Phase 2 open-label efficacy and safety study of the apical sodium-dependent bile acid transporter inhibitor maralixibat in children with progressive familial intrahepatic cholestasis: 48-week interim efficacy analysis

Richard J Thompson

King's College London, London, UK

Study funded by Shire Development LLC

Co-authors

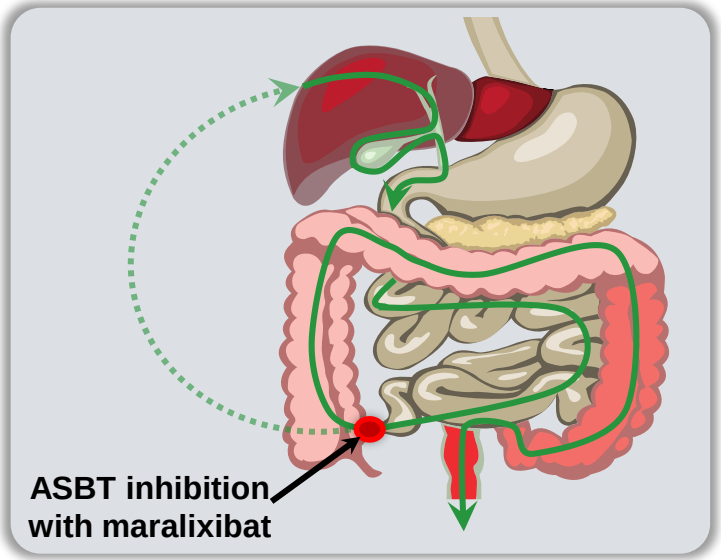
- Deirdre A Kelly,[1] Patricia McClean,[2] Alexander G Miethke,[3] Nisreen Soufi,[4] Christine Rivet,[5] Irena Jankowska,[6] Cara L Mack,[7] Palaniswamy Karthikeyan,[8] Joan Gu,[9] Thomas Jaecklin,[10] Robert H Squires,[11] Kathleen M Loomes[12]
  1. Birmingham Children's Hospital, Birmingham, UK
  2. Leeds General Infirmary, Leeds, UK
  3. Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, OH, USA
  4. Children's Hospital Los Angeles and Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
  5. Hôpital Femme-Mère-Enfant, Bron, France
  6. Children's Memorial Health Institute, Warsaw, Poland
  7. Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA
  8. King's College London, London, UK
  9. Shire, Lexington, MA, USA
  10. Shire, Zug, Switzerland
  11. Children's Hospital of Pittsburgh and University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
  12. Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Disclosures

- Note to authors: AASLD will add a disclosures slide based on the information you provided for the abstract submission

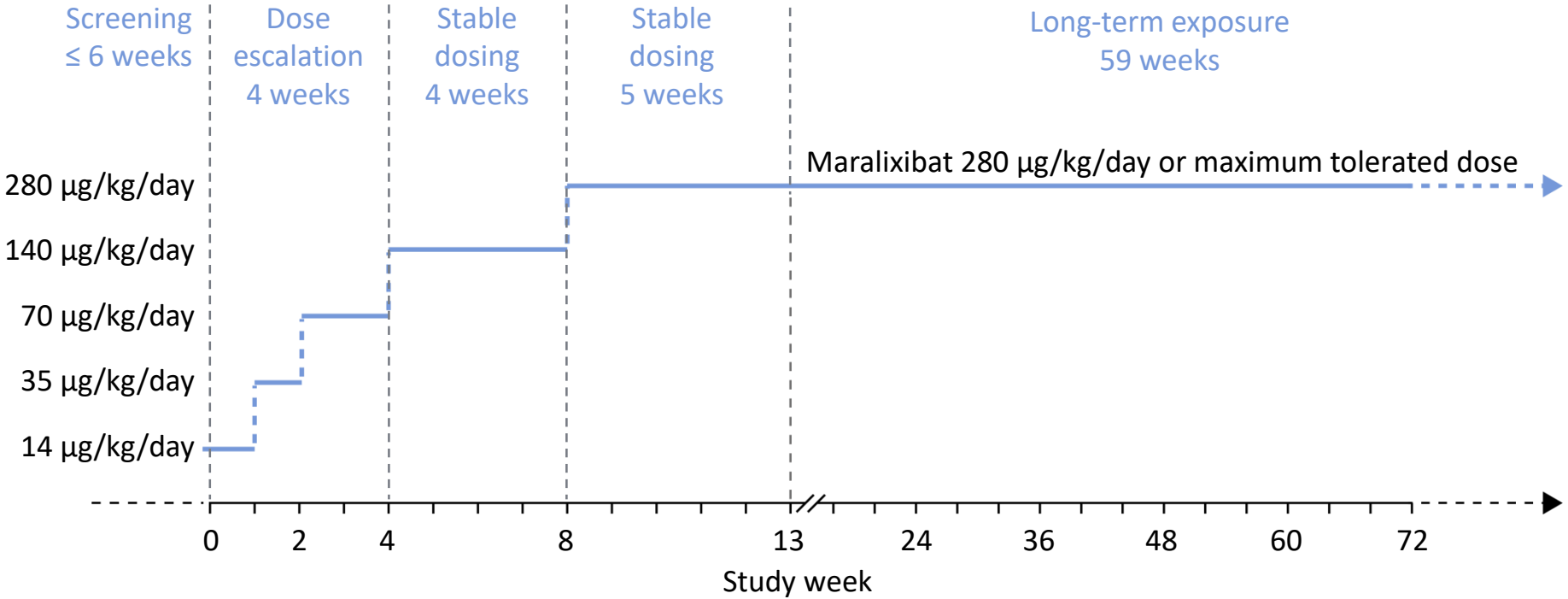
Maralixibat: potential treatment for children with progressive familial intrahepatic cholestasis (PFIC)

- PFIC is a group of debilitating childhood genetic disorders characterized by defects in bile acid transport
- Patients with PFIC lack approved pharmacotherapies to relieve pruritus and to prevent liver damage and early death
  - Partial external biliary diversion surgery can lower serum bile acid (sBA) concentrations
- Maralixibat is a potent, selective, minimally absorbed inhibitor of the ileal apical sodium-dependent bile acid transporter (ASBT)
- Pharmacological inhibition of enterohepatic bile acid recirculation may benefit patients with PFIC



Maralixibat = SHP625 = LUM001

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



We present results from a pre-specified 48-week interim analysis (subsequent data are preliminary and are not available for all patients)

Inclusion/exclusion criteria and outcomes

Key inclusion criteria

- Aged 1–18 years
- Clinically diagnosed PFIC
- Two mutant *ABCB11* or *ATB8B1* alleles

Key exclusion criteria

- Surgically disrupted enterohepatic circulation
- Liver transplant
- Decompensated cirrhosis

Key outcomes

- Levels of cholestasis biomarkers
  - sBA (primary efficacy measure)
  - ALT, AST, bilirubin and C4 in serum
- Pruritus assessments
  - ItchRO(Obs) weekly average score (parent-rated e-diary)
  - CSS score (investigator-rated)
- HRQoL assessment
  - PedsQL total score (parent-rated)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; C4, 7α-hydroxy-4-cholesten-3-one; CSS, clinician scratch scale; HRQoL, health-related quality of life; ItchRO(Obs), Itch-Reported Outcome (Observer); PedsQL, Paediatric Quality of Life Inventory

Disposition, demographics and disease characteristics

Enrolled participant characteristics (n = 33)

Diagnosis, n	
PFIC1 (*ATP8B1* mutation)	8
PFIC2 (*ABCB11* mutation)	25
Age, years, median (range)	3.0 (1–13)
Boys, n (%)	14 (42)
White, n (%)	26 (79)

Disposition to week 48

Reached week 48, n	29
Efficacy data available, n	26
PFIC1	6
PFIC2	20
Maralixibat dose, n	
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 measures at baseline and changes at week 48

sBA, µmol/L	ALT, UI/L	Total bilirubin, mg/dL	C4, ng/mL	ItchRO(Obs) score	PedsQL total score
Baseline, mean (range)					
352 (34, 602)	108 (13, 438)	2.9 (0.1, 15.1)	4.2 (0.1, 47.3)	2.3 (0.1, 3.8)	61.5 (18.1, 85.9)
Change from baseline to week 48, mean (95% CI)					
–32 (–110, +46)	–12 (–36, +13)	+0.8 (–0.1, +1.7)	+6.0 (–0.6, +12.5)	–1.0[a] (–1.4, –0.6)	+8.2[a] (+0.7, +15.6)

[a]95% CIs exclude zero, indicating nominal statistical significance
CI, confidence interval

Responders at week 48: 6/26 patients, all with PFIC2

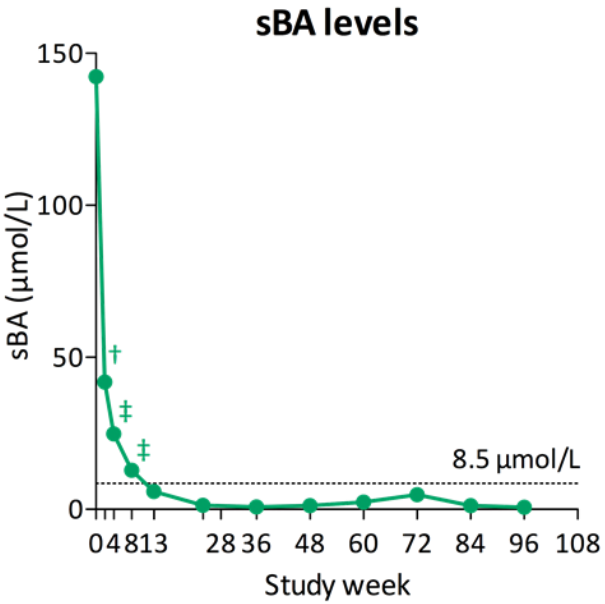
Responders (n = 6)

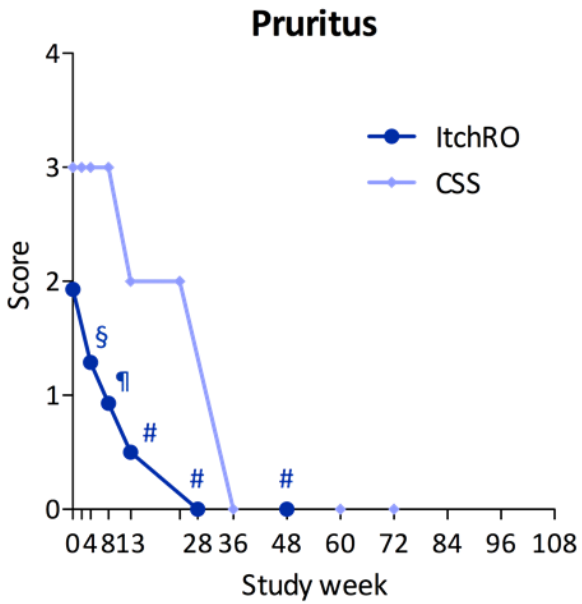
Diagnosis, n	
PFIC1 (*ATP8B1* mutation)	0
PFIC2 (*ABCB11* mutation)	6
Reached week 48, n	6
Maralixibat dose, n	
280 µg/kg/day	6

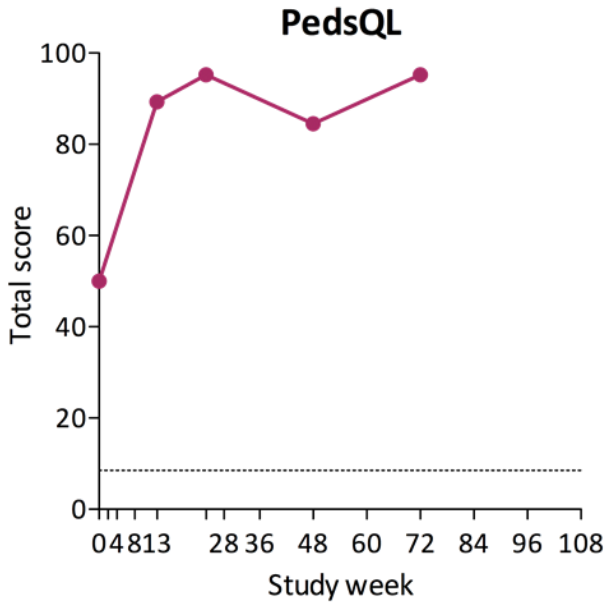
Response indicators (n = 6)

sBA levels, n	
Normalized (≤ 8.5 µmol/L)	4
Reduced by ≥ 70% or ≥ 80% from baseline	2
ItchRO score, n	
Zero (no pruritus)	2
Improved by ≥ 1.0 points from baseline	4

Responder A (girl aged 3 years)





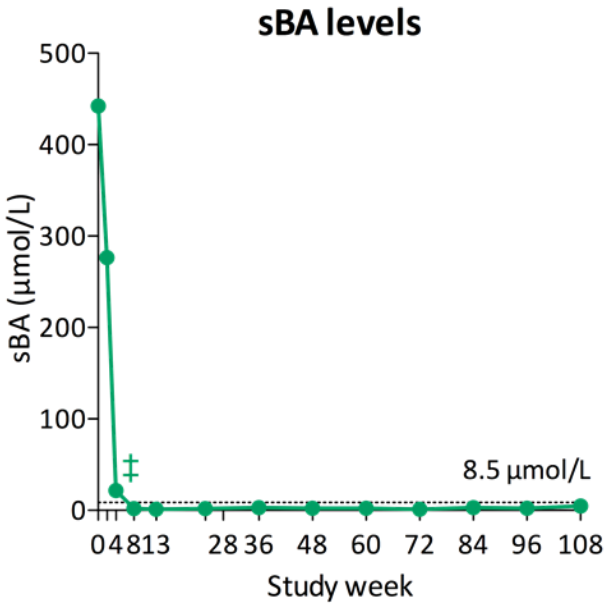


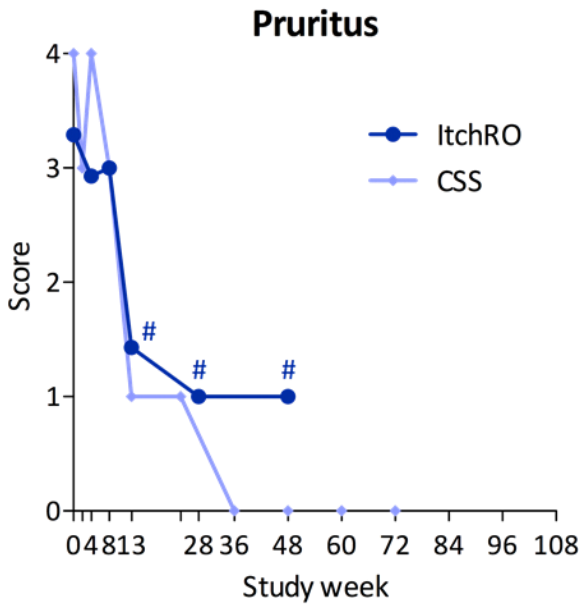
ALT and AST levels	Bilirubin levels	C4 levels
Baseline elevations normalized within 2–3 months	Baseline elevations normalized within 2–3 months	> 2.5-fold increase by week 2

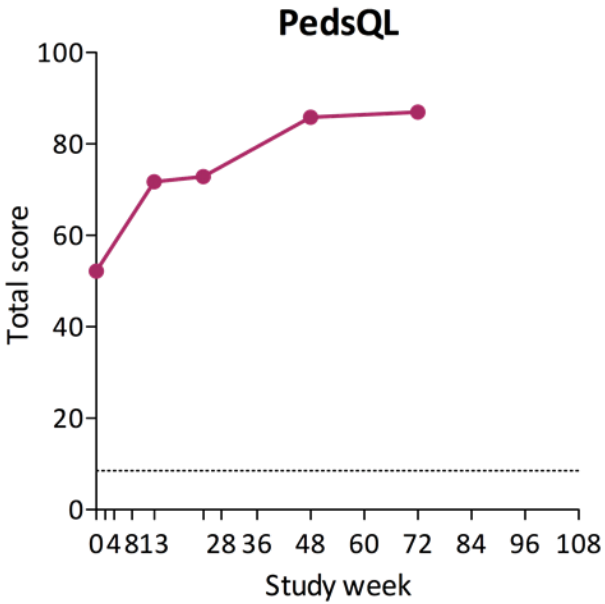
† ≥ 70%; ‡ ≥ 80% reduction from baseline

§ ≥ 0.5; ¶ ≥ 1.0; # ≥ 1.33 point reduction from baseline

Responder B (boy aged 10 years)





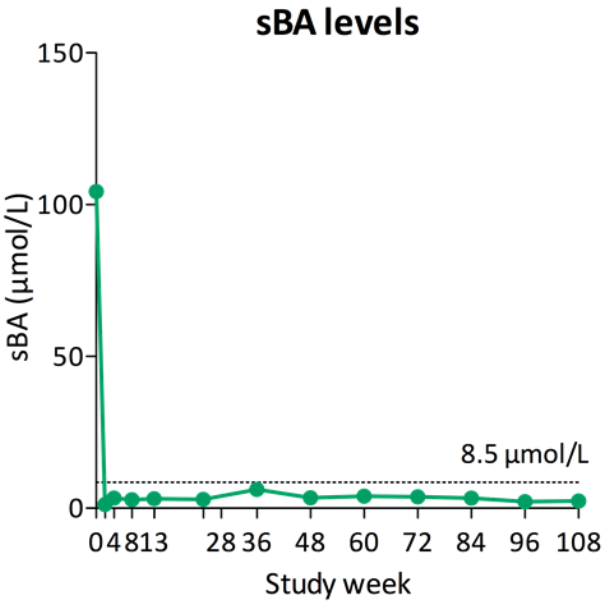


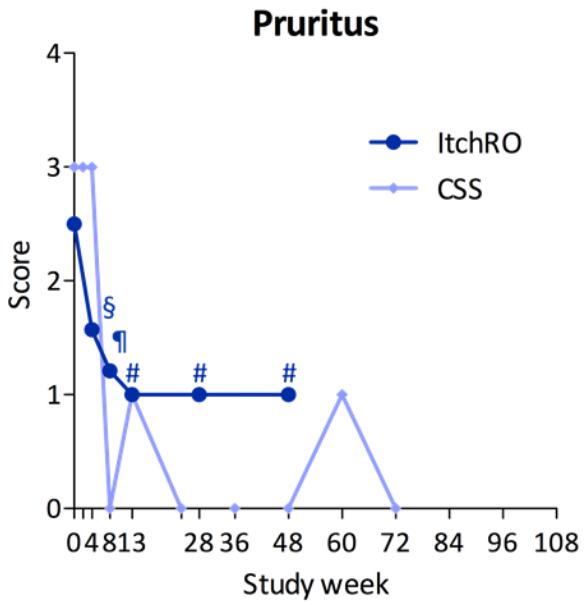
ALT and AST levels	Bilirubin levels	C4 levels
Baseline elevations normalized within 2–3 months	Always within normal range	> 6-fold increase by week 4

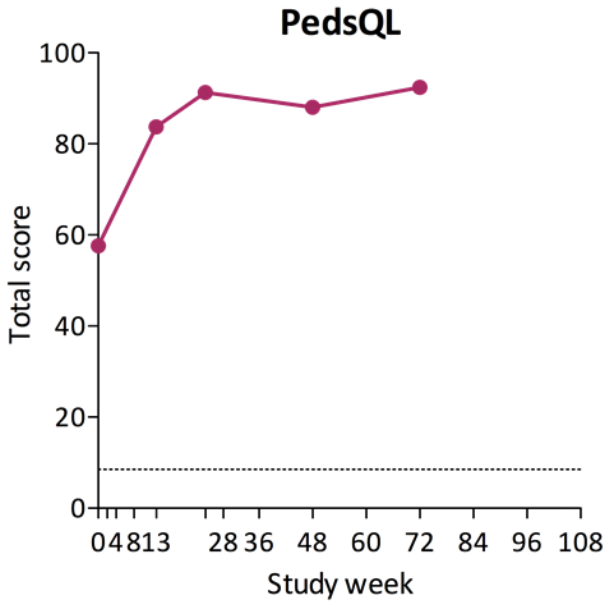
† ≥ 70%; ‡ ≥ 80% reduction from baseline

§ ≥ 0.5; ¶ ≥ 1.0; # ≥ 1.33 point reduction from baseline

Responder C (girl aged 6 years; sister of responder B)





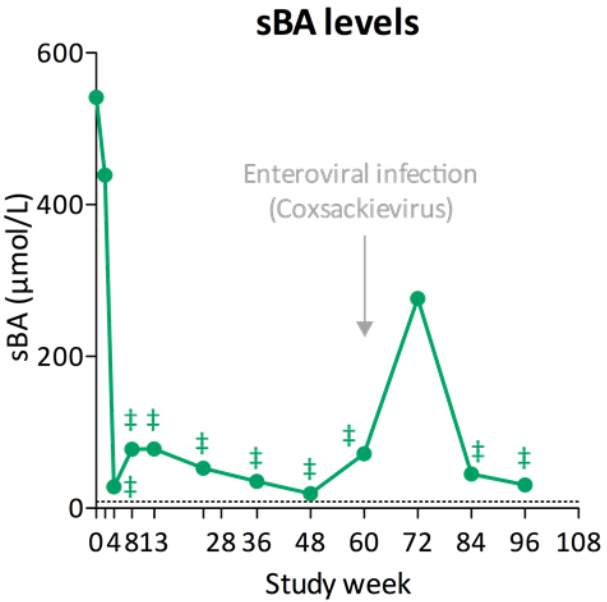


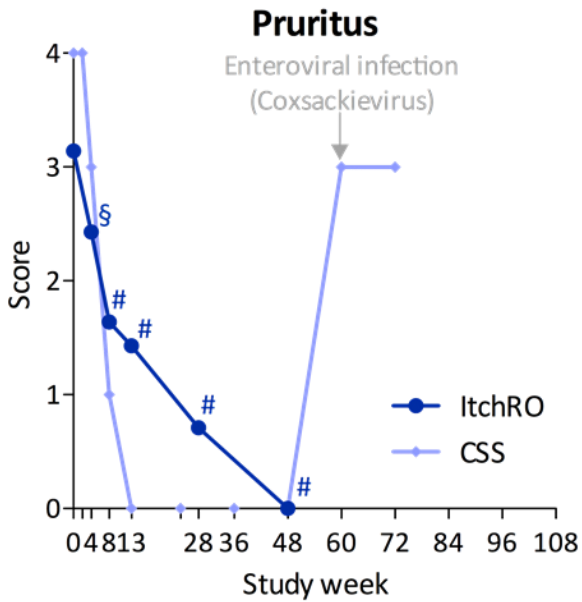
ALT and AST levels	Bilirubin levels	C4 levels
Always within normal range	Always within normal range	4-fold increase by week 2

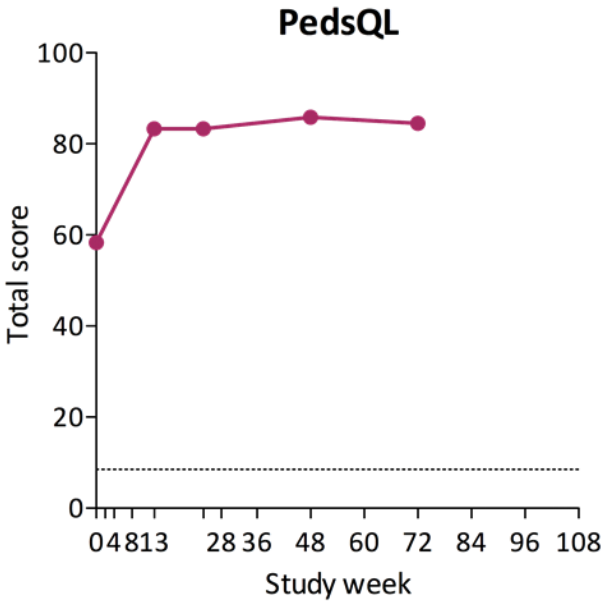
† ≥ 70%; ‡ ≥ 80% reduction from baseline

§ ≥ 0.5; ¶ ≥ 1.0; # ≥ 1.33 point reduction from baseline

Responder D (girl aged 4 years)





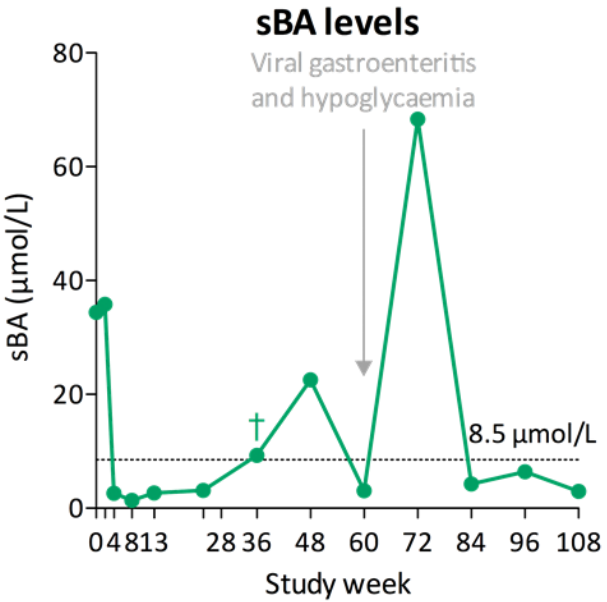


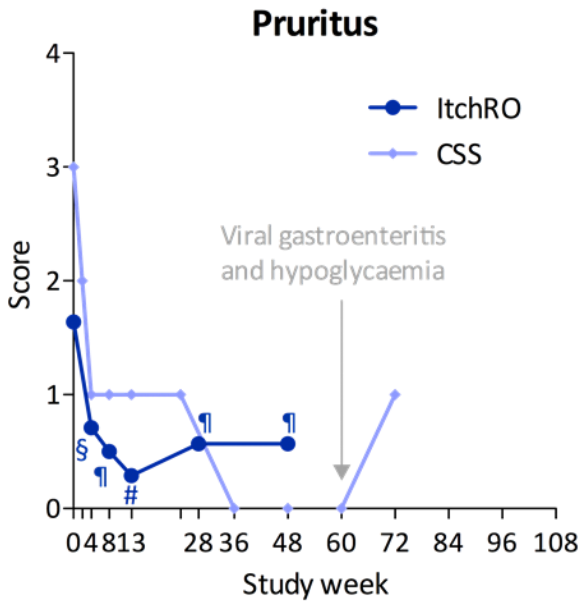
ALT and AST levels	Bilirubin levels	C4 levels
Always within normal range	Always within normal range	6-fold increase by week 2

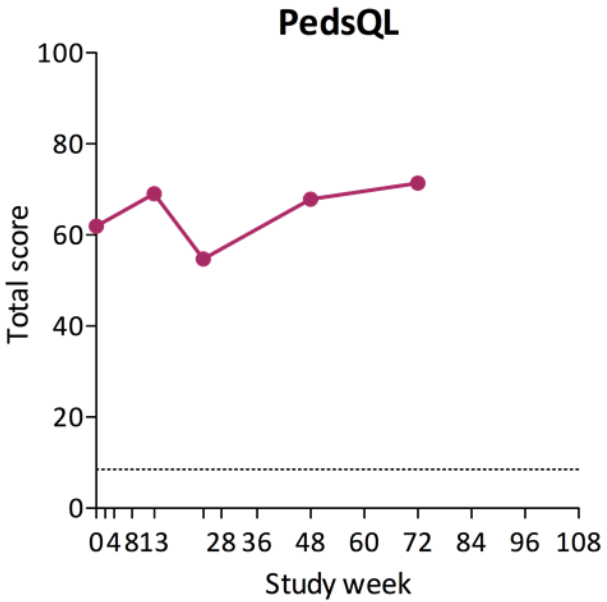
† ≥ 70%; ‡ ≥ 80% reduction from baseline

§ ≥ 0.5; ¶ ≥ 1.0; # ≥ 1.33 point reduction from baseline

Responder E (boy aged 3 years)





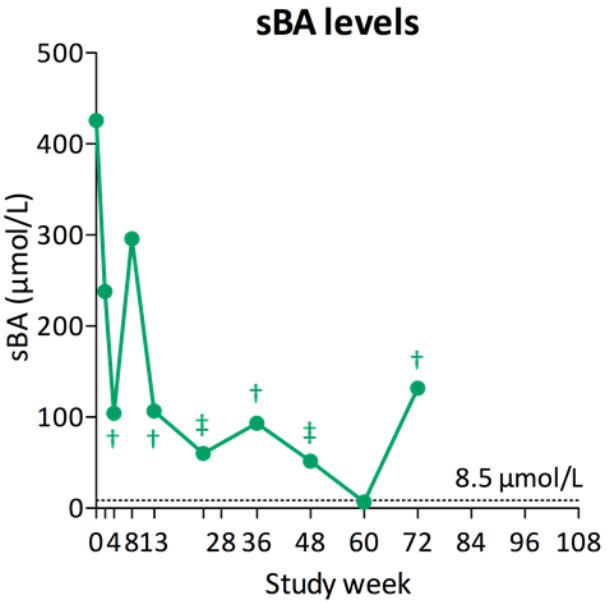


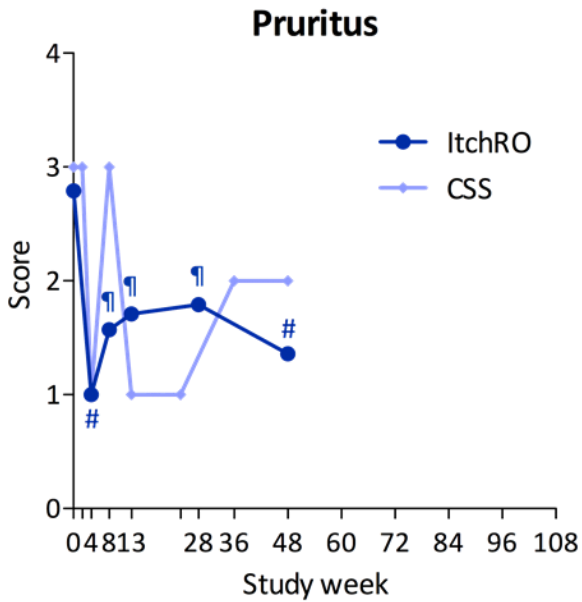
ALT and AST levels	Bilirubin levels	C4 levels
Always within normal range	Always within normal range	Nearly 9-fold increase by week 2

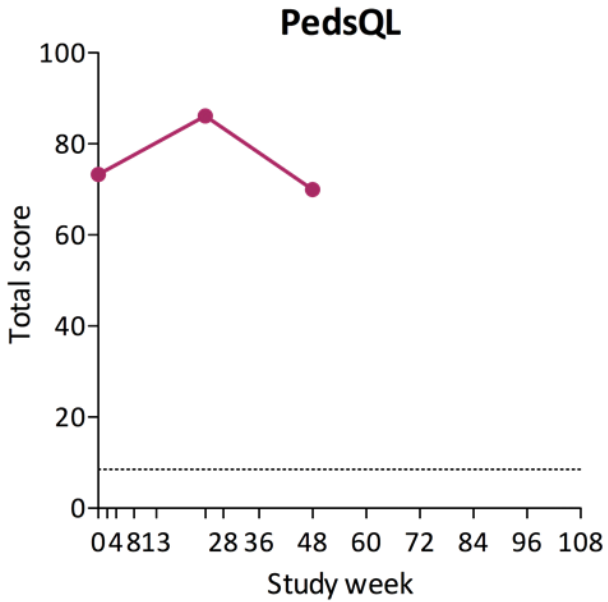
† ≥ 70%; ‡ ≥ 80% reduction from baseline

§ ≥ 0.5; ¶ ≥ 1.0; # ≥ 1.33 point reduction from baseline

Responder F (girl aged 1 year)







ALT and AST levels	Bilirubin levels	C4 levels
AST: always within normal range ALT: mild non-resolving elevation	Always within normal range	> 5-fold increase by week 13

† ≥ 70%; ‡ ≥ 80% reduction from baseline

§ ≥ 0.5; ¶ ≥ 1.0; # ≥ 1.33 point reduction from baseline

Treatment-emergent adverse events (TEAEs) in the safety population (N = 33)

TEAEs	Participants, n (%)
Any TEAE	33 (100)
Potentially maralixibat-related	22 (67)
Leading to discontinuation	1 (3)
Leading to death	0 (0)
Any serious TEAE	15 (45)
Potentially maralixibat-related	5 (15)

Most frequently reported TEAEs	Participants, n (%)
Pyrexia	15 (45)
Diarrhoea	14 (42)
Cough	13 (39)
Abdominal pain	10 (30)
Vomiting	10 (30)
Nasopharyngitis	8 (24)
Pruritus	8 (24)

Summary and conclusions

- ASBT blockade with maralixibat appears to benefit a subset of children with PFIC2
  - Normalization or substantial reduction in sBA levels
  - Complete or substantial relief of pruritus
  - Improvement in HRQoL
  - Normalization of bilirubin and liver enzyme levels, if elevated
- Gastroenteric infections may interfere with maralixibat treatment
- Future genetic studies may identify the responding subset
  - 6/20 children with PFIC2 and 0/6 with PFIC1 were responders at week 48
- Further studies of ASBT inhibitors in children with PFIC are warranted

Acknowledgements

- We thank the participants, caregivers, investigators and co-ordinators involved in the study