Growth analysis in children with PFIC treated with the ASBT inhibitor maralixibat

INDIGO Study

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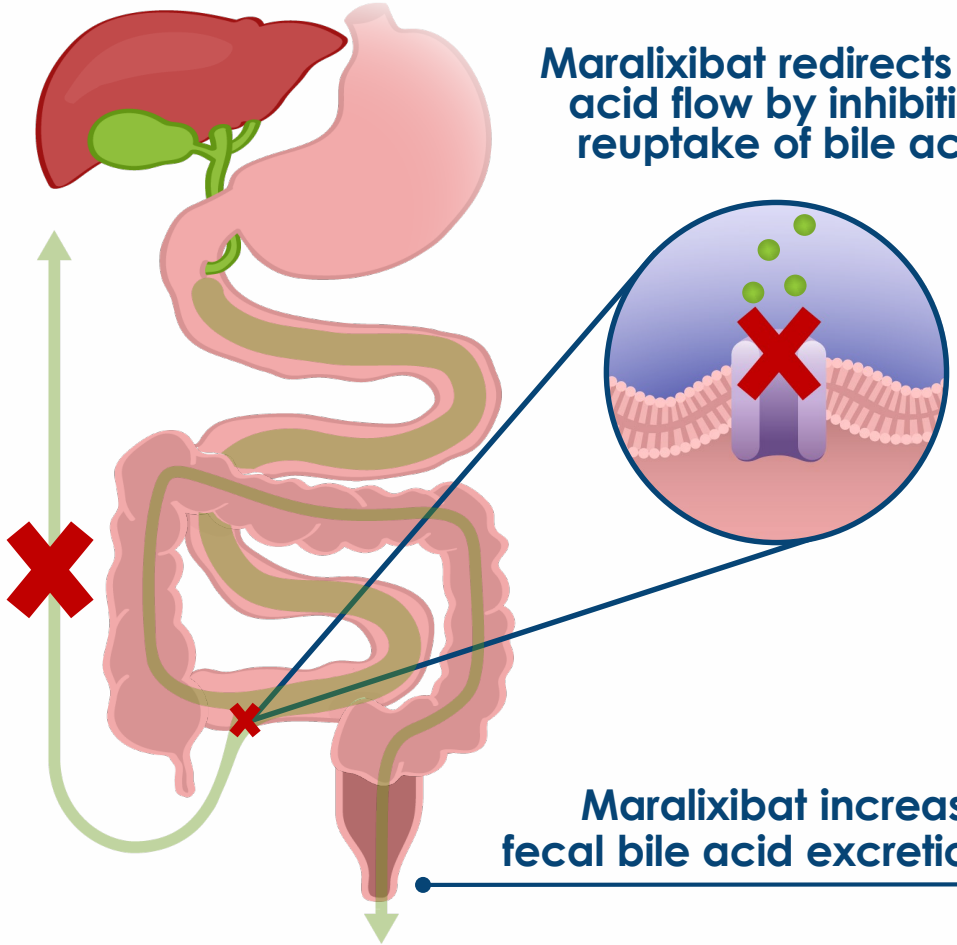
Treatment of children with progressive familial intrahepatic cholestasis

- **Progressive Familial Intrahepatic Cholestasis (PFIC)**
  - A progressive childhood cholestatic liver disease
  - Caused by rare genetic defects of bile acid excretion
  - Leading to debilitating pruritus, lipid-soluble vitamin deficiency, growth deficit
- **Standard of care**
  - Pharmacotherapy is only partially/temporarily effective and off-label
  - Partial external biliary diversion (PEBD) reduces serum bile acids (sBA) and pruritus, and improves growth, but may have serious complications
  - Liver transplantation can treat pruritus, but complications/recurrence are not uncommon in PFIC
- **Maralixibat**
  - A potent, minimally absorbed, selective ASBTi (inhibitor of the ileal apical sodium-dependent bile acid transporter)
  - Pharmacological interruption of enterohepatic bile acid recirculation may benefit patients with PFIC

Maralixibat is a potent, selective inhibitor of the ileal apical sodium-dependent bile acid transporter (ASBT)



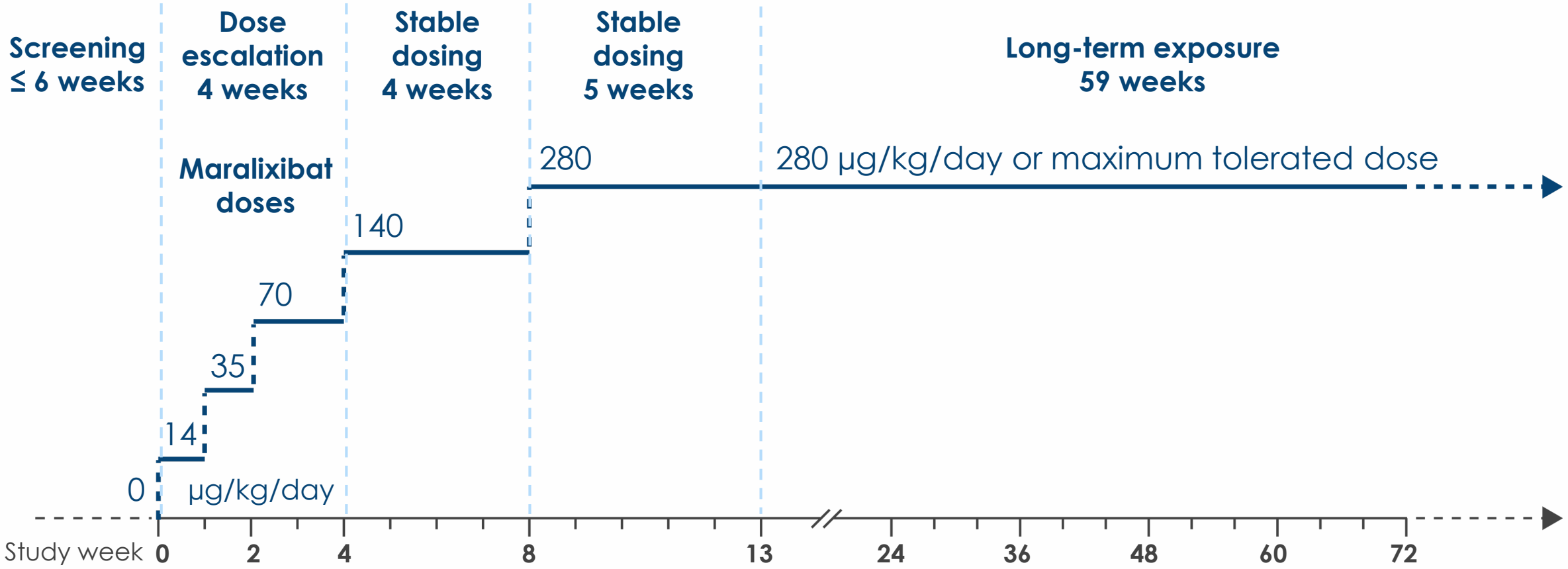
Clinical effects of ASBT inhibition

- ASBT inhibitors, including maralixibat, decrease pruritus, sBA and cholesterol, and increase C4 in PBC[2–4] and improve growth in a cholestasis model[5]
- Maralixibat studies show a trend towards decreases in pruritus in ALGS[6]

ALGS, Alagille syndrome; C4, 7-a-hydroxy-4-cholesten-3-one; PBC, primary biliary cholangitis.

1. Keller B, Falk Symposium 2014, Freiburg, Germany; 2. Al-Dury S. *Sci Rep* 2018; 3. Hegade VS. *Lancet* 2017; 4. Shneider BL. *Hepatol Commun* 2018; 5. Miethke A. *Hepatology* 2016; 6. Mayo MJ. *Hepatol Commun* 2019;

INDIGO: phase 2, open-label, safety and efficacy study of maralixibat in children with PFIC



Results from a pre-specified 48-week analysis are presented (subsequent data are preliminary and are not available for all patients)

Key entry criteria and efficacy endpoints

Key inclusion criteria

- 1–18 years old
- PFIC phenotype
- PFIC genotype (biallelic *ABCB11* or *ATP8B1* mutation)

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

Disposition, demographics, disease characteristics

Participant characteristics

N = 33	PFIC1, n = 8 *ATP8B1*	PFIC2, n = 25 *ABCB11*
Median age (range), year	2.0 (1–7)	4.0 (1–13)
Boys, n (%)	6 (75)	8 (32)
White, n (%)	6 (75)	20 (80)
Mean (SD) z-scores		
Height	–2.96 (1.47)	–1.29 (0.98)
Weight	–2.70 (2.82)	–0.63 (0.88)

Disposition to week 48

	Participants (n)
Reached week 48	26
Efficacy data available	
PFIC1	6
PFIC2	20
Maralixibat dose	
280 µg/kg/day	23
140 µg/kg/day	2
< 140 µg/kg/day[a]	1

[a] One patient receiving 280 µg/kg/day had a treatment interruption and was re-escalating at week 48

Efficacy in overall PFIC2 population (n = 25)

After 48 weeks of treatment:

- Significant pruritus[a] improvement
- Trend towards sBA improvement
- Trend towards QoL improvement
- No change in ALT or bilirubin

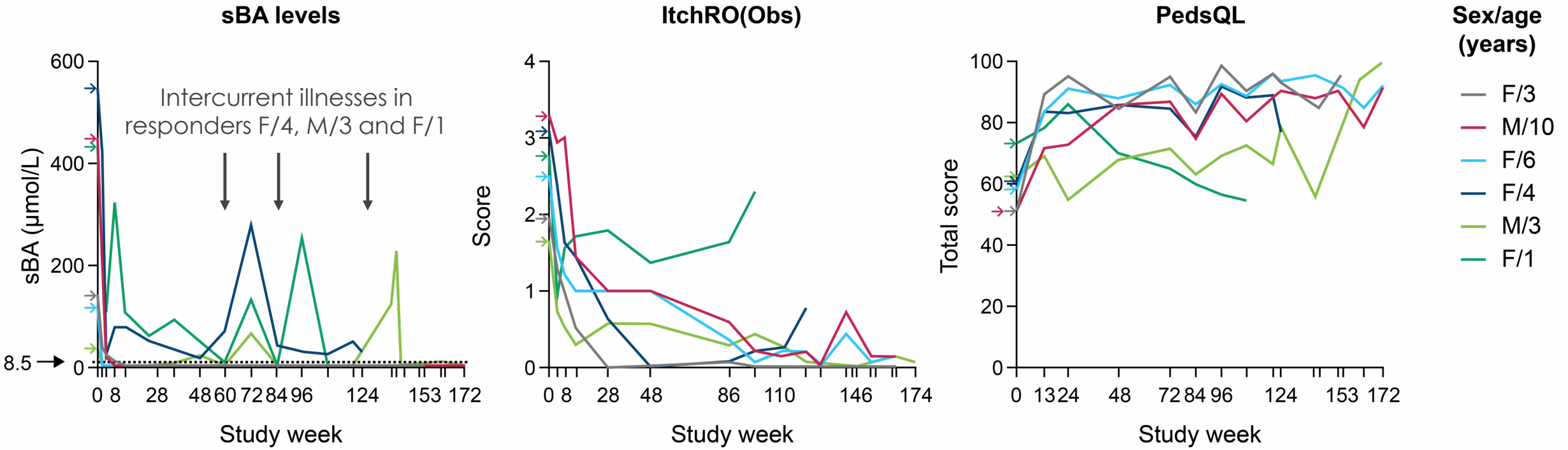
	Baseline Mean (range)	Week 48 Mean (95% CI)
ItchRO(Obs)	2.3 (0.1, 3.8)	-1.1 (-1.5, -0.6)
CSS	2.9 (0, 4)	-1.3 (-2.0, -0.6)
sBA [µmol/L]	381 (34, 602)	-59 (-157, 39)
PedsQL total	62.9 (34.5, 85.9)	4.4 (-4.0, 12.7)
C4 [ng/L]	4.6 (0.3, 47.3)	7.7 (-0.8, 16.1)

Part of the data presented by Thompson et al., AASLD 2017

[a] Pruritus measured by ItchRO(Obs)

QoL: Quality of Life as measured by PedsQL; sBA: serum bile acids; CSS: Clinician Scratch Scale

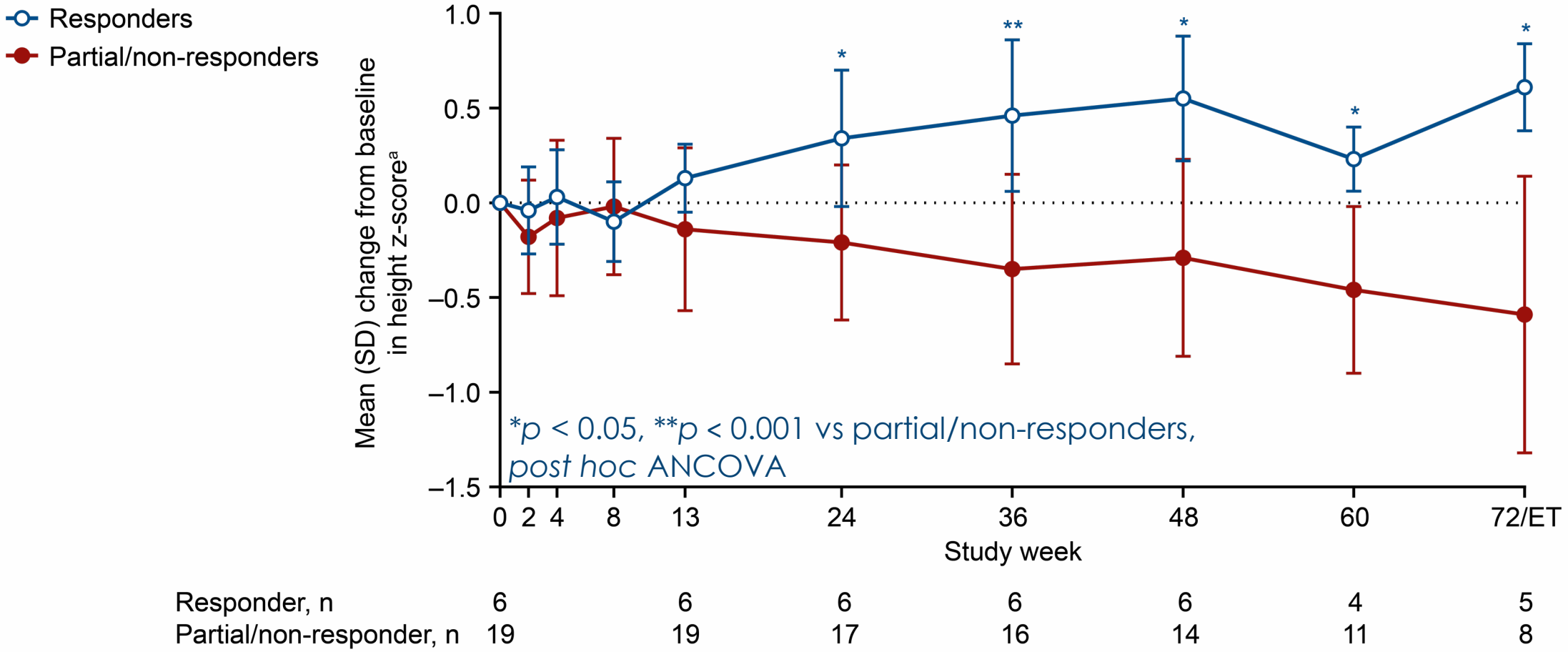
Profound/sustained treatment response in n = 6



Response criteria: sBA levels – normalized (≤ 8.5 µmol/L; n = 4) or reduced ≥ 70% from baseline (n = 2) AND ItchRO(Obs) – no pruritus (n = 2) or improved ≥ 1.0 points from baseline (n = 4)

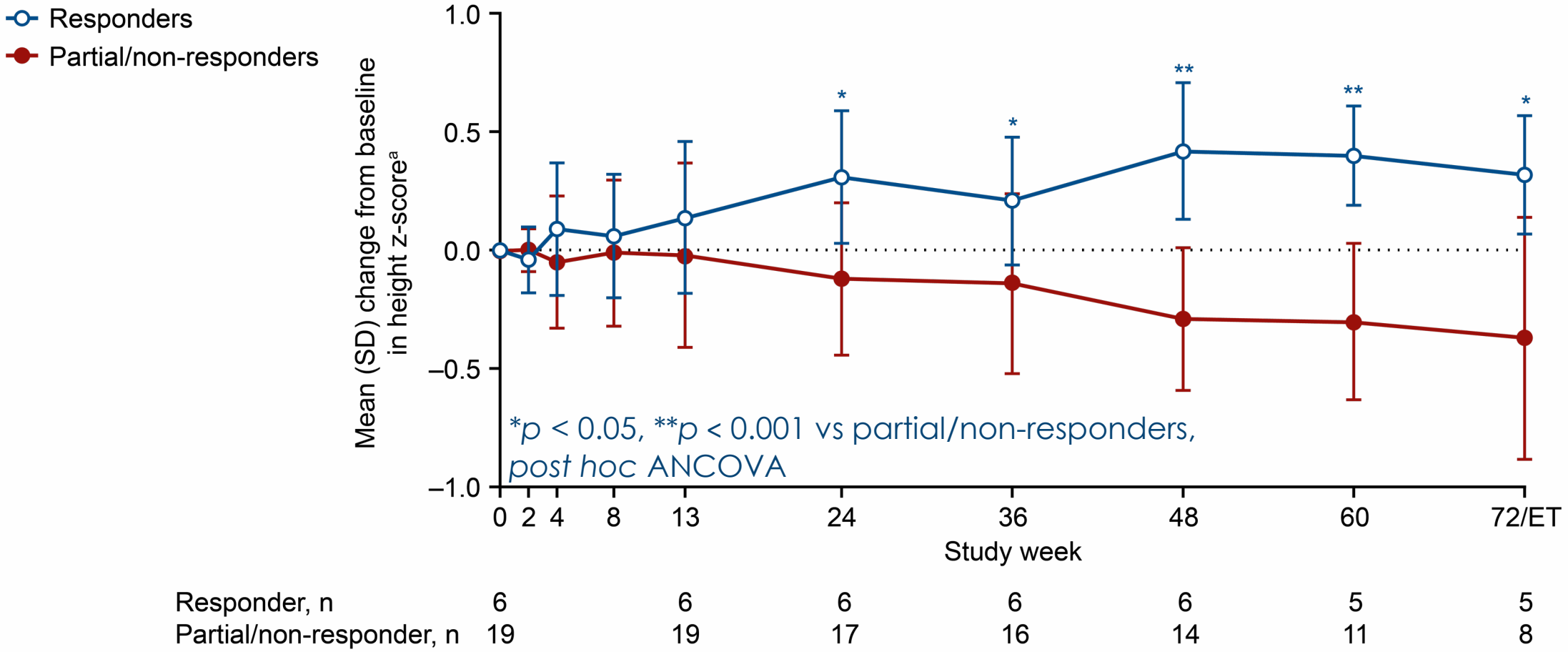
Responder characteristics: All non-truncating PFIC2 (ABCB11) mutations, all on 280 µg/kg/day; no other predictive characteristics
ALT, AST and bilirubin normalized, if elevated at baseline (ALT remained mildly elevated in responder F/1)

Height z-scores increased in PFIC2 responders vs decreased in partial/non-responders



[a] z-score: number of standard deviations that a measure deviates from the mean value of healthy age-matched controls

Weight z-scores increased in PFIC2 responders vs decreased in partial/non-responders



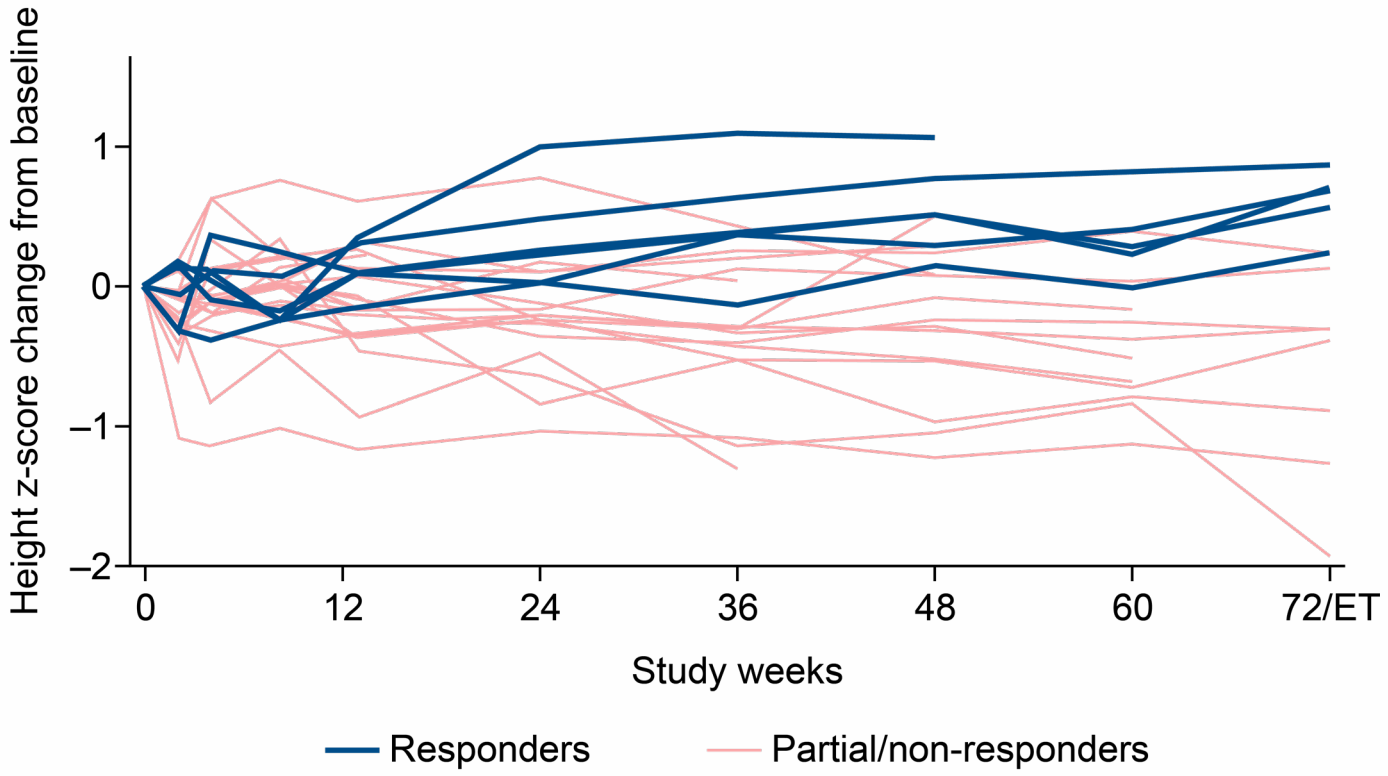
[a] z-score: number of standard deviations that a measure deviates from the mean value of healthy age-matched controls

Improvements in growth may be related to disease modifications induced by maralixibat

- Possible explanations for growth increases:
  - Pruritus relief?
  - Improved sleep?
  - Greater absorption of fats due to modified bile acid profile in the gut?
- Growth spurt with maralixibat comparable to those documented after PEBD[1,2] or liver transplantation[3,4]

Individual height z-scores change from baseline

Consistent effect within each group

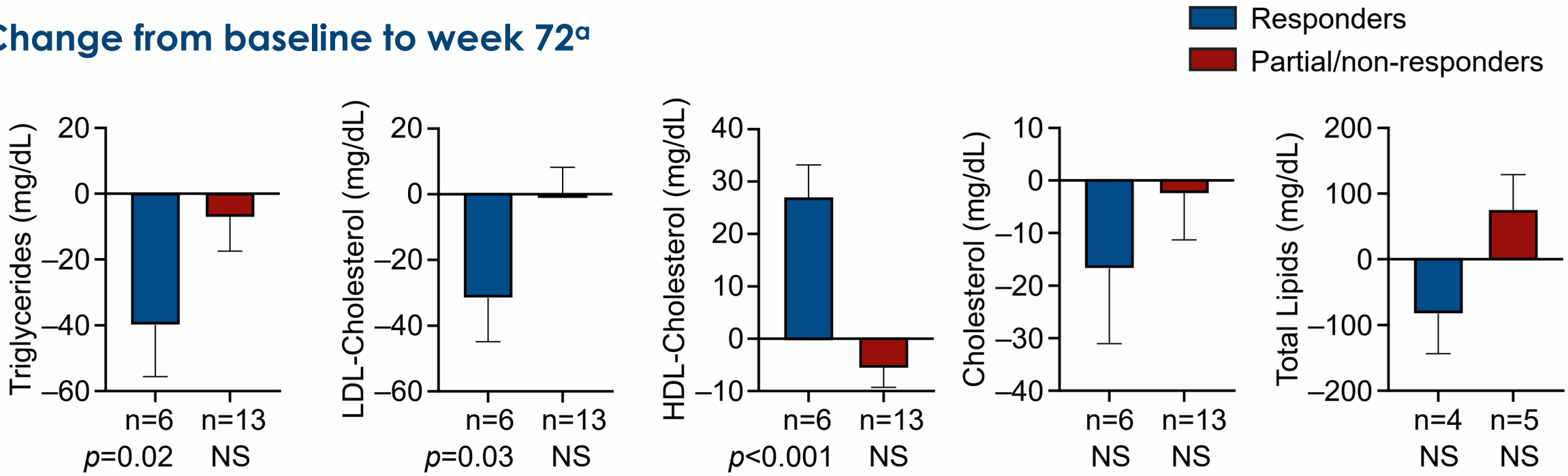


1. Arnell H. *Pediatr Surg* 2008; 2. Melter M. *Am J Gastroenterol* 2000; 3. El Moghazy WM. *Liver Transpl* 2010; 4. Pawlowska J. *Ann Transplant* 2010

Improvement of lipid profile in responders

- Response is associated with improvement in lipid profiles

Change from baseline to week 72[a]

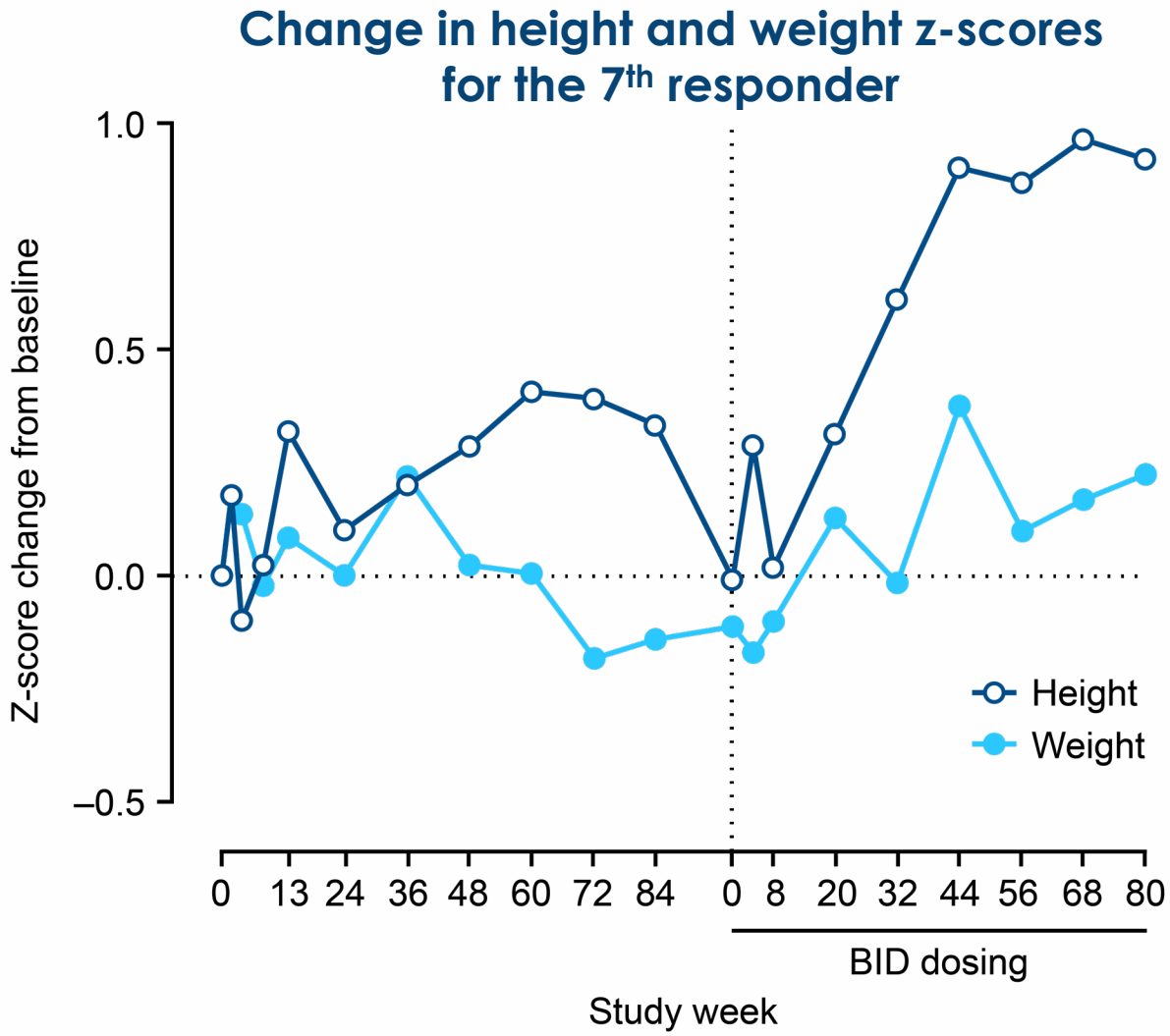


- Changes in the serum lipid profile with maralixibat are comparable to those reported after PEBD[1]
- ASBT inhibition upregulates hepatic LDL-receptor mRNA levels in a piglet model[2]

[a] LS mean (SE). 1. Jankowska I. *J Pediatr Gastroenterol Nutr* 2016; 2. Huff MW. *Arterioscler Thromb Vasc Biol* 2002

Higher doses may lead to higher response rate

- Protocol amendment doubled maralixibat dose to 280 µg/kg BID
- 7th responder with PFIC2 manifested on BID treatment
- Growth benefit was reproducible after meeting response criteria
- Change in z-scores after starting BID dosing:
  - Height: +0.93
  - Weight: +0.34



BID, twice daily

Summary and conclusions

- Maralixibat leads to marked treatment benefit in a subset of children with PFIC2
  - Improvement in growth
  - Normalization or substantial reduction in sBA levels
  - Disappearance or substantial reduction in pruritus
  - Normalization of bilirubin and liver enzyme levels, if elevated at baseline
  - Improvement in lipid profile
  - Improvement in HRQoL
- Improvement in growth may be related to reductions in pruritus, better sleep or better fat absorption and may indicate disease-modifying potential of maralixibat
- A phase 3 study will be conducted to further investigate maralixibat in children with PFIC

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- Children's Hospital of Pittsburgh, PA
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