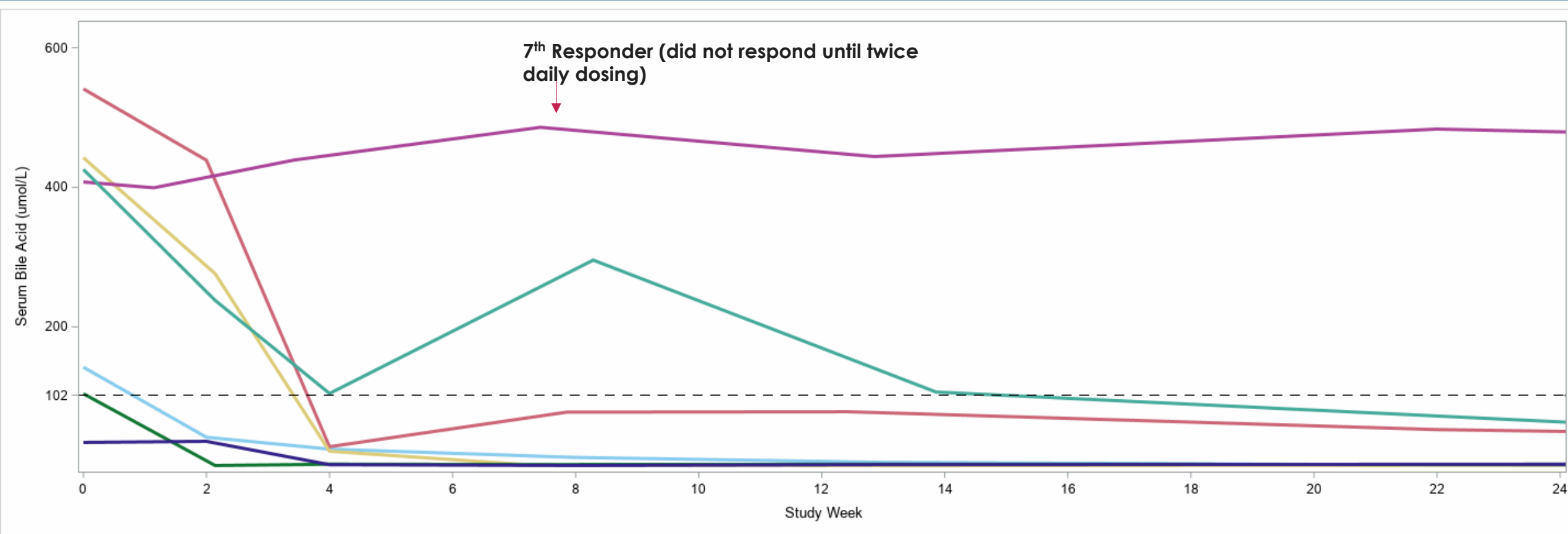
INDIGO: Patient Disposition

Subjects Ongoing with >5 years of Maralixibat Treatment

Seven sBA responders (75% reduction or $<102\mu\text{mol/L}$, per NAPPED); 1 non-responder remains on study

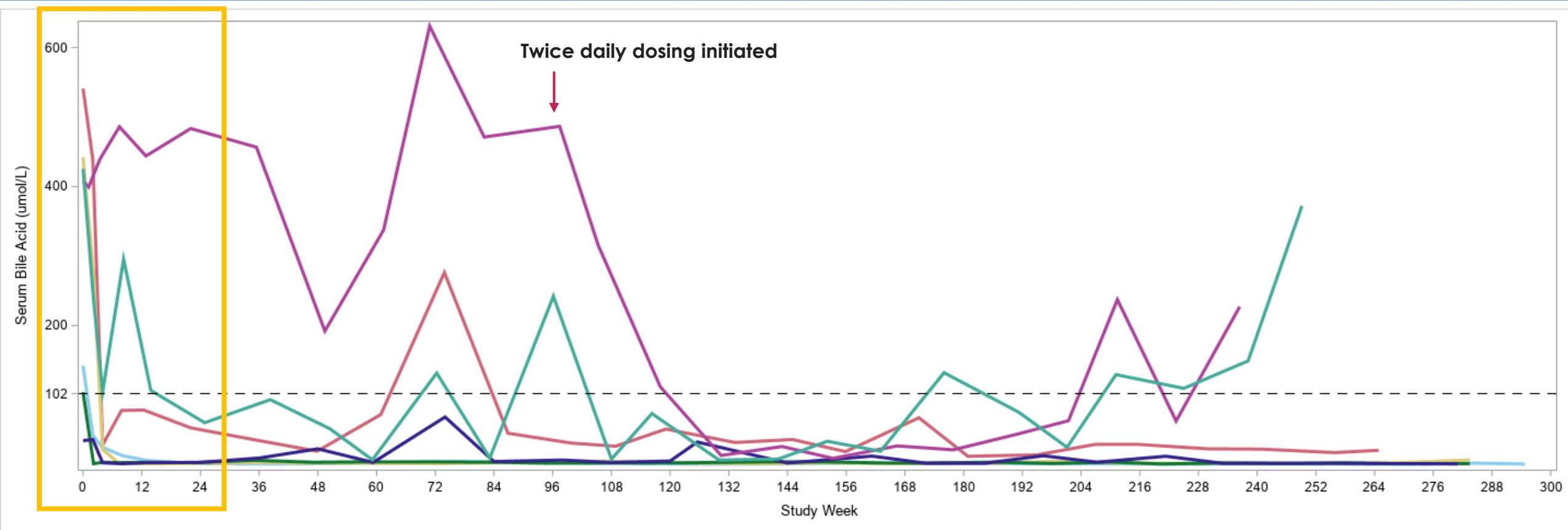


INDIGO: sBA Response on Maralixibat is Observed Early for Responders



Early sBA response observed at 280 $\mu\text{g/kg/day}$ for 6 subjects; between 2-4 weeks on maralixibat

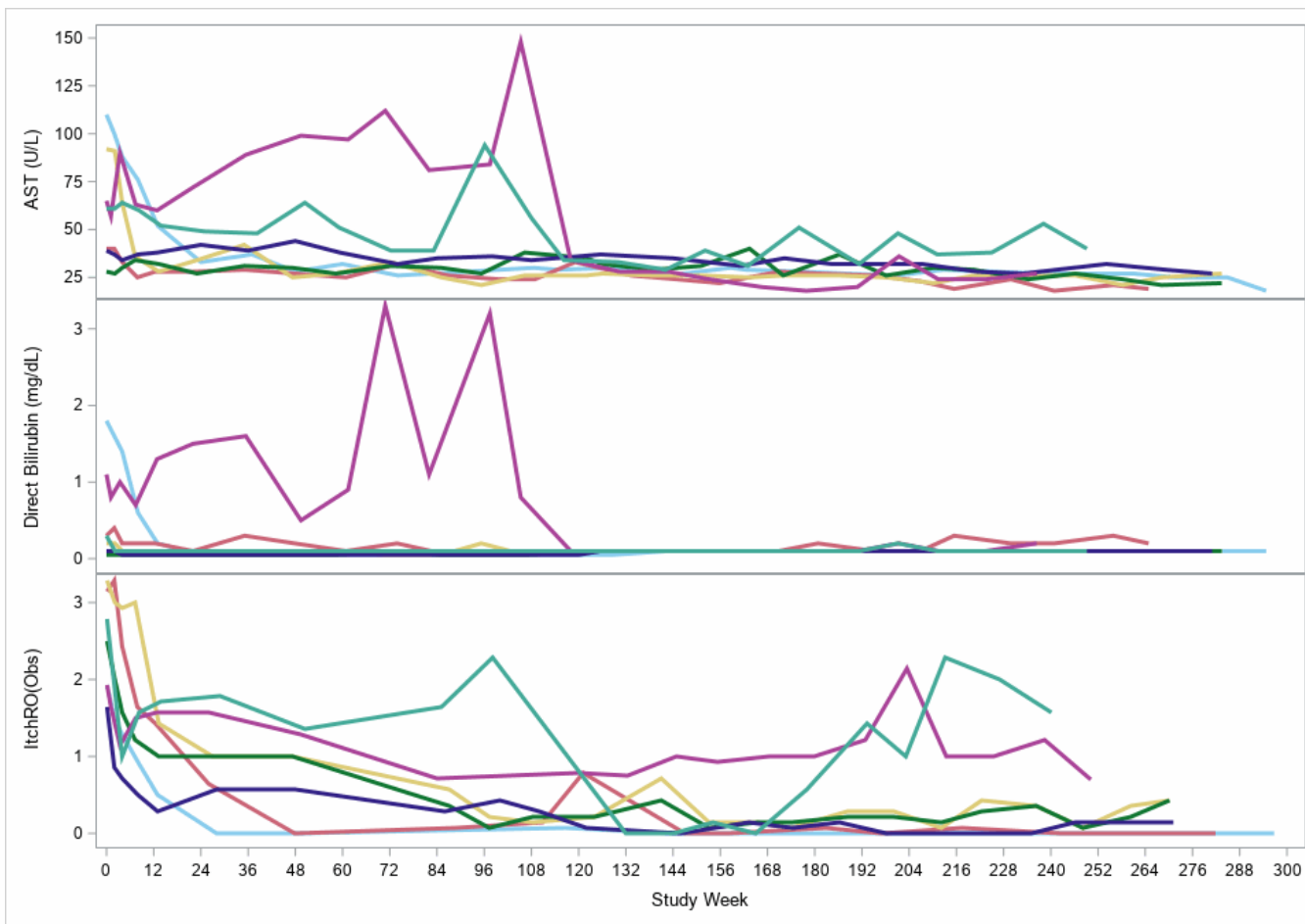
INDIGO: Maralixibat sBA Response is Maintained Long-Term



- 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: Improved Growth, Pruritus and Liver Enzymes

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

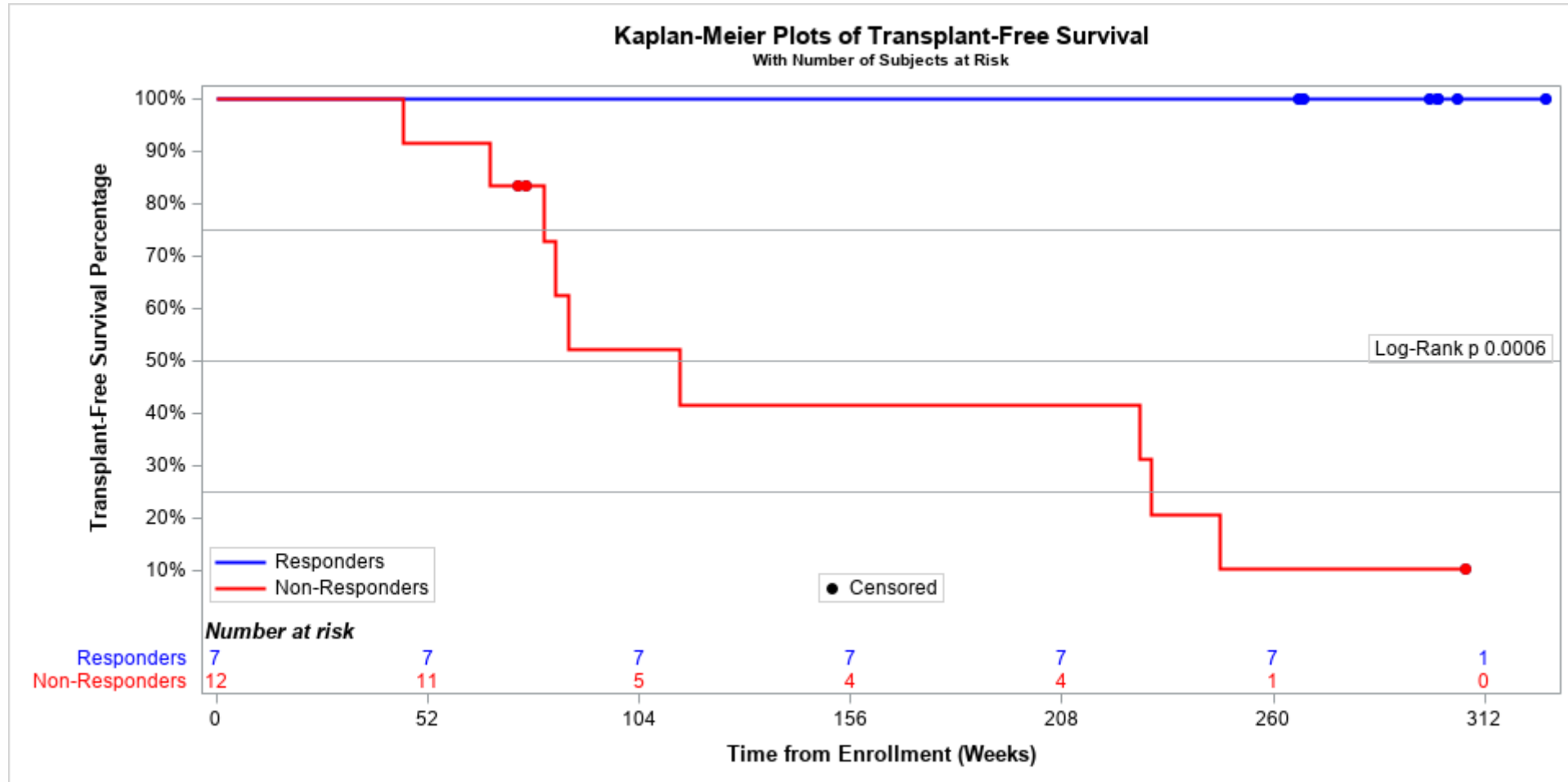


Week 240 (n=7)	Mean Value	Mean Change	P value ^a
sBA (SE) $\mu\text{mol/L}$	57.8 (92.1)	-241.8 (68.1)	0.016
ALT (SE) U/L	23.7	-34.1 (15.7)	0.08
AST (SE) U/L	28.9	-33.3 (11.6)	0.016
Bilirubin (SE) mg/dL	0.7	-0.1 (0.3)	0.78
Direct Bili (SE) mg/dL	0.1	-0.4 (0.2)	0.06
ItchRO(Obs) (score 0-4)	0.5	-2.0 (0.3)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

^a P-value from Wilcoxon signed-rank test

INDIGO: Serum Bile Acid 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



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

TEAEs	Participants, n (%)	Most frequently reported TEAEs	Participants, n (%)
Any TEAE	19 (100.0)	Nasopharyngitis	12 (63.2)
Potentially maralixibat-related	15 (78.9)	Vomiting	12 (63.2)
Leading to discontinuation ^a	3 (15.8)	Cough	11 (57.9)
Leading to death	0	Diarrhea	11 (57.9)
Any serious TEAE	7 (36.8)	Pyrexia	11 (57.9)
Potentially maralixibat-related ^a	2 (10.5)	Abdominal pain	9 (47.4)
		Oropharyngeal pain	8 (42.1)
		Pruritus	8 (42.1)

^a Pancreatitis, blood bilirubin increased

Summary and Conclusions

- Patients with serum bile acid control with long-term (>5 years) maralixibat treatment experience native liver survival, along with:
 - normalization and/or reductions of ALT, AST and bilirubin, if elevated at baseline
 - Improved growth
 - Controlled pruritus
- In line with NAPPED, which demonstrated serum bile acid control after surgical interruption of the enterohepatic circulation, is associated with NSL to 15 years¹
- Maralixibat interrupts the enterohepatic circulation by inhibiting ASBT and may offer a pharmacological treatment option in lieu of surgical biliary diversion or liver transplant in some patients
- Maralixibat is generally safe and well-tolerated the most common AEs were mild to moderate in severity and included diarrhea and abdominal pain

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