Genotype and dose-dependent response to maralixibat in patients with bile salt export pump deficiency

Richard Thompson, Kings College London, London, UK

Thomas Jaecklin, Chris Peetz, Pamela Vig on behalf of the LUM001-501 INDIGO Study Group

Author disclosures

I disclose the following financial relationships with commercial interest:

Consultancy

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Share options

Qing Bile Therapeutics, GenerationBio

PFIC is a group of genetic progressive liver diseases

- PFIC is associated with:
  - debilitating pruritus, growth deficit, lipid-soluble vitamin deficiency, progressive liver disease
- If medical management fails:
  - partial external biliary diversion surgery or liver transplant for pruritus

Aim

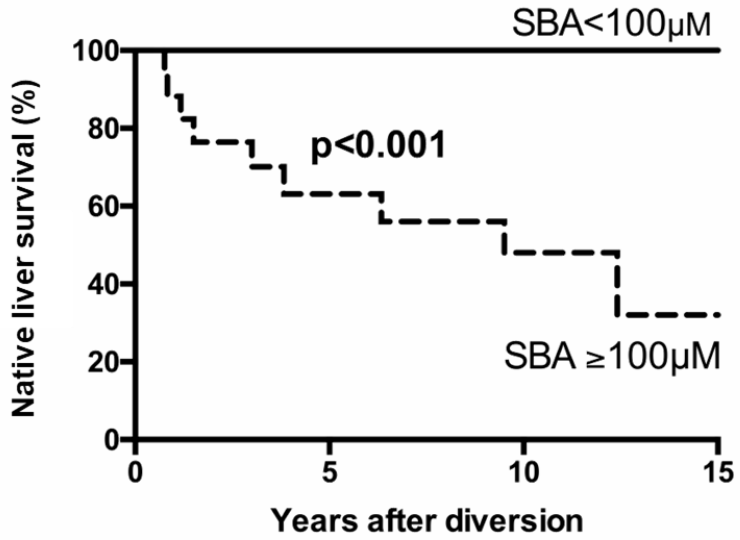
- To investigate the response to pharmacological interruption of the enterohepatic circulation of bile acids in BSEP deficiency

Methods

- Analysis of treatment response from maralixibat Phase 2 INDIGO trial in children with PFIC due to bile salt export pump (BSEP) deficiency

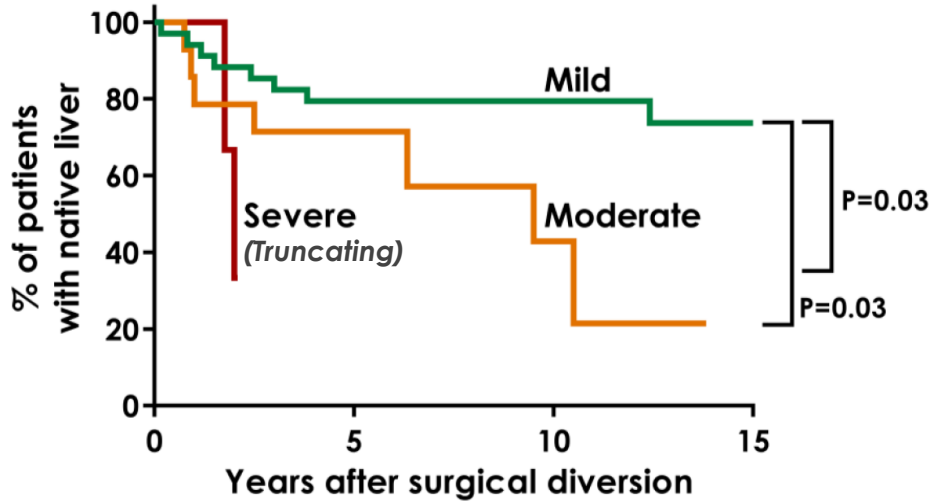
Natural history background: NAPPED outcomes post PEBD

Early post-surgical sBA associated with transplant-free survival



# at risk <100μM	*24*	*20*	*14*	*8*
≥100μM	*18*	*9*	*6*	*1*

Transplant-free survival after biliary diversion is associated with genotype

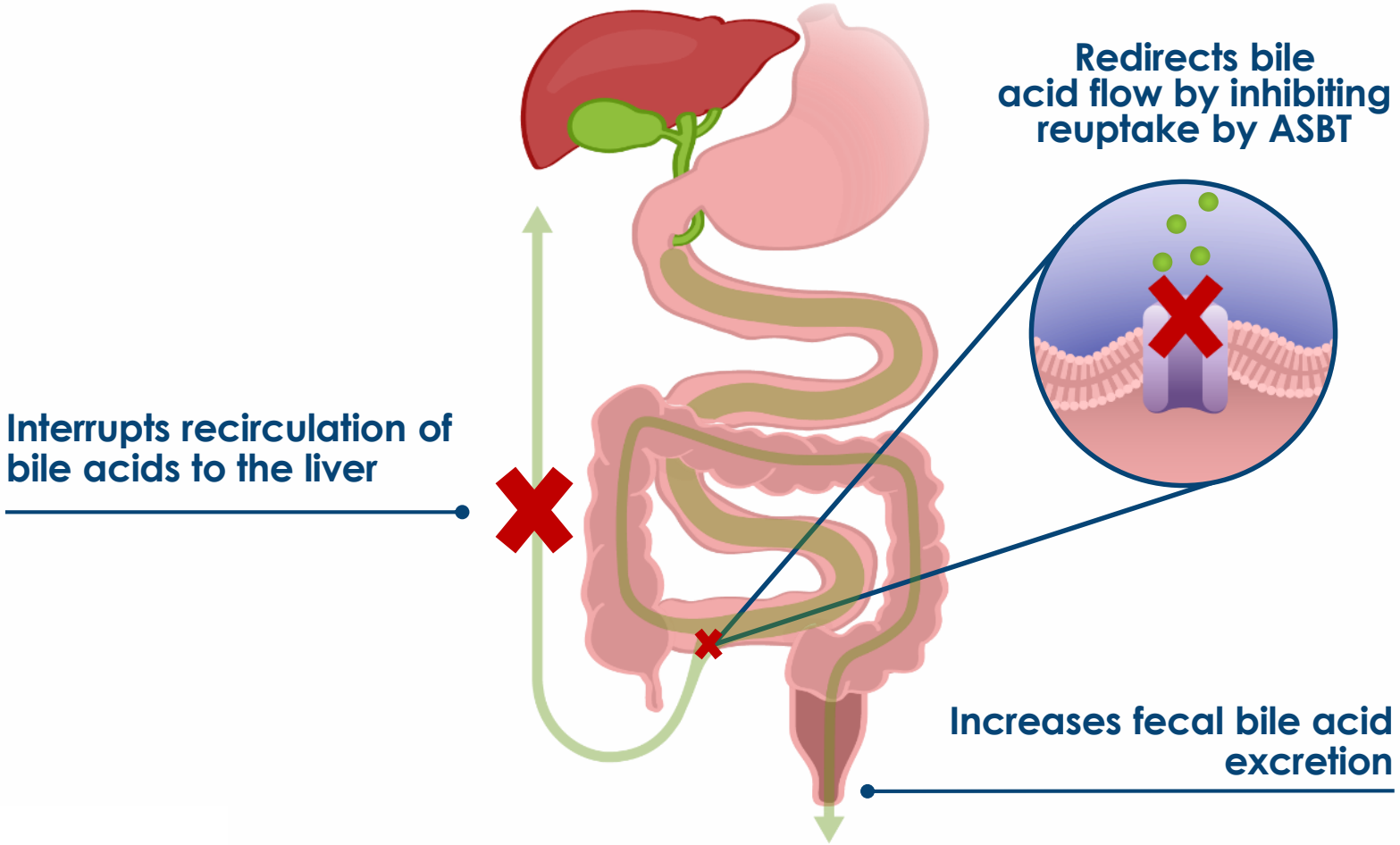


# at risk				
Mild	34	27	21	10
Moderate	21	5	2	0
Severe	6	0	0	0

sBA levels <100 μM post-biliary diversion predict transplant-free survival[1]

1. Van Wessel, EASL/ILC 2019 https://easl.meta-dcr.com/ilc2019/slides?page=1&q=napped,;

Maralixibat: an oral, minimally absorbed, selective inhibitor of ASBT (apical sodium-dependent bile acid transporter)



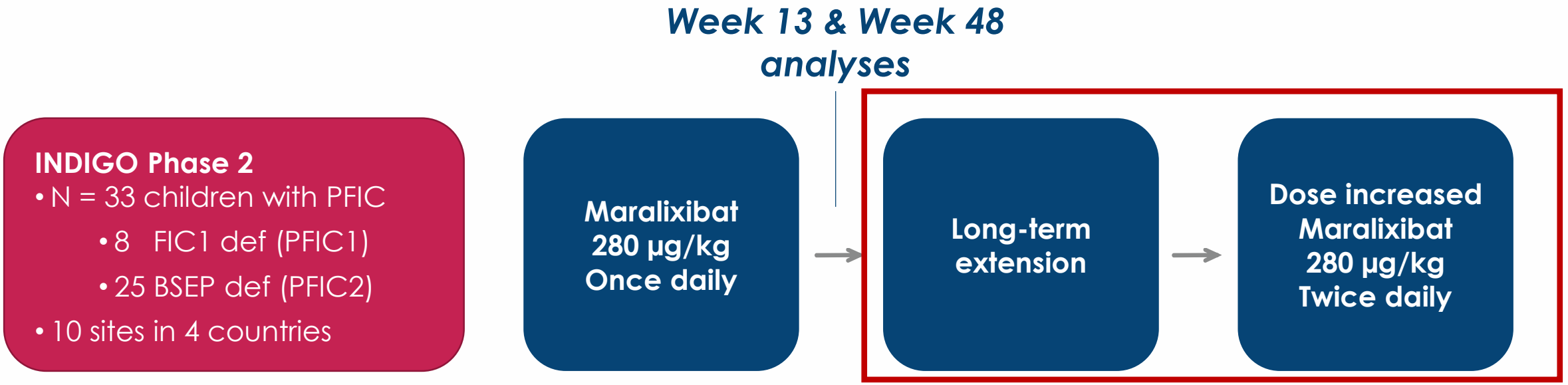
Clinical effects seen in cholestasis

ASBTi clinical studies show:

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

Abbreviations: sBA: serum bile acid; ASBT: apical sodium-dependent bile acid transporter

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



Endpoints:

- Serum bile acids, pruritus, QoL, growth
- Safety and tolerability

Analysis of long-term treatment response in the BSEP deficient group

Patient disposition, demographics, disease characteristics

Patient characteristics

N=33	PFIC1, n = 8 FIC1 def	PFIC2, n = 25 BSEP def
Median age (range), year	2.0 (1–7)	**4.0 (1–13)**
Boys, n (%)	6 (75)	**8 (32)**
White, n (%)	6 (75)	**20 (80)**
Serum bile acid (range), µmol/L	261.9 (159.8-423.5)	**381.0 (34.4-602.1)**
Mean (SD) z-scores		
Height	–2.96 (1.47)	**–1.29 (0.98)**
Weight	–2.70 (2.82)	**–0.63 (0.88)**

BSEP Genetic Status

	Participants (n)
Non-truncating (mild/moderate)	19
Truncating	6

INDIGO: Multi-parameter response in BSEP deficiency

Subject Genotype Status	Multi-parameter Responders
Non-truncating BSEP (N=19)	**7/19 (36.8%)**
Mild (N=7)	1/7 (14.3%)
Moderate (N=12)	6/12 (50%)
Truncating BSEP (N=6)	**0/6 (0%)**

RESPONDER DEFINITION:

- **≥ 70% reduction or normalization of sBA**

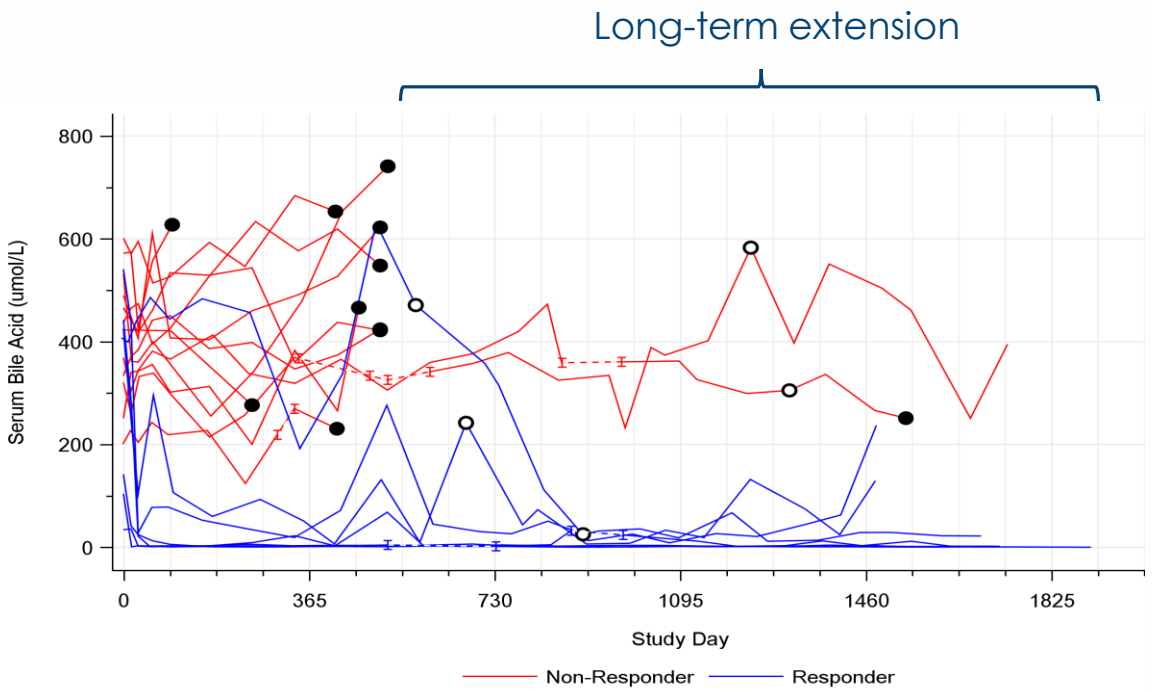
AND

- **≥1.0 reduction in ItchRO(Obs)***

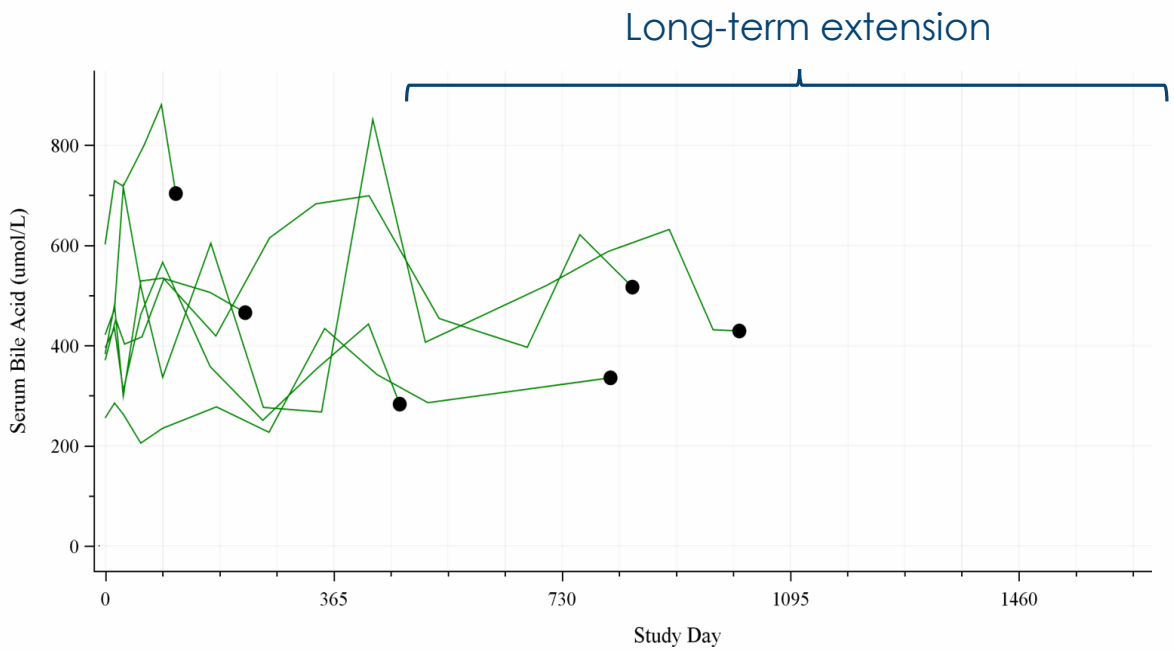
**ItchRO Observer Score: 0-4 observer-rated pruritus scale,*

Serum bile acid responses differ by BSEP mutation status

Non-truncating (nt) BSEP mutations



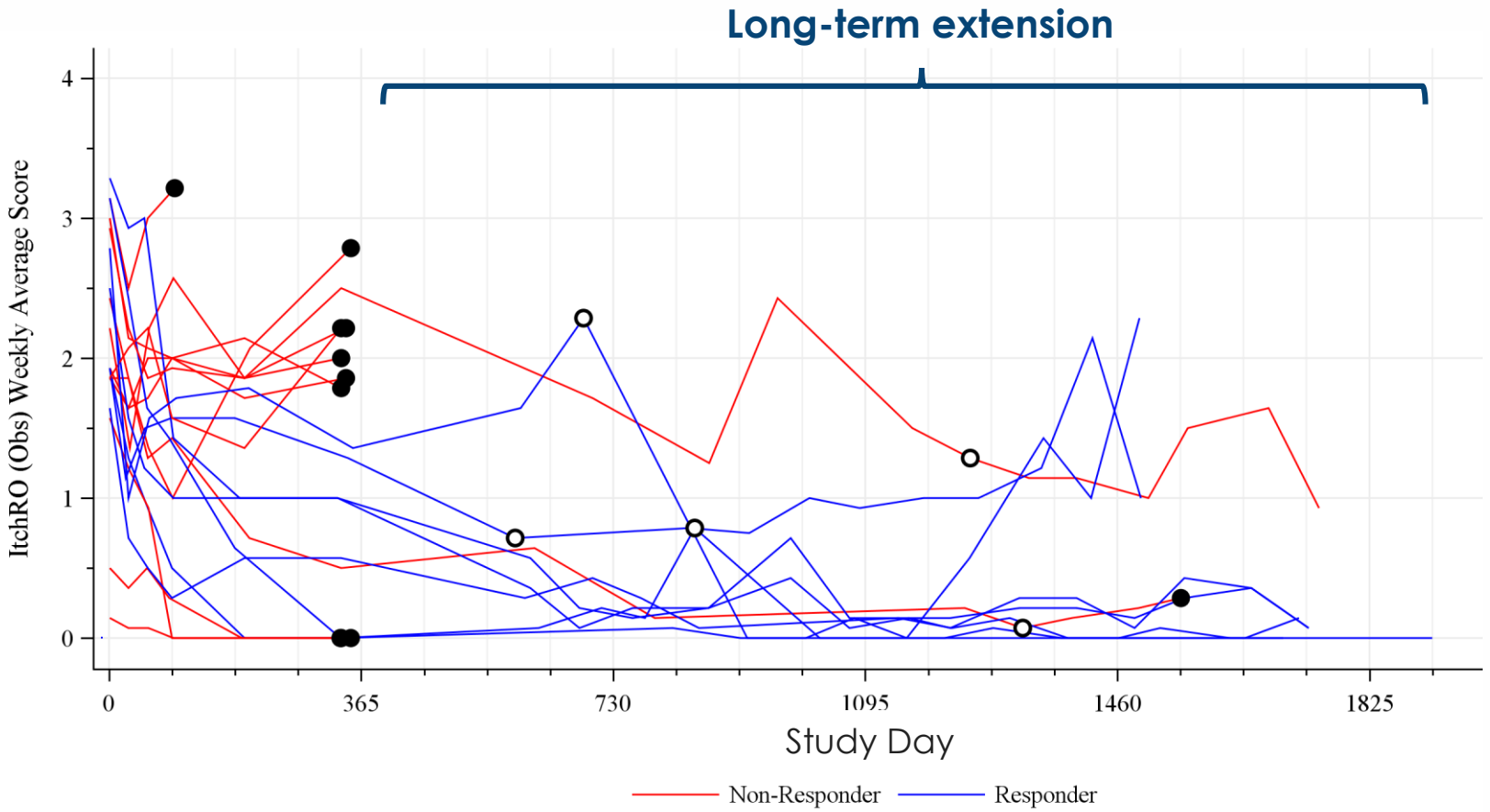
Truncating BSEP mutations



The black filled circle refers to termination.
The white filled circle refers to the start of BID dosing (280µg/kg BID)

sBA responders maintain response long-term with maralixibat

Non-truncating BSEP subjects: long-term pruritus response



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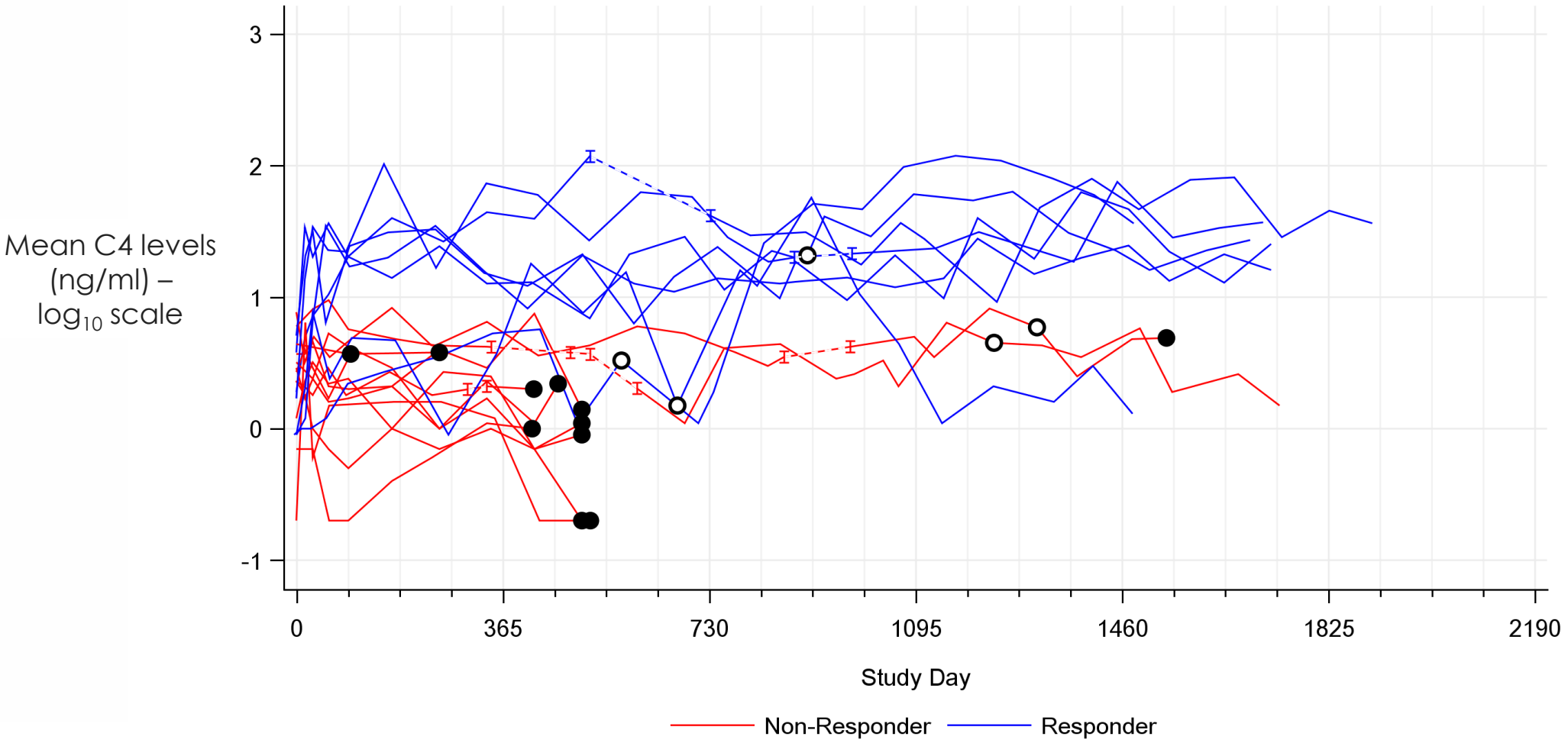
ItchRO Observer Score: 0-4 observer-rated pruritus scale

KEY POINTS

- 12 patients into 5th year of treatment
- >50% (10/19) patients with ≥1.0 pt reduction
- ItchRO(Obs) response is sustained over years

Non-truncating BSEP responders showed significant increases in 7α-hydroxy-4-cholesten-3-one (C4)



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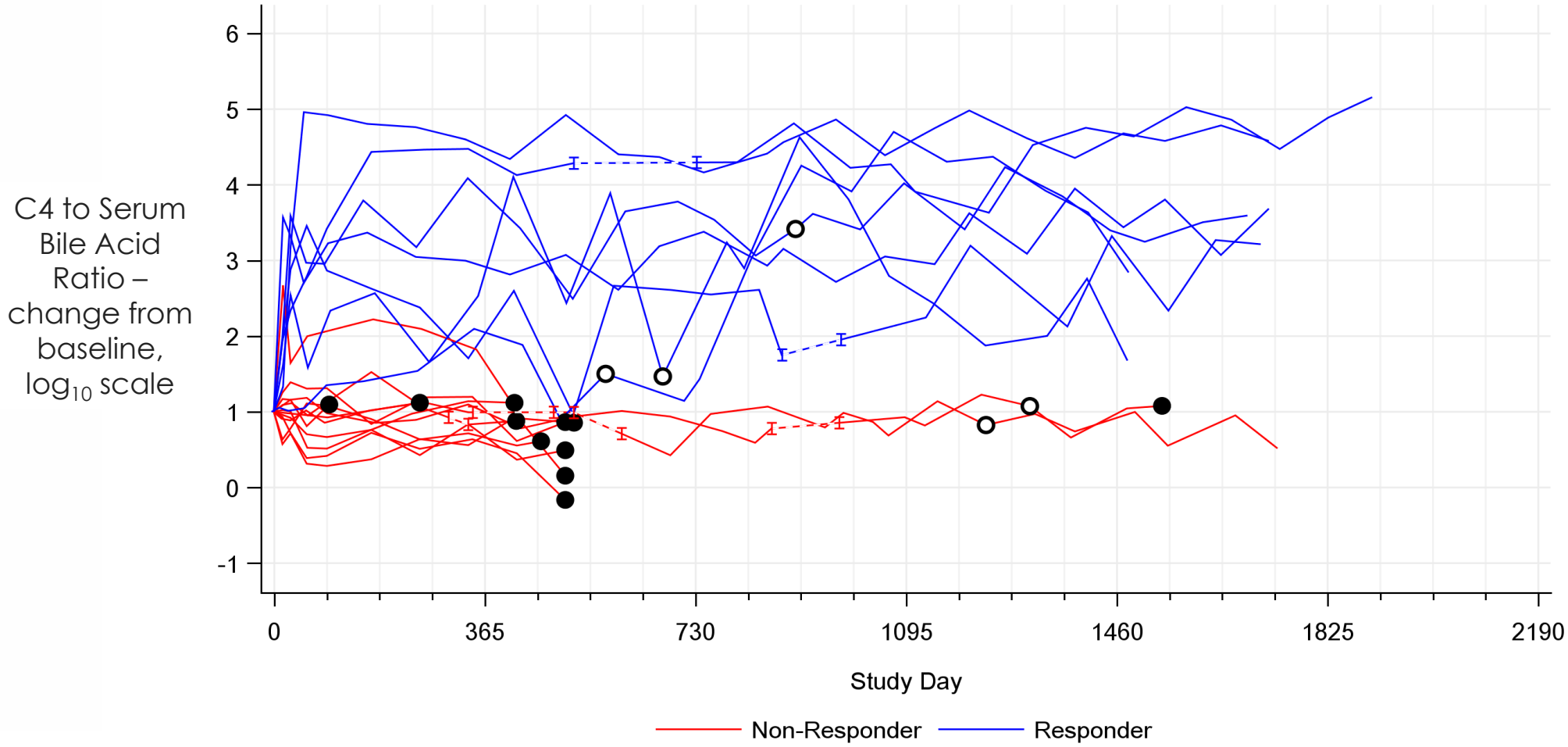
Non-truncating BSEP responders had significantly different C4 to serum bile acid ratios vs non-responders



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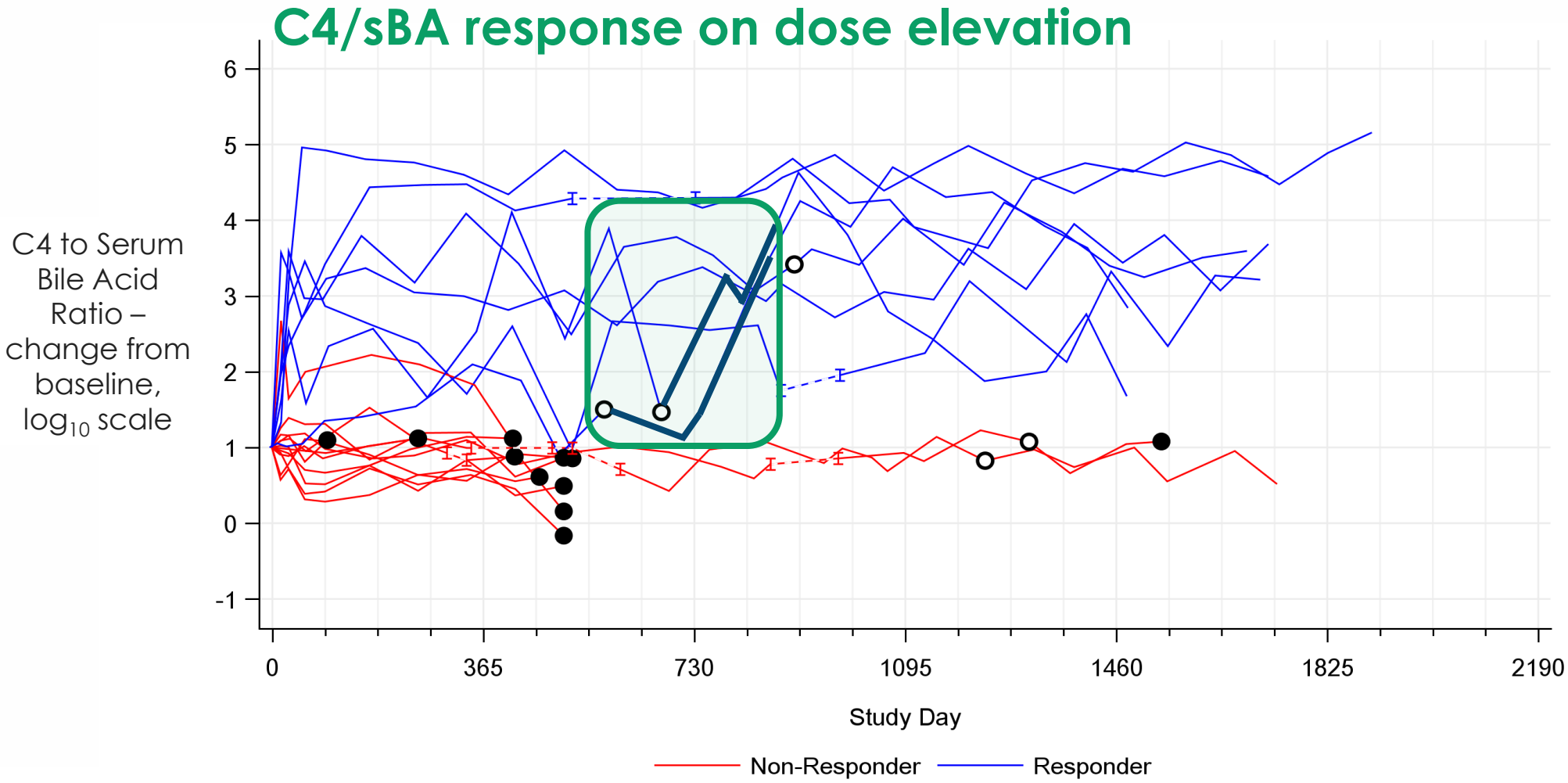

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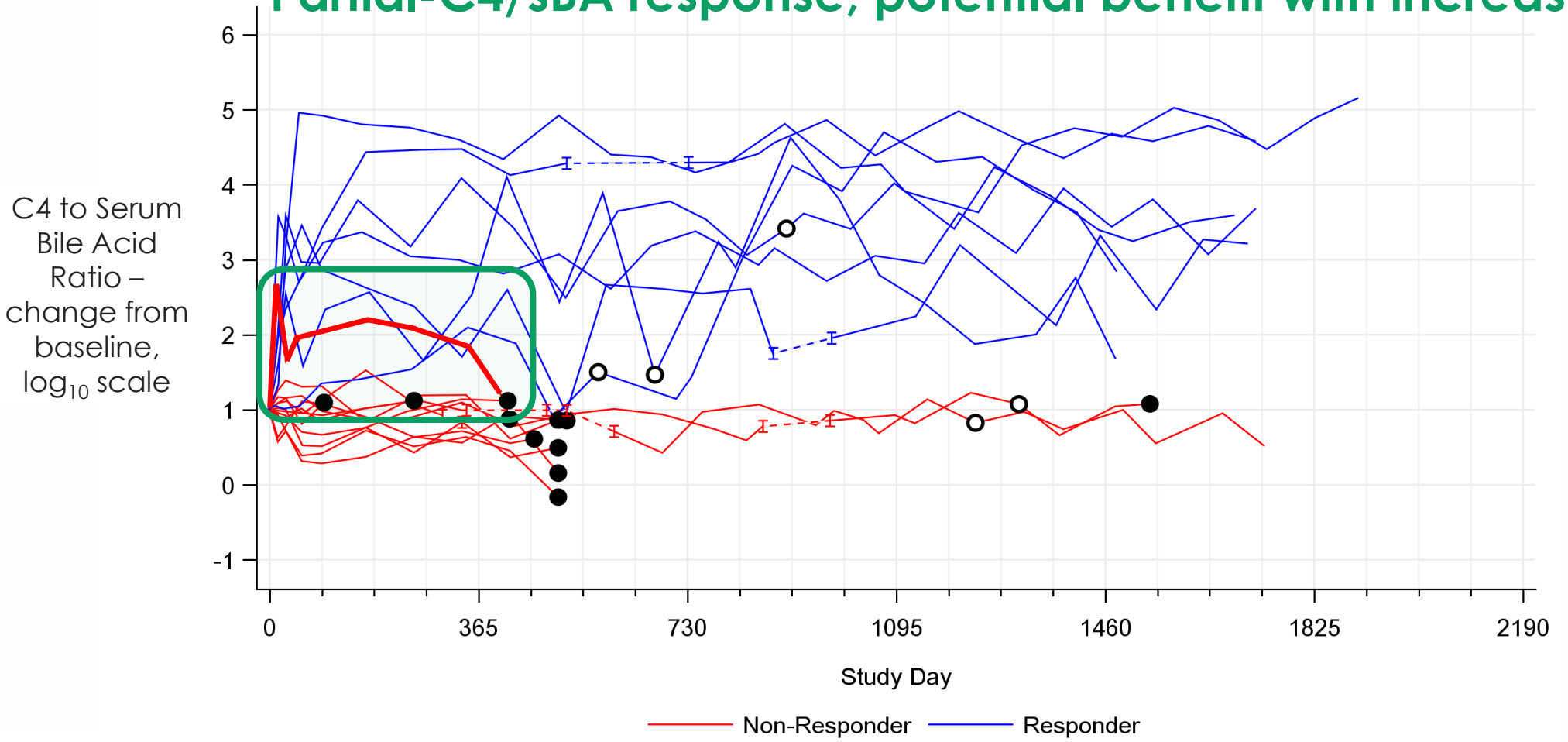
Non-truncating BSEP responders had significantly different C4 to serum bile acid ratios vs non-responders

Partial-C4/sBA response; potential benefit with increased dose



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Conclusions

- **Change in C4/serum bile acid ratio is good predictor of response to ASBTi**
- **Initial non-responders may benefit from increased doses of maralixibat**
  - Particularly those with greater BSEP function (i.e. mild mutation)
  - Patients predicted to have biallelic truncating mutations show no response, in line with results from partial external biliary diversion surgery
- **Patients with non-truncating BSEP deficiency can have durable control of pruritus and cholestasis with maralixibat**

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Thank You!