Phase 2 placebo-controlled withdrawal study of the ASBT inhibitor maralixibat in children with Alagille syndrome

48-week efficacy analysis

ICONIC Study

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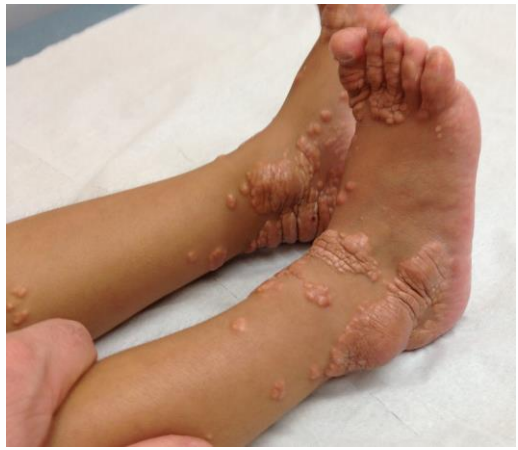
Alagille syndrome is a rare cause of pediatric cholestasis

Alagille syndrome (ALGS) is a genetic multisystemic developmental disease

- Also known as syndromic intrahepatic bile duct paucity or arteriohepatic dysplasia
- Autosomal dominant, with mutations in JAG1 (> 90% of cases) or NOTCH2
- Characterized by abnormalities of the liver, heart, eyes, vertebrae, kidney and facies

Bile duct paucity leads to chronic cholestasis, severe pruritus and xanthoma

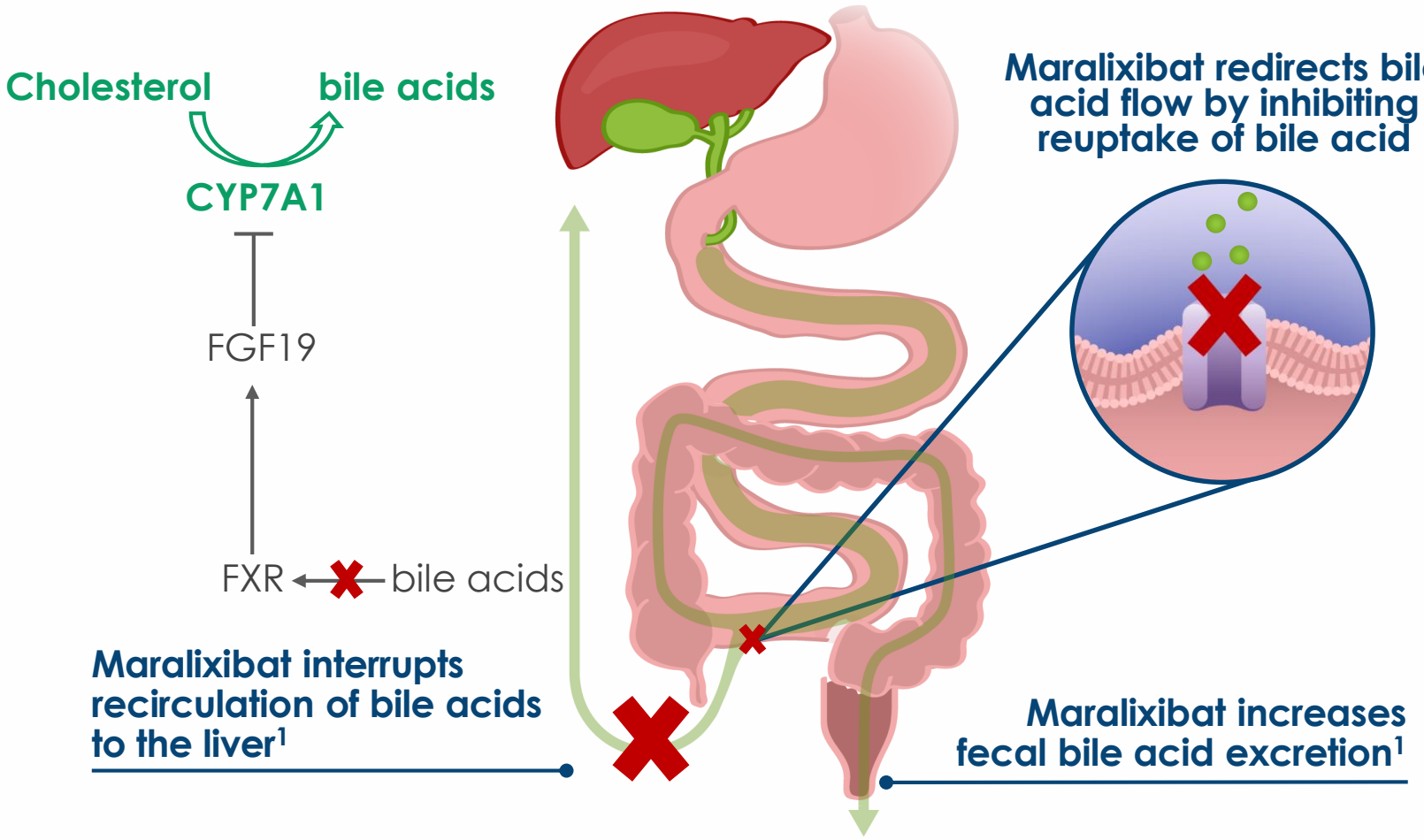
- Liver transplantation may be indicated to improve quality of life in patients with severe pruritus



Pharmacological inhibition of enterohepatic bile acid circulation may:

- decrease serum bile acid (sBA) and cholesterol levels
- relieve pruritus and xanthoma

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



Clinical effects of ASBT inhibition

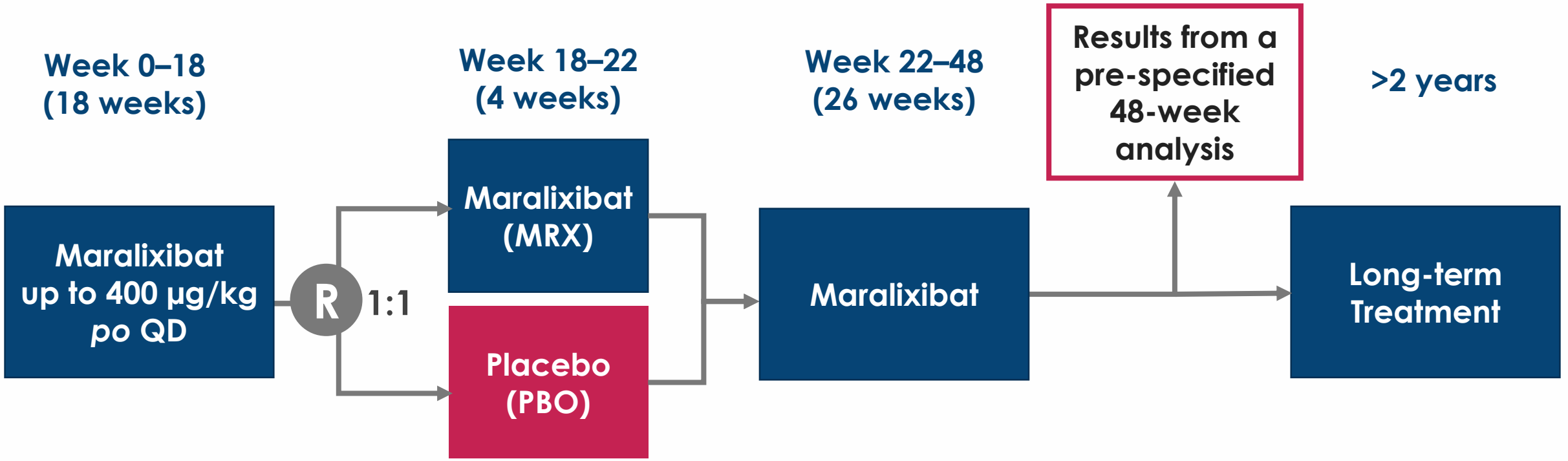
- ASBT inhibitors, including maralixibat, decrease pruritus, sBA and cholesterol, and increase C4 in PBC[2–4]
- Maralixibat shows a trend towards decreases in pruritus in ALGS[5]

C4, 7-a-hydroxy-4-cholesten-3-one; CYP7A1, cholesterol 7α-hydroxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; PBC, primary biliary cholangitis

1. Keller B, Falk Symposium 2014; 2. Al-Dury S, Sci Rep 2018; 3. Hegade VS, Lancet 2017; 4. Mayo MJ, Hepatol Commun 2019; 5. Shneider BL, Hepatol Communi 2018

ICONIC: Phase 2 placebo-controlled double-blind drug-withdrawal study of maralixibat in children with ALGS

ICONIC:
- Higher dose of maralixibat than previous ALGS trials[1,2]
- Randomized placebo-controlled withdrawal design



1. Baker A, J Hepatol 2015; 2. Shneider BL, Hepatol Communi 2018

ICONIC - Methodology

Key inclusion criteria

- **Children 1–18 years with ALGS** (clinical and/or genetic criteria)
- **Chronic cholestasis** (clinical/biochemical criteria)
- **Significant pruritus** (>2 on Itch Reported Outcome [Observer] - ItchRO[Obs]; 0–4)
- **No biliary diversion, liver transplant or decompensated cirrhosis**

Primary endpoint

- **sBA change from week 18 to 22 in those with ≥50% sBA reduction from baseline at week 12 or 18**

Additional endpoints

- **Pruritus** (caregiver-rated ItchRO[Obs]; 0–4)
- **Clinician Scratch Scale** (CSS) score (investigator rated; 0–4)
- **Cholestasis and bile acid metabolism biomarkers** (sBA, serum cholesterol, C4)
- **Clinician xanthoma scale** (CXS) score (investigator rated; 0–4)
- **Pediatric Quality of Life Inventory** (PedsQL) total score (caregiver rated; 0–100)
- **Safety** (adverse events, total bilirubin levels, alanine aminotransferase [ALT] levels)

Disposition, demographics and disease characteristics

Disposition and demographics	
Enrolled, n	31
Mean age, years (range)	5.4 (1–15)
Male, %	61.3
Genotype, n (%): *JAG1*	31 (100)
Randomized week 18, n[a]	29
Maralixibat	13
Placebo	16
Completed week 48, n[a]	28

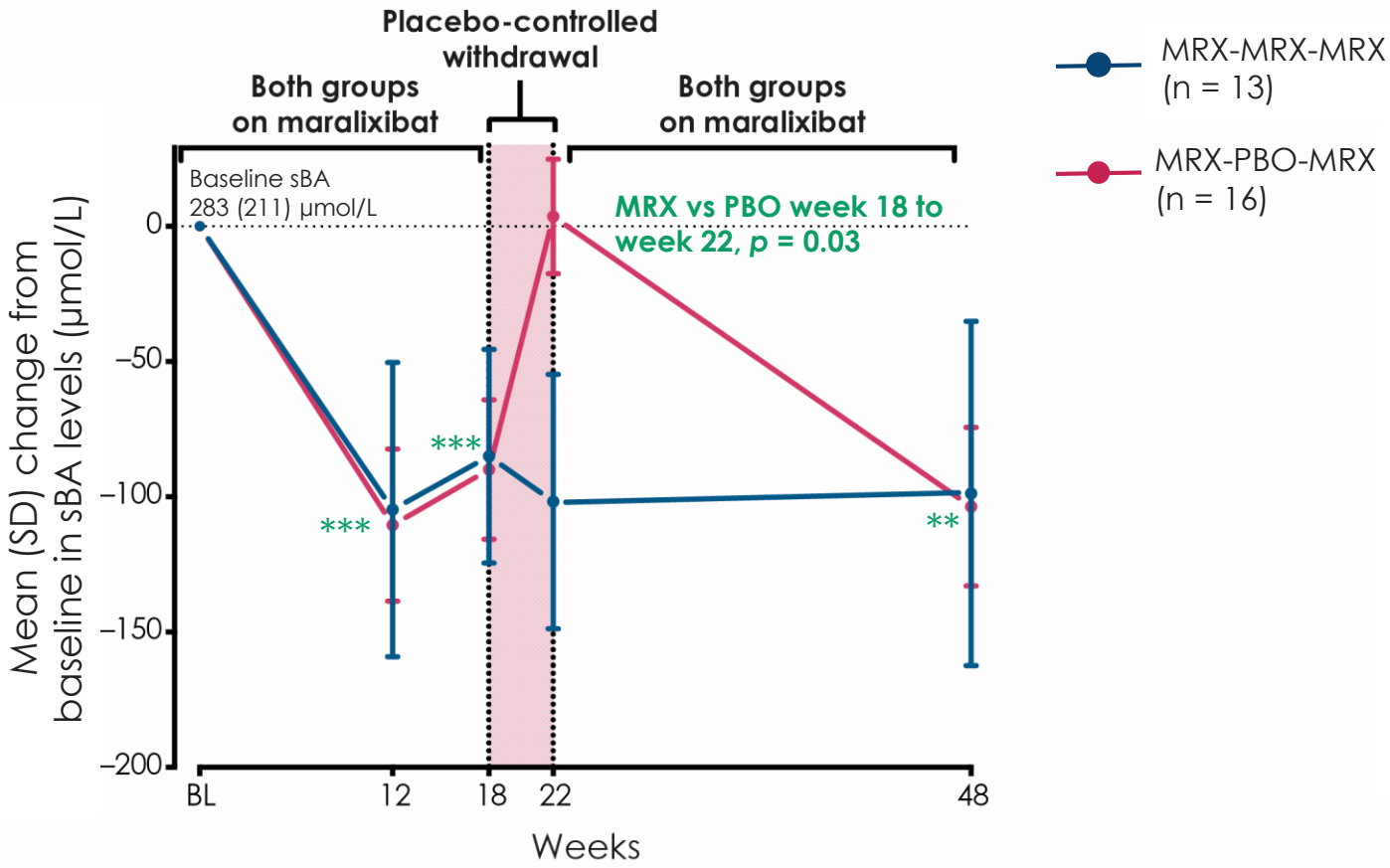
Baseline characteristics, mean (SD)	
ItchRO(Obs) score, 0–4	2.9 (0.5)
CSS score, 0–4	3.3 (0.9)
sBA, µmol/L	283 (211)
C4, ng/mL	10.3 (14.7)
Total bilirubin, mg/dL	6.1 (5.8)
ALT, U/L	181 (109)
Clinician xanthoma scale score, 0–4	0.9 (1.26)
PedsQL score, 0–100	61.2 (17.3)

Similar baseline characteristics in MRX-MRX-MRX and MRX-PBO-MRX group

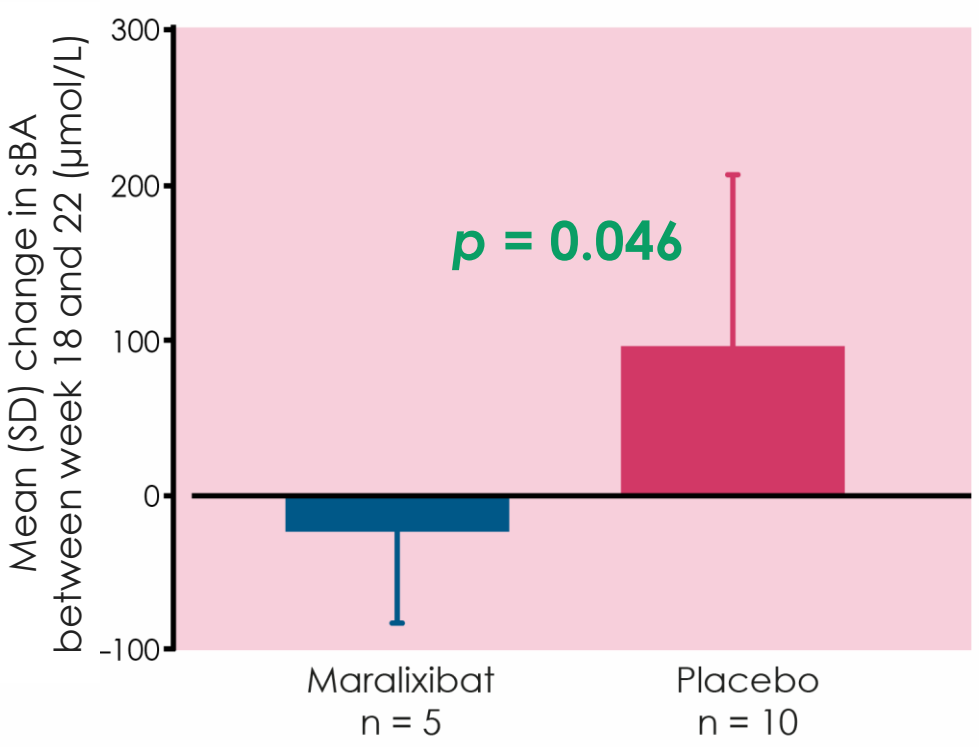
[a] Early discontinuations of three patients due to adverse events, two before and one after the drug withdrawal period. All unrelated to maralixibat.

Significant improvements in sBA levels versus placebo and baseline

sBA in all patients

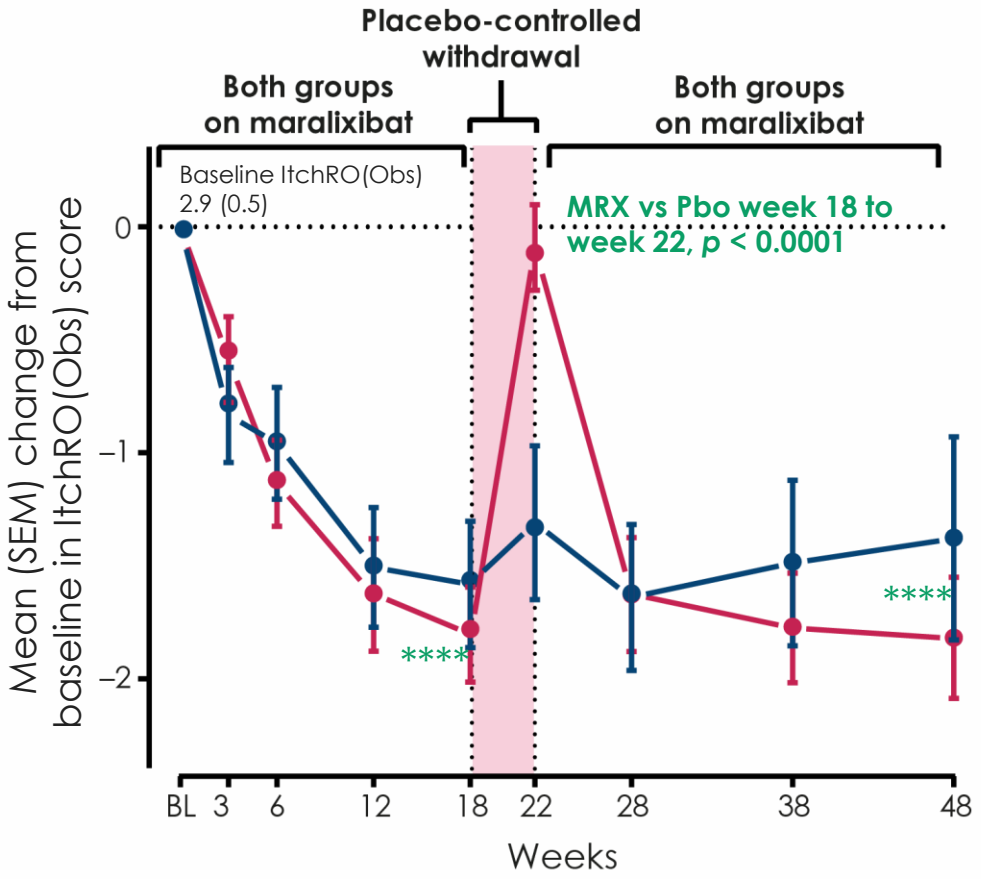


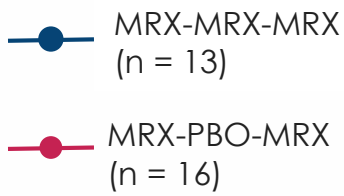
sBA during randomized withdrawal in subjects with ≥50% sBA reduction

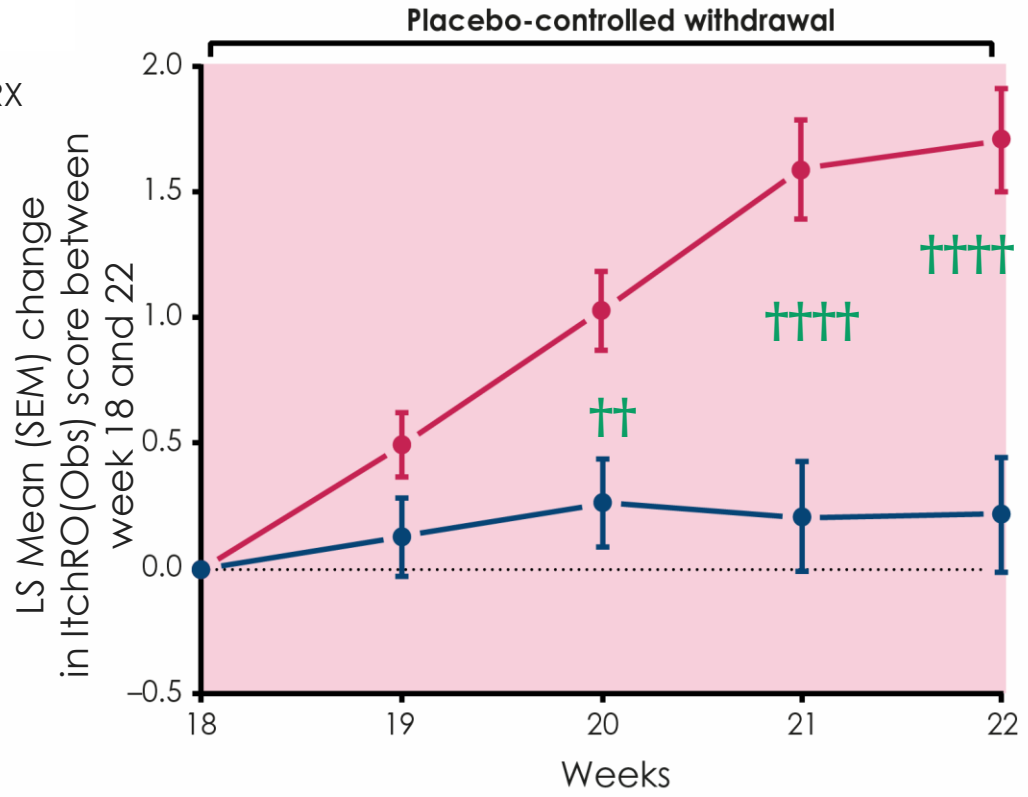


**p < 0.01, ***p < 0.001, change from baseline (overall population)

Improvements in ItchRO(Obs) scores maintained during randomized withdrawal with maralixibat







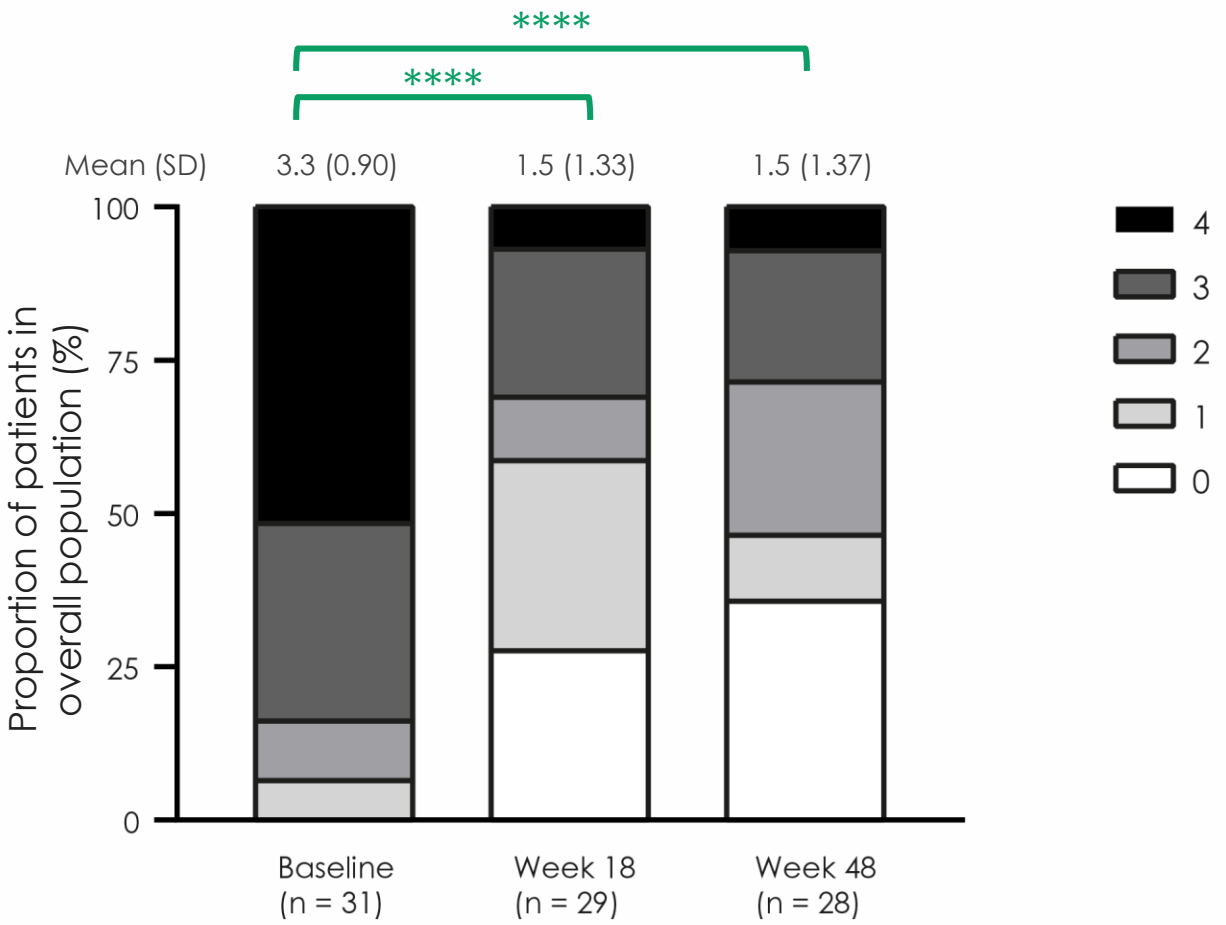
****$p < 0.0001$, change from baseline (overall population)

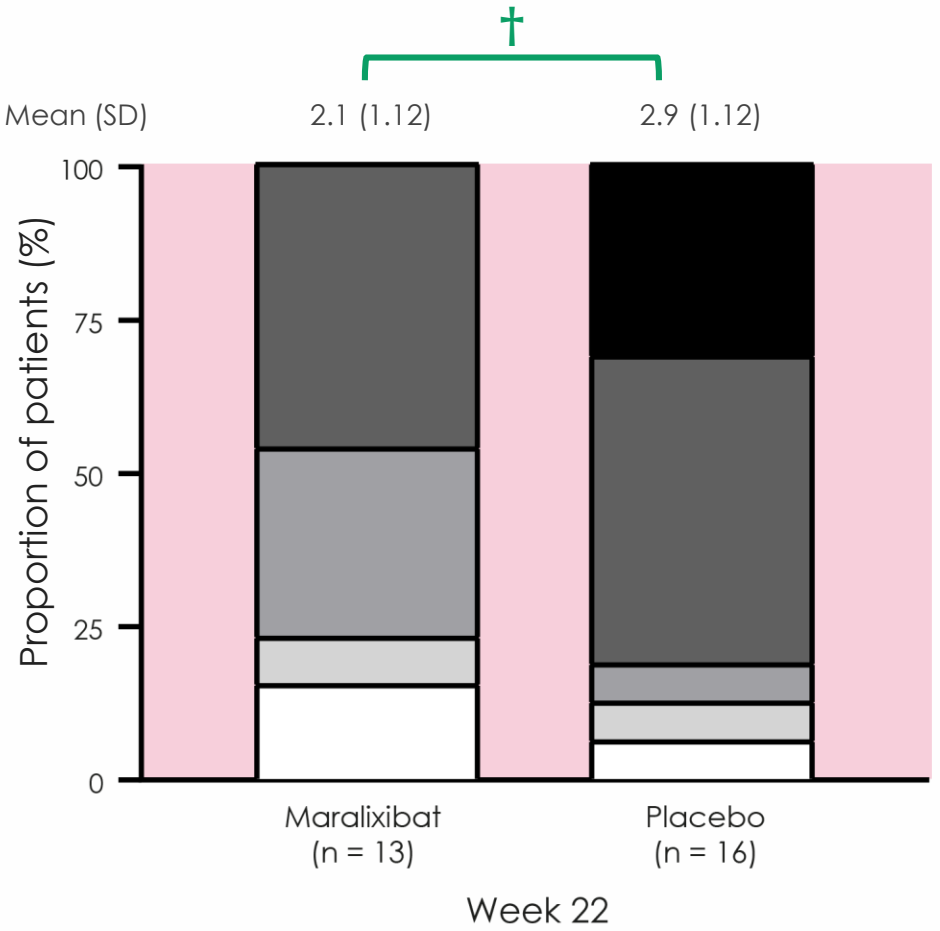
††$p < 0.01$, ††††$p < 0.0001$ maralixibat versus placebo

LS, least-squares

Improvements from baseline in Clinician Scratch Scale scores throughout the study

Clinician Scratch Scale scores





**** $p < 0.0001$, change from baseline (overall population)

† $p < 0.05$ maralixibat versus placebo (change from week 18)

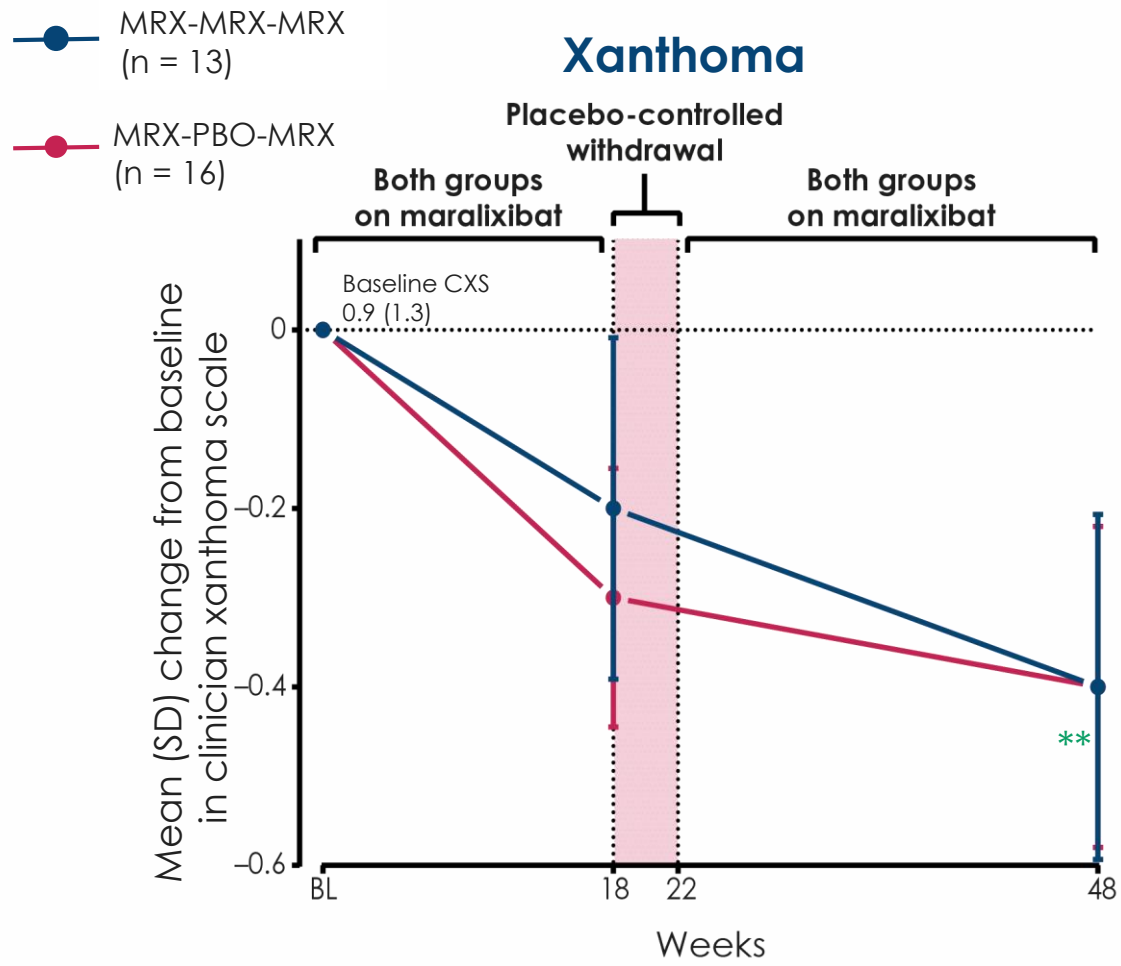
Improvements from baseline in cholesterol levels and clinician xanthoma scores

Serum cholesterol and C4

Mean (SD)	Baseline	Week 18	Week 48
Serum cholesterol, mg/dL	512.1 (419.8)	417.1 (310.9)	413.7 (344.8)
p-value[a]		<0.01	<0.01
C4, ng/mL	10.3 (14.7)	24.3 (27.7)	16.9 (25.2)
p-value[a]		<0.01	0.07

[a] Change from baseline (overall population)

Xanthoma



**p < 0.01, change from baseline (overall population)

Improvements over time in caregiver HRQoL scores

Health-related Quality of Life scale

- Caregiver-rated PedsQL score (0–100)

Open-label period (week 0–18 and week 22–48)

- **Significant mean (SD) improvement at week 18: 11 (17) points, *p* = 0.001**
- **Significant mean (SD) improvement at week 48: 10 (19) points, *p* = 0.016**
- **Significant correlation between PedsQL and ItchRO(Obs) change from baseline at week 48: -0.43 (95% CI -0.71–0.15; *p* = 0.046)**

Randomized drug withdrawal period (week 18–22)

- No difference between placebo and maralixibat

Maralixibat was generally well tolerated

AE, regardless of relatedness n (%)	Maralixibat week 0–18 (n = 31)	Withdrawal, week 18–22		Maralixibat week 22–48 (n = 29)
		Maralixibat (n = 13)	Placebo (n = 16)	
Any AE	30 (96.8%)	7 (53.8%)	12 (75.0%)	25 (86.2%)
Mild or moderate	24 (77.4%)	7 (53.8%)	11 (68.8%)	23 (79.3%)
Grade 3-4 AEs	6 (19.4%)	0	1 (6.3%)	2 (6.9%)
Leading to discontinuation (**all unrelated** to maralixibat)	2 (6.5%)	0	0	2 (6.9%)
Potentially **related** AEs	12 (38.7%)	1 (7.7%)	3 (18.8%)	1 (3.4%)
Any serious AE (**all unrelated** to maralixibat)	4 (12.9%)	1 (7.7%)	1 (6.3%)	5 (17.2%)
Gastrointestinal AEs	22 (71.0%)	2 (15.4%)	3 (18.8%)	15 (51.7%)
Diarrhoea	13 (41.9%)	1 (7.7%)	1 (6.3%)	5 (17.2%)

Summary and conclusions

- ICONIC investigated the highest dose of maralixibat in patients with ALGS to date
- Maralixibat significantly reduced pruritus and sBA levels over time and vs placebo in children with ALGS
- Maralixibat also improved xanthomas and quality of life
- Treatment effects were maintained over a 48-week period; 15 participants treated ≥3 years
- Maralixibat was generally well tolerated, with AEs of mainly mild or moderate severity
- Therapeutic benefits of maralixibat in children with ALGS and moderate to severe pruritus were clinically relevant and statistically significant
- A confirmatory phase 3 study is planned

Acknowledgments

- Hôpital Bicêtre, Paris, France
- University Hospital for Children and Adolescents, Tübingen, Germany
- Children's Hospital at Westmead, Westmead, Sydney, Australia
- Cliniques Universitaires St Luc, Brussels, Belgium
- Royal Children's Hospital Melbourne, Parkville, Australia
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- Children's Memorial Health Institute, Warsaw, Poland
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