INDIGO study

Maralixibat treatment response is associated with improved health-related quality of life in patients with bile salt export pump (BSEP) deficiency

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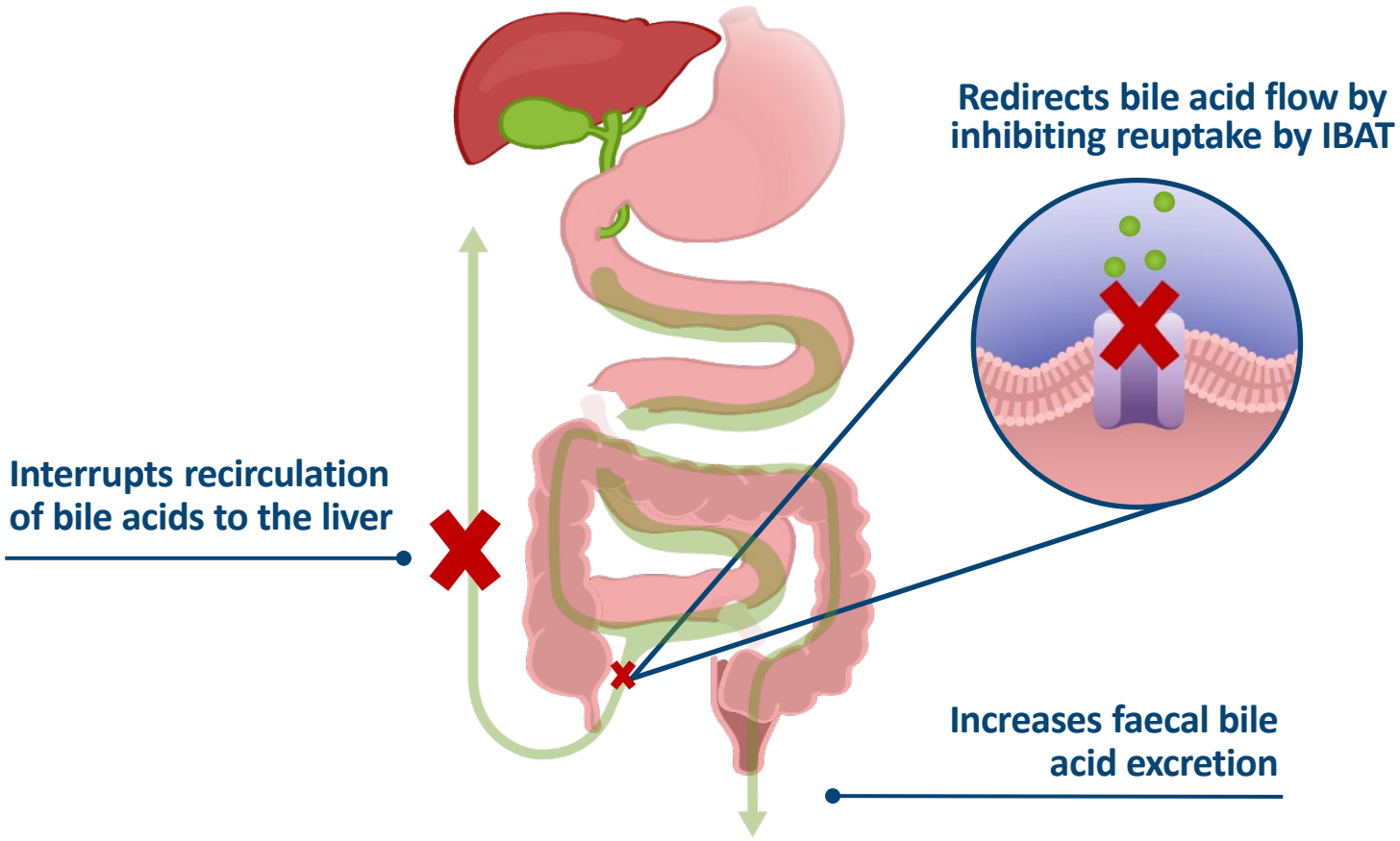
Background and treatment landscape for BSEP deficiency

- Progressive familial intrahepatic cholestasis (PFIC):[1]
  - A group of rare disorders caused by defects in bile transport and secretion
  - Presents with intrahepatic cholestasis
- BSEP deficiency (PFIC2) is the most common genetic cause of PFIC[2]
  - Results in the accumulation of bile acids[3]
  - Broad range of manifestations that usually present in early childhood, including jaundice, pruritus, failure to thrive and progressive liver disease[2,3]
- The pruritus associated with cholestatic liver disease can have a profound impact on patients' HRQoL[4–6]
- To reduce bile acid accumulation, surgical or pharmacological approaches can be used to block the recirculation of bile acids to the liver[2,7,8]
  - Odevixibat is an ileal bile acid transporter (IBAT) inhibitor that received FDA approval for the treatment of pruritus in patients 3 months of age and older with PFIC and is approved in the EU for the treatment of PFIC in patients 6 months of age and older[8,9]
  - Maralixibat is an IBAT inhibitor under investigation for the treatment of PFIC[10]

BSEP, bile salt export pump; HRQoL, health-related quality of life; IBAT, ileal bile acid transporter; PFIC, progressive familial intrahepatic cholestasis.

1. Jacquemin E, *et al*. *Clin Res Hepatol Gastroenterol* 2012;36(Suppl 1):S26–S35; 2. van Wessel DBE, *et al*. *J Hepatol* 2020;73:84–93; 3. Henkel SA, *et al*. *World J Hepatol* 2019;11:450–463;
4. Kamath BM, *et al*. *Liver Int* 2020;40:1812–1822; 5. Kamath BM, *et al*. *Patient* 2018;11:69–82; 6. Kamath BM, *et al*. *J Pediatr* 2015;167:390–396.e3;
7. Mirum Pharmaceuticals, Inc. LIVMARLI® (maralixibat) PI; 8. Albireo Pharma, Inc. BYLVAY® (odevixibat) PI. 9. Albireo AB. BYLVAY® (odevixibat) SmPC. 10. https://mirumpharma.com/our-science/pipeline/. Accessed on June 6, 2022.

Maralixibat: IBAT inhibitor that interrupts enterohepatic circulation



Clinical effects of maralixibat in cholestasis:

- ✓ Improvements in pruritus (itch)
- ✓ Reductions in sBA
- ✓ Improved transplant-free survival

Maralixibat received FDA approval for the treatment of cholestatic pruritus in patients with ALGS 1 year of age and older[1,2]

ALGS, Alagille syndrome; FDA, US Food and Drug Administration; sBA, serum bile acid.

1. Gonzales E, *et al. Lancet* 2021;398:1581–1592; 2. Mirum Pharmaceuticals, Inc. LIVMARLI® (maralixibat) PI.

INDIGO: Open-label Phase 2 study of maralixibat in PFIC

INDIGO Phase 2
N = 33 children with PFIC
- **19 non-truncating (BSEP)**
- 6 truncating (BSEP)
- 8 PFIC1

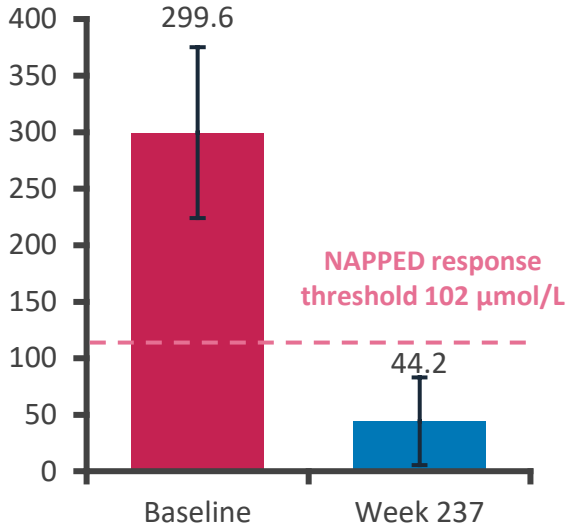
Maralixibat 266 µg/kg once-daily*,† → **Long-term extension** → **Maralixibat 266 µg/kg twice-daily permitted‡,§**

0–72 weeks | Week 72 onwards

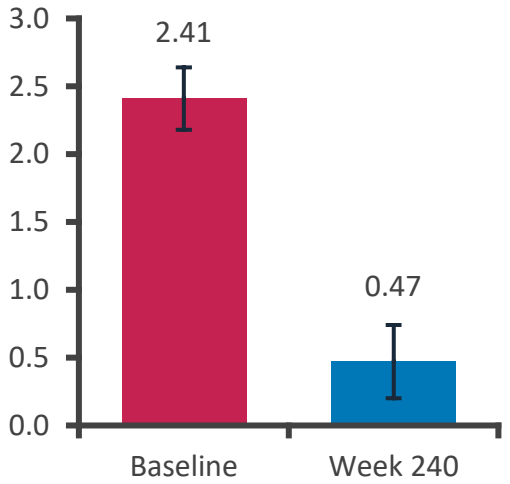
Study endpoints: sBA, pruritus, QoL, growth, safety and tolerability

sBA responders (n = 7/19 nt-BSEP)

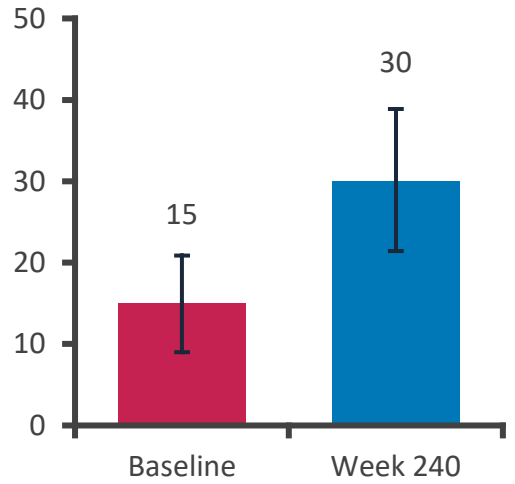
Mean sBA (µmol/L)



Mean ItchRO(Obs) score



Mean height percentile (%)



Response to treatment with maralixibat was defined *a priori* as a >75% decrease from baseline or reduction in sBA to <102 µmol/L from baseline to week 48 [NCT02057718].
*Equivalent to maralixibat chloride 280 µg/kg; †Included a 4-week dose escalation period; ‡Equivalent to maralixibat chloride 560 µg/kg; §Included a 4-week dose escalation period for patients who had gone ≥7 days without receiving maralixibat.
ItchRO(Obs), Itch-Reported Outcome (Observer); NAPPED, NAtural Course and Prognosis of PFIC and Effect of Biliary Diversion; nt, non-truncating; QoL, quality of life.
Loomes KM, *et al. Hepatol Comms* 2022; ePub ahead of print; Thompson R, *et al*. Oral presentation presented at WCPGHAN 2021.

INDIGO: HRQoL sub-analysis

- **Aim:** to assess the impact of maralixibat treatment response at week 48 on HRQoL among a subset of children with BSEP deficiency (PFIC2) from INDIGO

Pediatric Quality of Life Inventory™ (PedsQL) Generic Core Scale

Multidimensional Fatigue Scale

Family Impact Scale

Minimal clinically important difference (MCID): 4–5 points[1,*]

Scores were compared between sBA responders and non-responders to maralixibat

sBA response definition:[2]

- >75% decrease from baseline
- OR reduction to <102 µmol/L from baseline to week 48

*MCID for the HRQoL assessments ranges from 4 to 5 points, depending on the scale, as validated in previous analyses.
MCID, minimal clinically important difference.

1. Varni JW, *et al. Ambul Pediatr* 2003;3:329–341; 2. van Wessel DBE, *et al. J Hepatol* 2020;73:84–93.

Baseline characteristics were similar for responders and non-responders, but baseline HRQoL Multidimensional Fatigue Score was lower for responders

Baseline characteristics*†	Responders (n = 6)‡§	Non-responders (n = 15)	p value
Age, years	4.5 ± 3.2	5.0 ± 3.6	0.77
Male, n (%)	2 (33.3)	4 (26.7)	1.00
Height z-score	–1.2 ± 0.7	–1.3 ± 1.0	0.73
Weight z-score	–0.6 ± 0.9	–0.6 ± 0.9	0.90
sBA, µmol/L	281.6 ± 212.6	390.2 ± 108.9	0.13
PedsQL Generic Core Total Scale Score‖	58.9 ± 8.3	66.7 ± 14.9	0.25
PedsQL Family Impact Total Scale Score‖	52.0 ± 13.4	65.2 ± 15.4	0.09
PedsQL Multidimensional Fatigue Total Scale Score‖	42.5 ± 11.7	68.5 ± 22.1	**0.03**
ItchRO(Obs) 0–4 scale	2.5 ± 0.6	2.1 ± 0.9	0.33

*Twenty-two patients with BSEP deficiency (PFIC2) had HRQoL data at week 48 and were eligible for this analysis. One patient was lost to follow-up at week 48 and was therefore not evaluable for sBA treatment response;
†Eighteen patients had non-truncating BSEP mutations, and four patients had truncating BSEP mutations; ‡Six responders had non-truncating BSEP mutations;
§A seventh participant receiving maralixibat twice-daily responded to treatment at week 100; ‖QoL scores are rated on a scale from 0–100.
All data are mean ± SD unless otherwise indicated. p value is for the comparison of baseline characteristics according to treatment response status. Statistical comparisons conducted using t-test or ANOVA for continuous variables and chi-squared for categorical variables. ANOVA, analysis of variance; SD, standard deviation.

Maralixibat responders demonstrated meaningful improvements across several HRQoL measures at week 48

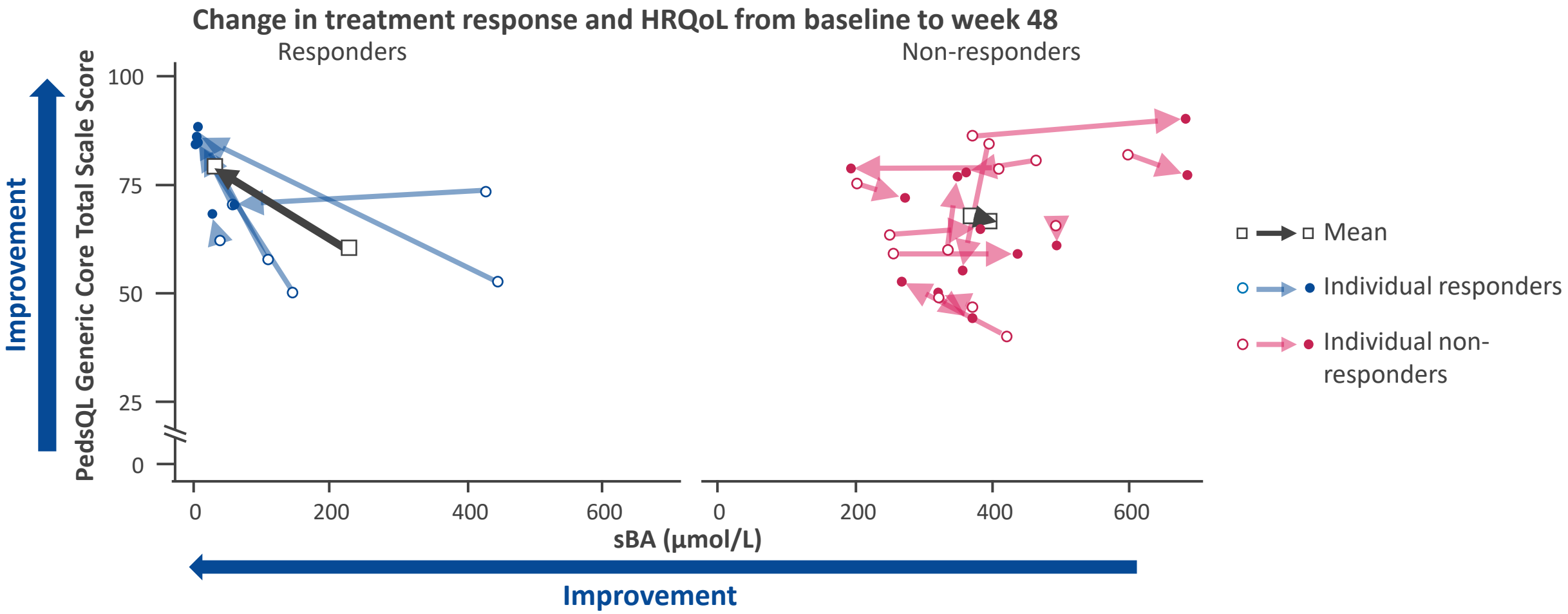
HRQoL score change from baseline to week 48	PedsQL Generic Core Scale (n = 18)*	Multidimensional Fatigue Scale (n = 16)*	Family Impact Scale (n = 20)*
Responders (n = 6)	20.3 ± 17.7	35.8 ± 15.1	8.0 ± 20.7
5-point change, n (%)[†]	4 (80.0)[‡]	4 (100)[§]	4 (66.7)
10-point change, n (%)[†]	3 (60.0)[‡]	4 (100)[§]	4 (66.7)
Non-responders (n = 15)	–0.8 ± 10.9	0.7 ± 16.7	–2.5 ± 9.8
5-point change, n (%)[†]	2 (15.4)[‖]	3 (25.0)[¶]	1 (7.1)**
10-point change, n (%)[†]	2 (15.4)[‖]	2 (16.7)[¶]	1 (7.1)**
p value[††]	0.01	<0.01	0.13

MCID:[‡‡] 4–5 points

Responders had an increase of ~4× the MCID for PedsQL, ~7× the MCID for the Multidimensional Fatigue Scale and ~2× the MCID for the Family Impact Scale

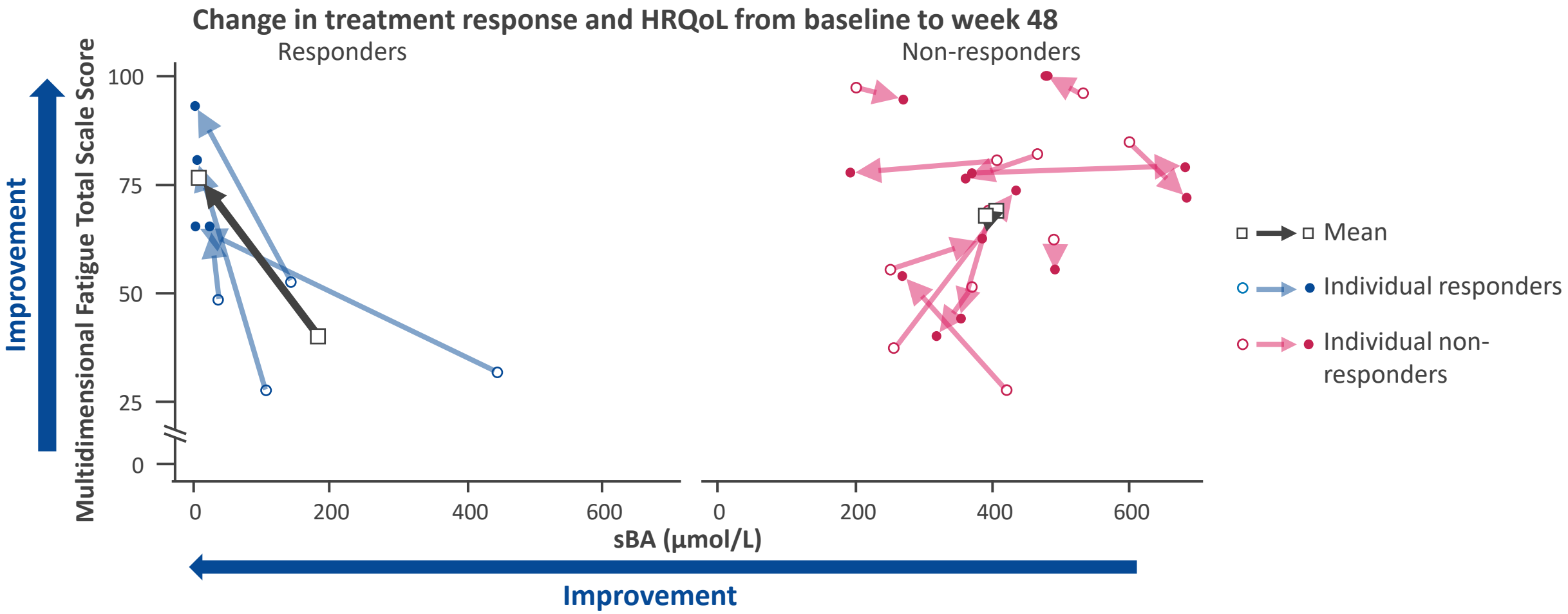
*Of the 21 patients included in the sample, 18 (85.7%), 16 (76.2%) and 20 (95.2%) had available data on PedsQL Generic Core Total Scale, Multidimensional Fatigue Total Scale, and Family Impact Total Scale, respectively, at week 48; †Proportions provided for 5- and 10-point changes were calculated among the number of patients with non-missing week 48 HRQoL data, for responders and non-responders, respectively; ‡One patient had missing data for this metric; §Two patients had missing data for this metric; ‖Two patients had missing data for this metric; ¶Three patients had missing data for this metric; **One patient had missing data for this metric; ††p value shows the observed difference between the responders' and non-responders' HRQoL scores from baseline to week 48; ‡‡MCID for the HRQoL assessments ranges from 4 to 5 points, depending on the scale, as validated in previous analyses.
All data are mean ± SD unless otherwise stated.

sBA treatment response at week 48 for individual patients was strongly associated with clinically meaningful improvements in PedsQL Generic Core Total Scale Score



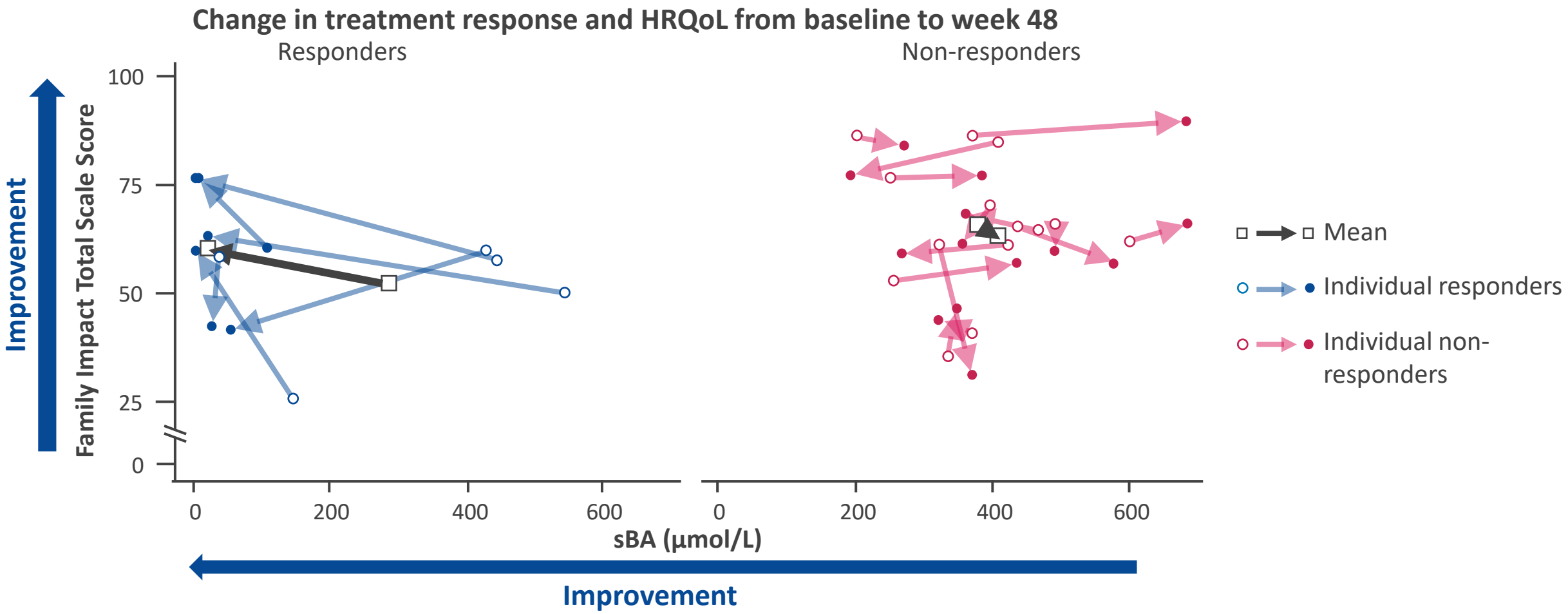
PedsQL Generic Core Total Scale Score	Responders	Non-responders	p value
Mean (SD) change in score from baseline to week 48	20.3 ± 17.7	–0.8 ± 10.9	**0.01**

sBA treatment response at week 48 for individual patients was strongly associated with clinically meaningful improvements in Multidimensional Fatigue Total Scale Score



Multidimensional Fatigue Total Scale Score	Responders	Non-responders	p value
Mean (SD) change in score from baseline to week 48	35.8 ± 15.1	0.7 ± 16.7	**<0.01**

sBA treatment response at week 48 for individual patients was associated with clinically meaningful improvements in Family Impact Total Scale Score



Family Impact Total Scale Score	Responders	Non-responders	p value
Mean (SD) change in score from baseline to week 48	8.0 ± 20.7	–2.5 ± 9.8	0.13

Multivariate regression models confirm clinically meaningful improvements in maralixibat responders at week 48

	PedsQL Generic Core Scale (n = 18)*		Multidimensional Fatigue Scale (n = 16)*		Family Impact Scale (n = 20)*	
Effect	Beta†	p value	Beta	p value	Beta	p value
sBA treatment response at week 48 Yes vs. No	17.2 (5.3; 29.1)	0.01	22.3 (3.5; 41.1)	0.04	5.8 (−7.7; 19.4)	0.41

- Minimal clinically important difference (MCID): 4–5 points
  - PedsQL Generic Core Total Scale Scores: responders increased significantly by >3× MCID (p=0.01)
  - Multidimensional Fatigue Scale: responders increased significantly by >4× MCID (p=0.04)
  - Family Impact Total Scale Scores: clinically meaningful increases did not reach statistical significance

*Of the 21 patients included in the sample, 18 (85.7%), 16 (76.2%, and 20 (95.2%) had available data on PedsQL Generic Core Total Scale, Multidimensional Fatigue Total Scale, and Family Impact Total Scale, respectively, at week 48; †Multivariate model adjusted for baseline QoL score.

Maralixibat responders experienced improvement in sleep based on a subset analysis

- A subset of individual items from the HRQoL scales was also selected independently by clinical experts, for their relevance in paediatric cholestatic liver disease

- Five of the 10 items demonstrated significant changes over time in sBA responders compared with non-responders

Individual items **Mean Change from baseline to week 48 (SD)**	**Responders**	**Non-responders**	**p value**
Feeling tired during the day	37.50 ± 49.37	1.79 ± 20.72	**<0.05**
Worried about how my child's illness is affecting other family members	25.00 ± 27.39	–12.50 ± 21.37	**<0.01**
Difficulty sleeping through the night	68.75 ± 12.50	12.50 ± 27.18	**<0.01**
Feeling tired upon waking	62.50 ± 14.43	14.58 ± 27.09	**<0.01**
Taking a lot of naps	37.50 ± 25.00	–6.25 ± 21.65	**<0.01**

Summary and conclusions

- Patients with PFIC suffer from poor HRQoL compared with healthy children,[1] sometimes requiring liver transplantation or surgical intervention
- Patients with BSEP deficiency (PFIC2) who responded to maralixibat treatment had:
  - Clinically meaningful improvements in HRQoL
  - Statistically significant improvements in sleep and fatigue measures
- Response to maralixibat has the potential to significantly improve HRQoL in patients with PFIC
- Maralixibat is currently being studied across all PFIC subtypes in a Phase 3 study (MARCH-PFIC)

1. Kamath B, *et al*. *J Pediatr* 2015;167:390–396.

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