# Durability of Treatment Effect with Long-Term Maralixibat in Children with Alagille Syndrome: 4-Year Safety and Efficacy

## ICONIC Study


## Emmanuel Gonzales

On behalf of Ekkehard Sturm, Michael Stormon, Etienne M. Sokal, Winita Hardikar, Florence Lacaille, Dorota Gliwicz-Miedzińska, Loreto Hierro, Thomas Jaecklin, Pamela Vig, Nirav K. Desai, Alejandro Dorenbaum, Ciara Kennedy, Alastair Baker, Emmanuel Jacquemin

# Conflicts of interests

- Consultancy : Albireo, CTRS, Mirum Pharmaceuticals

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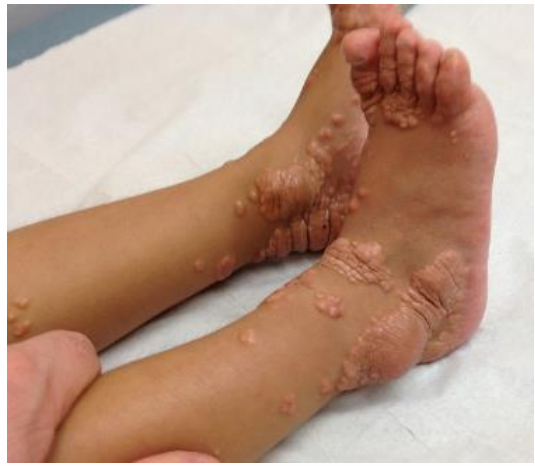
# Alagille syndrome is a rare cause of pediatric cholestasis

## Alagille syndrome (ALGS) is a genetic, multisystem, developmental disease

- Autosomal dominant, with mutations in *JAG1* (> 90% of cases) or *NOTCH2*
- Characterized by abnormalities of the liver, heart, eyes, vertebrae, kidney and facies
- Associated with growth deficit

## Bile duct paucity leads to chronic cholestasis, severe pruritus and xanthomas

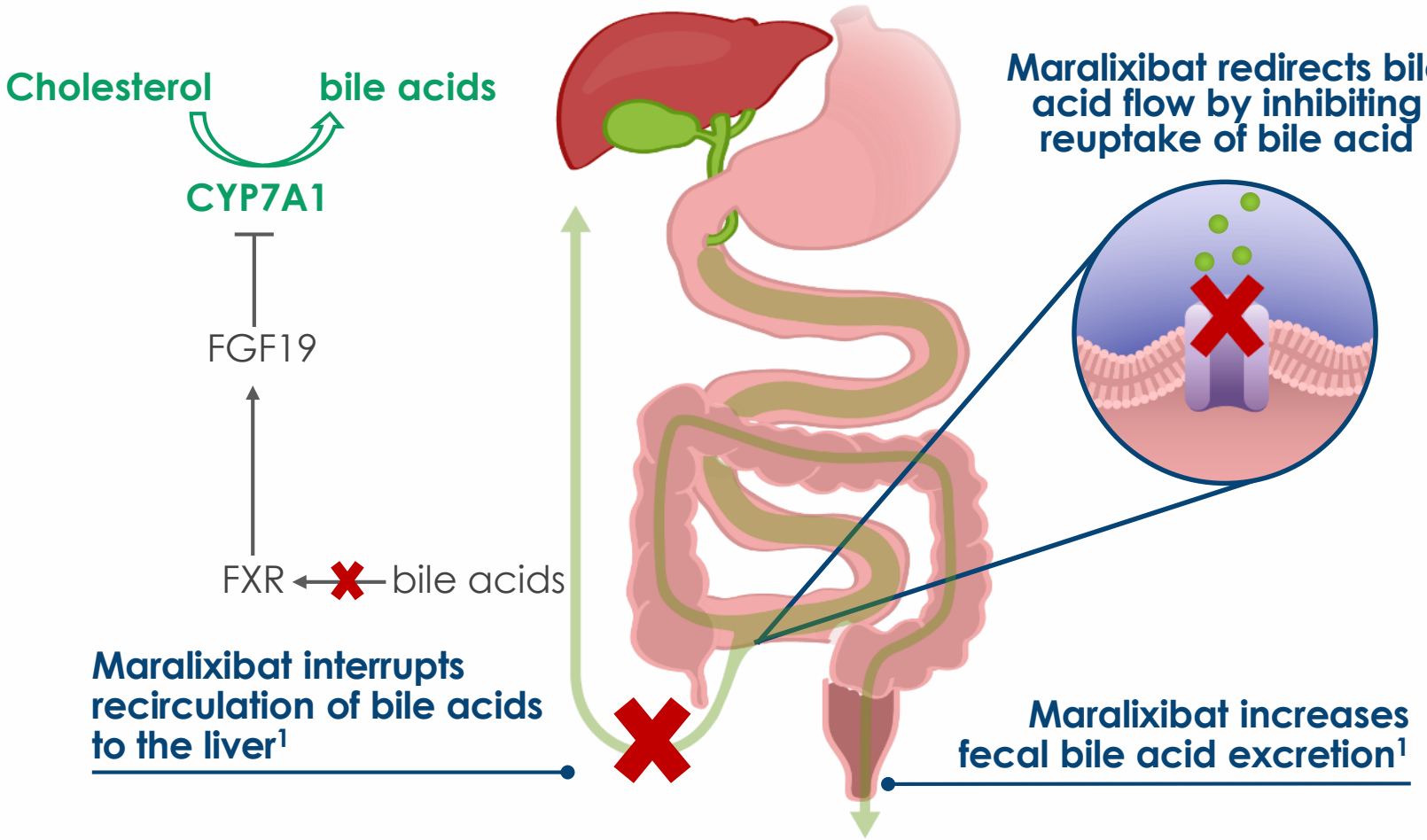
- Currently no approved pharmacological treatment options
- Liver transplantation (and at times partial external biliary diversion) are used to treat pruritus



## Pharmacological inhibition of enterohepatic bile acid circulation may:

- Decrease serum bile acid (sBA) levels and pruritus
- Reduce cholesterol levels and xanthomas

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




## Clinical effects of ASBT inhibition

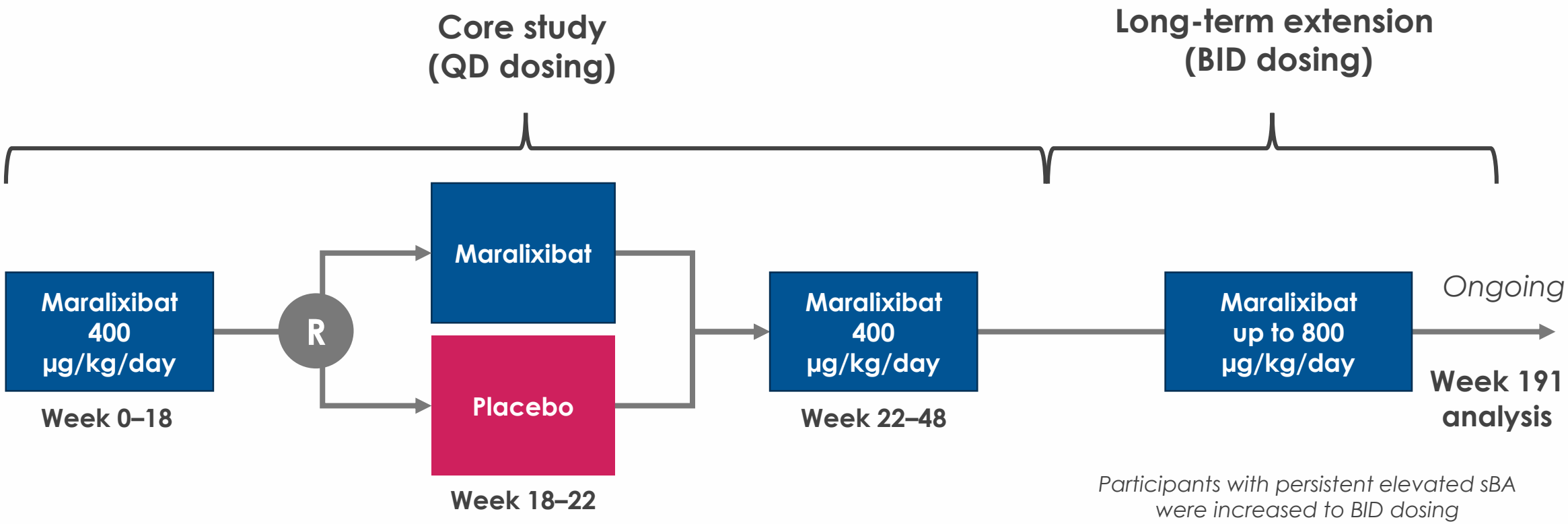
- ASBT inhibitors, including maralixibat, decrease pruritus, sBA and cholesterol, and increase C4 in PBC[2–4]
- Maralixibat shows a trend towards decreases in pruritus in ALGS[5]

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 *et al*. Poster 55 presented at the Falk Symposium 194, Oct 8–9, 2014, Freiburg, Germany; 2. Al-Dury S *et al. Sci Rep* 2018;8:6658; 3. Hegade VS *et al. Lancet* 2017;389:1114–23; 4. Mayo MJ *et al. Hepatol Commun* 2019;3:365–81; 5. Shneider BL *et al. Hepatol Commun* 2018;2:1184–98.

# Long-term extension to the core ICONIC study

**Objective:** to explore the long-term efficacy and safety of maralixibat (400 µg/kg QD and BID) in children with ALGS




BID, twice daily; QD, once daily; R, randomization.

# ICONIC study design

## Key eligibility criteria

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

## Efficacy and safety assessments

- The following were assessed during the core study and at 12 weekly intervals during long-term extension:
  - 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 score (investigator rated; 0–4)
  - Pediatric Quality of Life Inventory (PedsQL) fatigue scale score (caregiver rated; 0–100)
  - Height and weight z-score
  - Safety (treatment-emergent adverse events)

# Disposition from the core to extension period

| Disposition | N |
|---|---|
| Enrolled | 31 |
| Discontinued due to TEAE in core study [a] | 3 |
| Included in week 48 analysis | 29 |
| Consented to long-term extension | 23 |
| Withdrew consent | 4 |
| Liver transplant | 2 |
| Renal failure unrelated to maralixibat | 1 |
| Liver enzyme elevations | 1 |
| **Included in week 191 efficacy analysis (3.7 years)** | **15** |

[a] Infection; intracranial bleeding; increased bilirubin levels; all unrelated to maralixibat

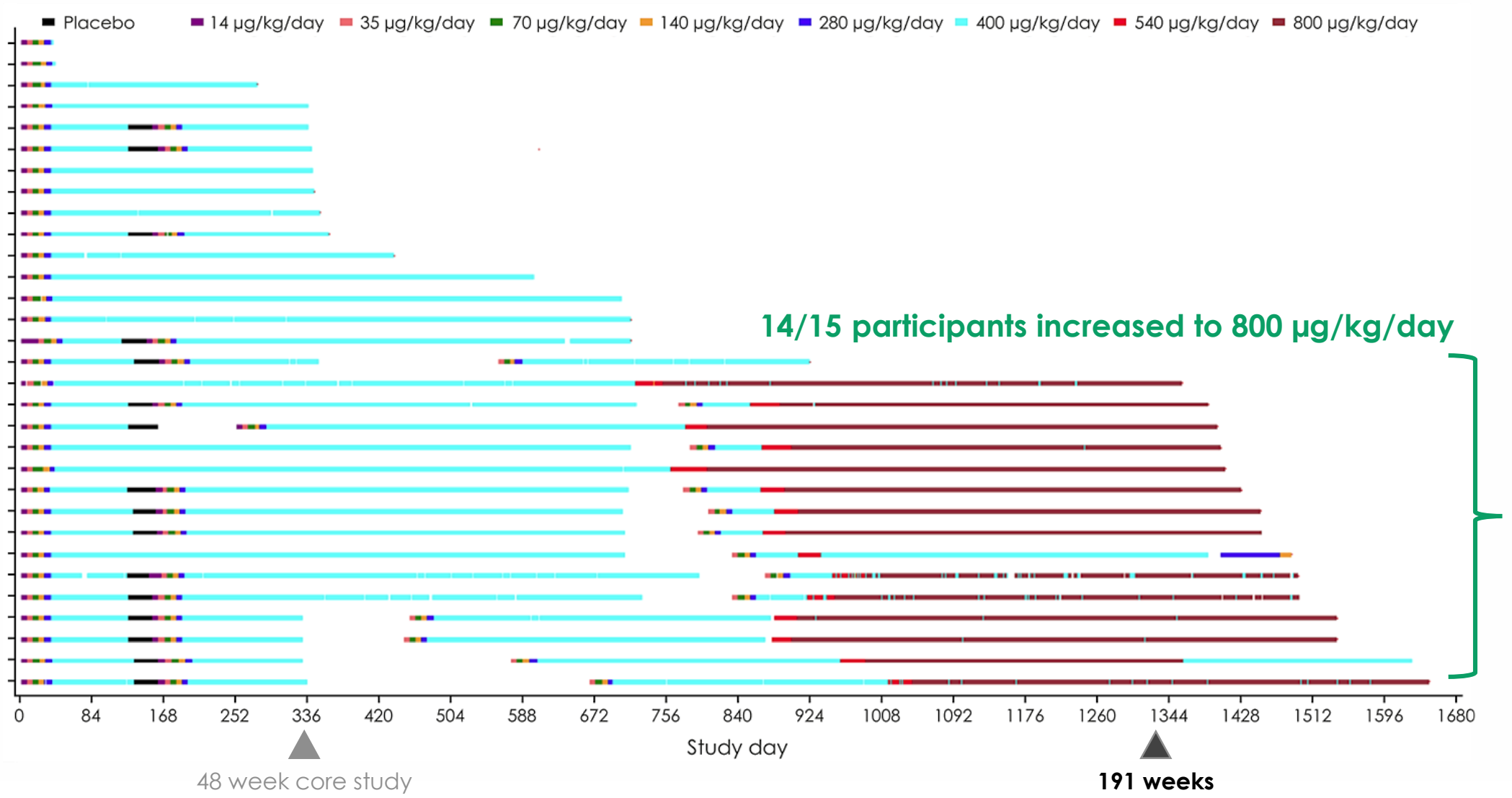
TEAE, treatment-emergent adverse event.

# Baseline characteristics

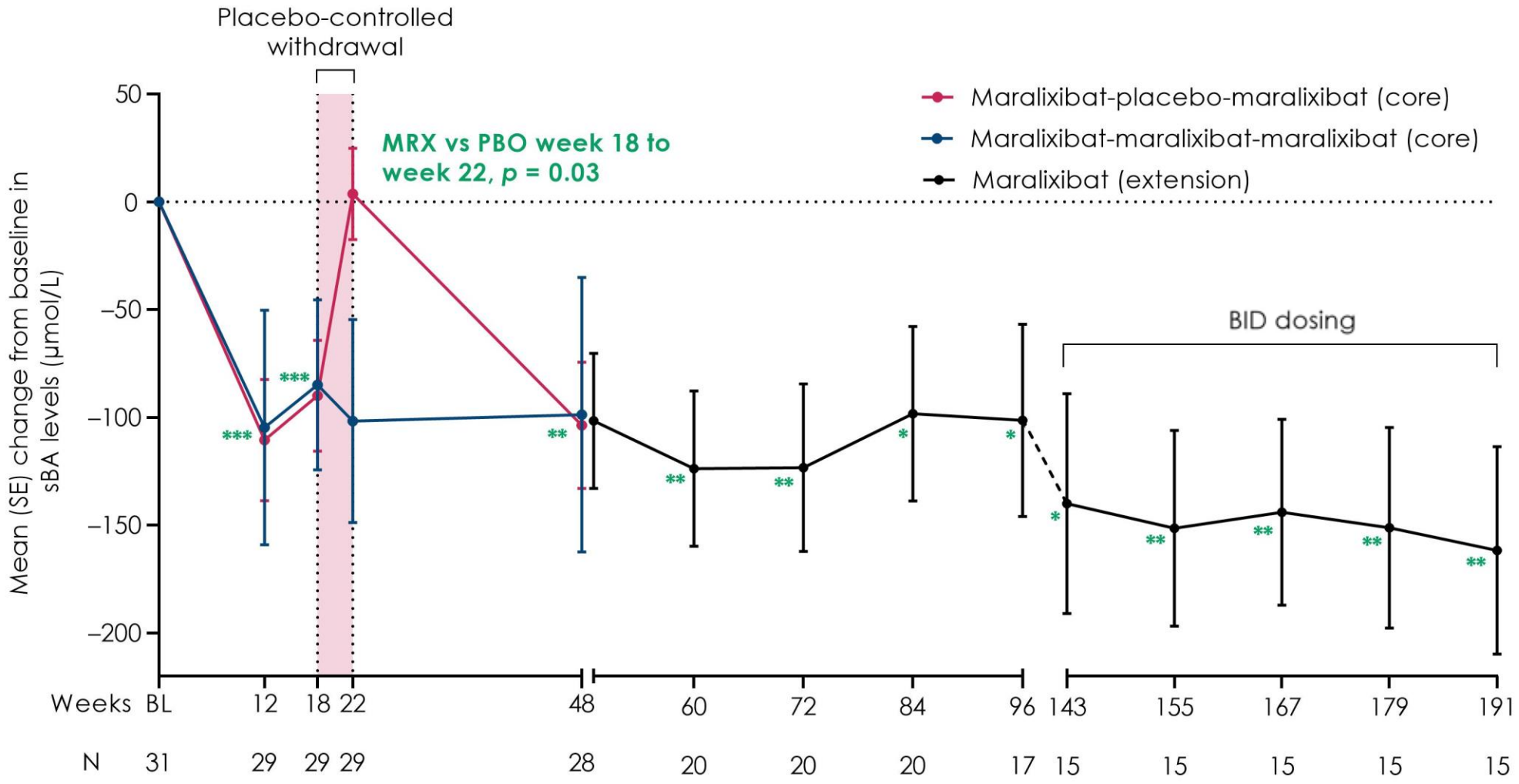
| Baseline characteristics | Enrolled participants (N = 31) | Extension participants (N = 15) |
|---|---|---|
| Median age (range), years | 5.0 (1–15) | 5.0 (1-12) |
| Male, n (%) | 19 (61.3) | 10 (66.7) |
| *JAG1* mutation , n (%) | 31 (100.0) | 15 (100.0) |
| Serum bile acid level, µmol/L | 283.4 (37.8) | 259.0 (55.3) |
| Total Bilirubin mg/dL | 6.1 (1.0) | 3.2 (0.9) |
| ItchRO(Obs) score (0-4) | 2.9 (0.1) | 2.8 (0.1) |
| CSS score (0-4) | 3.3 (0.2) | 3.2 (0.3) |
| Height z-score | –1.7 (0.2) | -1.8 (0.3) |

Data presented as mean (SE) unless otherwise specified.

# Study drug exposure for each participant

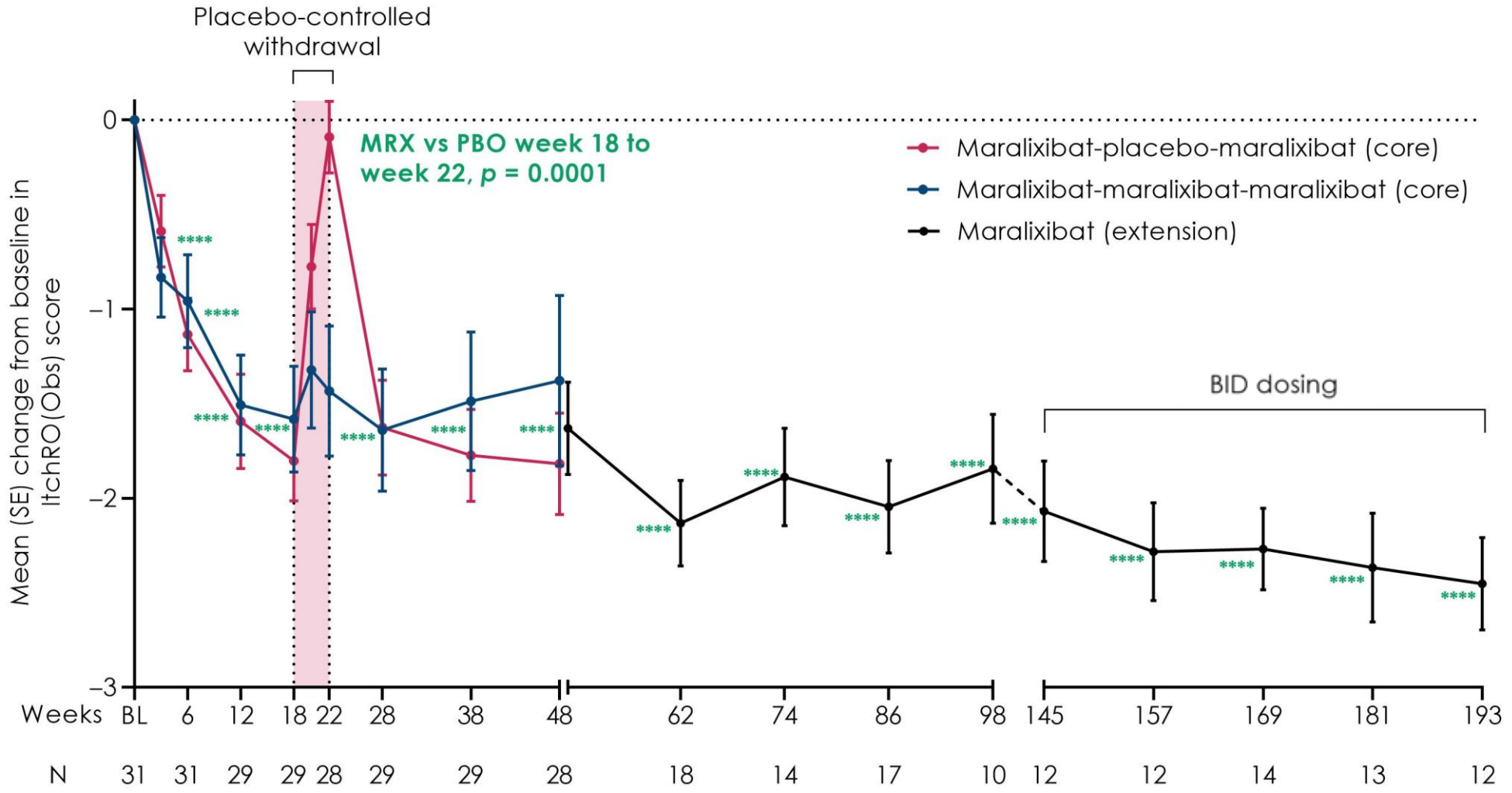


# Reduction in mean serum bile acid levels was maintained long-term




Change from baseline, * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ (overall population)

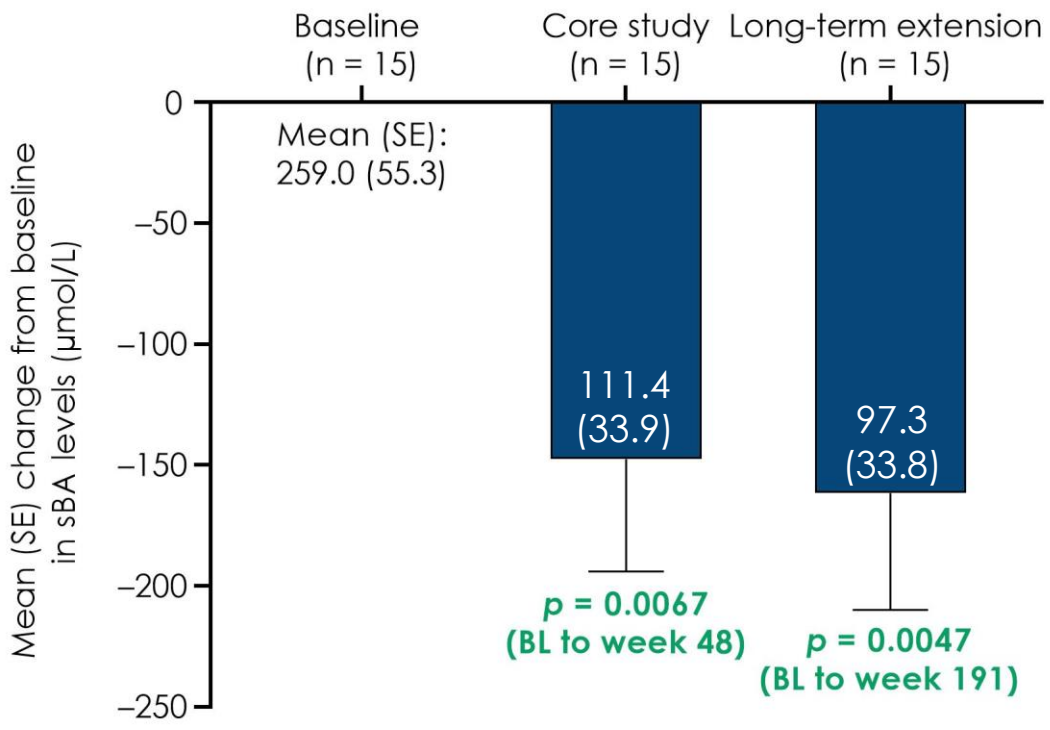
# Mean pruritus scores reduced in the core study and were maintained in the extension



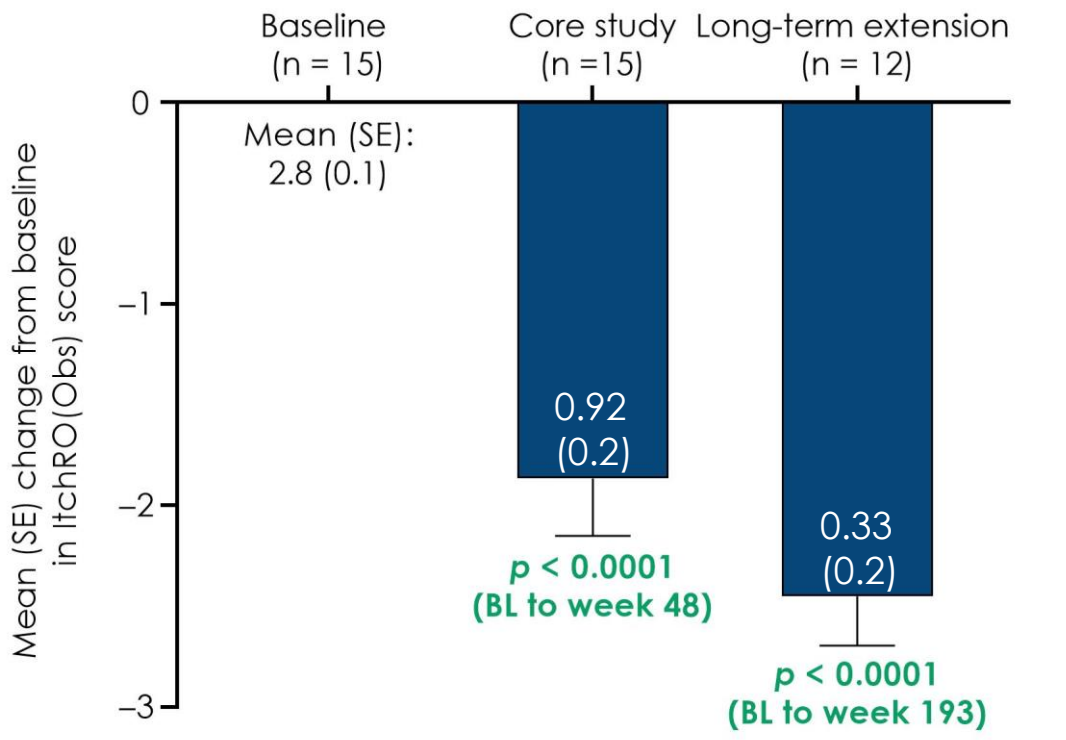

Change from baseline, **** $p \leq 0.0001$ (overall population)

# Serum bile acid levels and pruritus improved in the subgroup of patients treated long-term with maralixibat

## Change from BL in sBA levels

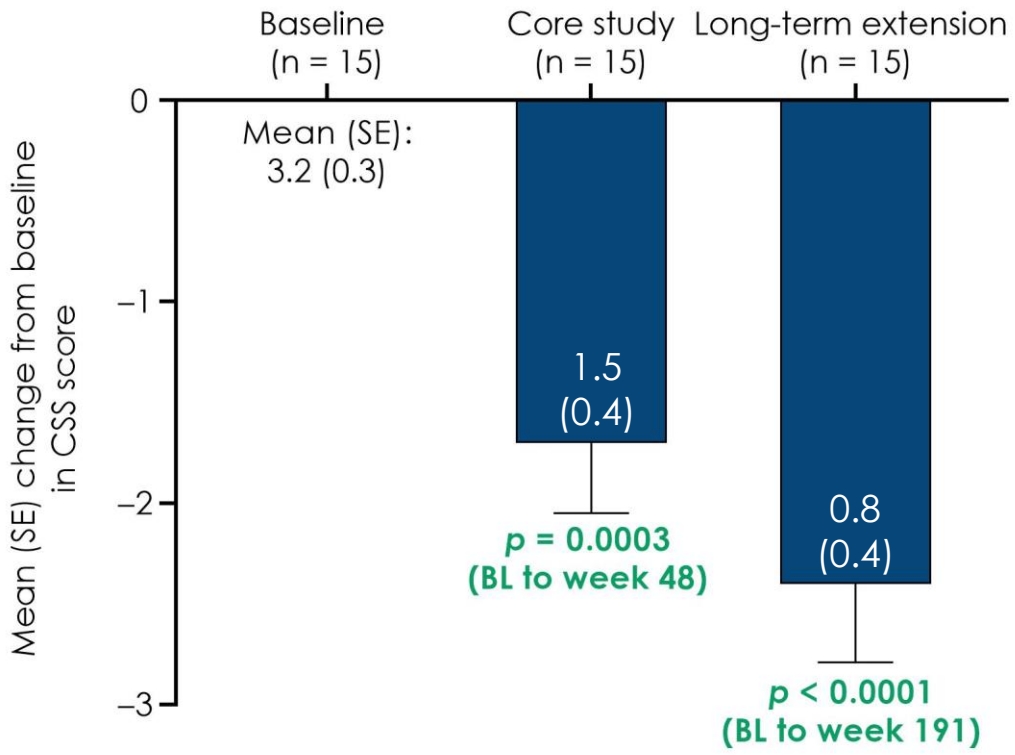



## Change from BL in ItchRO(Obs) score (0–4)

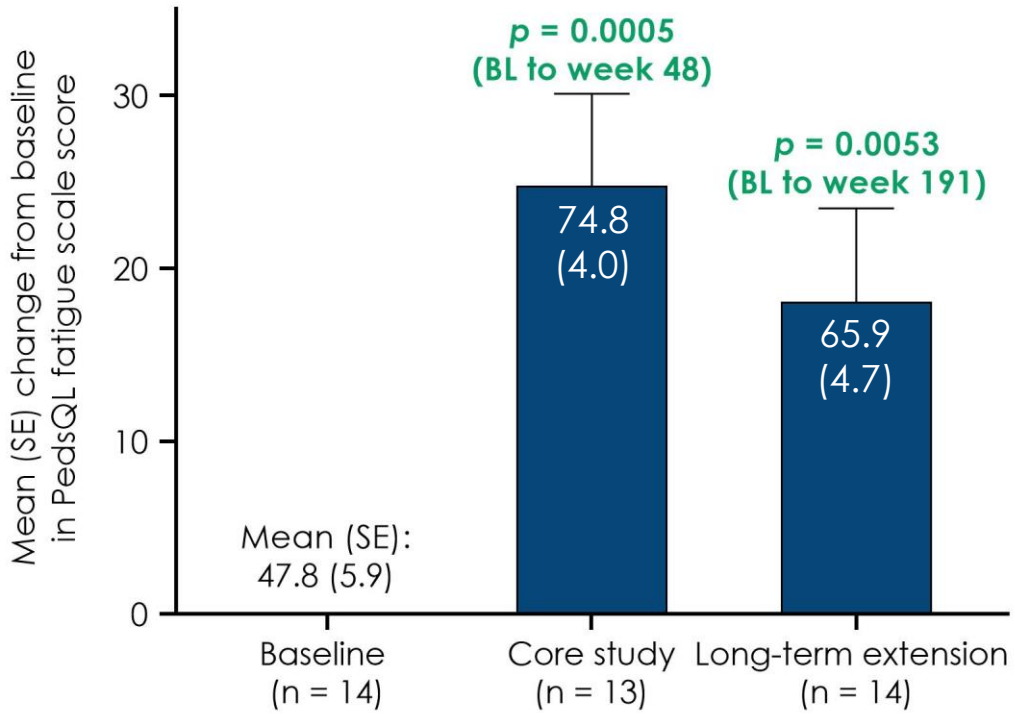


# CSS and fatigue improved in the subgroup of patients treated long-term with maralixibat

## Change from BL in CSS score (0–4)




## Change from BL in PedsQL fatigue scale score (0–100)



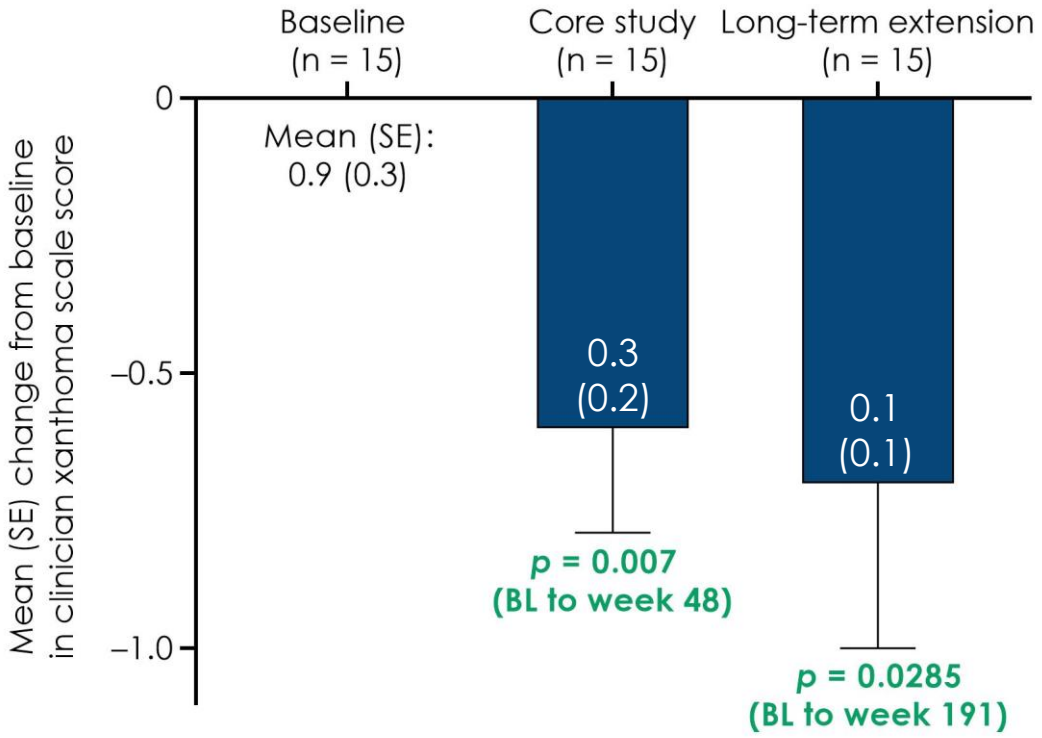
# Improvements from baseline in cholesterol levels and clinician xanthoma scores

## Serum cholesterol and C4 levels

| Mean (SD) | Baseline n = 15 | Week 48 n = 15 | Week 191 n = 15 |
|---|---|---|---|
| Serum cholesterol, mg/dL | 414.3 (182.1) | 340.3 (149.9) | 277.5 (65.7) |
| *p* value[a] | | < 0.01 | < 0.01 |
| C4, ng/mL | 7.4 (8.7) | 20.4 (32.2) | 30.4 (44.6) |
| *p* value[a] | | 0.1 | 0.04 |

[a] Change from baseline

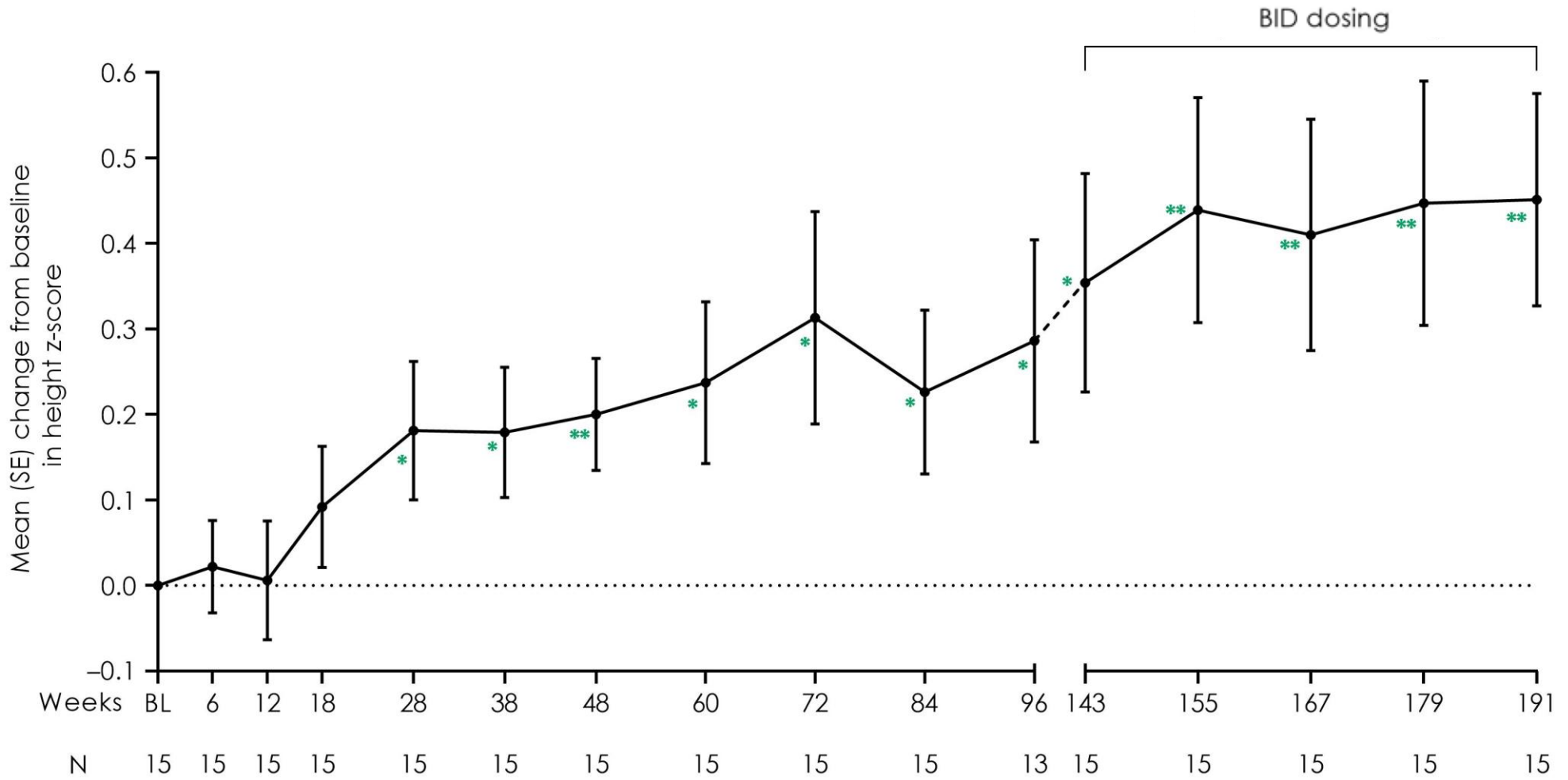
## Change from BL in clinician xanthoma scale score (0–4)



# Increased height z-scores with long-term maralixibat treatment

**Baseline z-score: –1.82 (SE, 0.3)**

**Week 191 z-score: –1.37 (SE, 0.3)**




Change from baseline, * $p \leq 0.05$, ** $p \leq 0.01$

# Long-term maralixibat treatment was well-tolerated

## 14 participants remain on maralixibat with median treatment duration of 1469.5 days (210 weeks; 4 years)

| Number of participants, n (%) | Core Study (week 0–18) (N = 31) | Core Study (week 19–22) Maralixibat (n = 13) | Core Study (week 19–22) Placebo (n = 16) | Core Study (week 23–48) (N = 29) | Extension Phase (week 49-present) (N = 29) |
|---|---|---|---|---|---|
| **Any TEAE** | 30 (96.8) | 7 (53.8) | 12 (75.0) | 25 (86.2) | 23 (79.3) |
| **Grade 3 or 4 TEAE** | 6 (19.4) | 0 | 1 (6.3) | 2 (6.9) | 6 (20.7) |
| **Serious TEAE (all unrelated to maralixibat)** | 4 (12.9) | 1 (7.7) | 1 (6.3) | 5 (17.2) | 5 (17.2) |
| **TEAE leading to death** | 0 | 0 | 0 | 0 | 0 |
| **TEAE leading to study drug discontinuation** | 2 (6.5)[a] | 0 | 0 | 1 (3.4)[a] | 3 (10.3)[b,c] |
| **TEAE potentially related to study drug** | 12 (38.7) | 1 (7.7) | 3 (18.8) | 1 (3.4) | 7 (24.1) |
| **Gastrointestinal disorders** | 22 (71.0) | 2 (15.4) | 3 (18.8) | 14 (48.3) | 16 (55.2) |
| **Diarrhea** | 13 (41.9) | 1 (7.7) | 1 (6.3) | 5 (17.2) | 8 (27.6) |

[a] Infection; intracranial bleeding; increased bilirubin levels; all unrelated to maralixibat
[b] Elevated ALT and/or AST levels (n = 2); hypertension/renal failure unrelated to maralixibat (n = 1)
[c] Third discontinuation occurred after the data cut-off, bringing n to 14

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

# Four years of maralixibat treatment in the ICONIC study: summary and conclusions

- **Long-term maralixibat treatment in ALGS patients was associated with significant and durable improvement in:**
  - Pruritus and serum bile acids
  - Quality of life, cholesterol and xanthoma
  - Height growth
- **Maralixibat was generally well tolerated up to 800 µg/kg per day for up to 4 years (total 73.1 patient years exposure)**
- **Treatment emergent adverse events did not increase in frequency or severity with long-term treatment**

# Acknowledgements


- Hôpital Universitaire Bicêtre, Paris, France
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- Children's Hospital at Westmead, Sydney, Australia
- Cliniques Universitaires Saint-Luc, Brussels, Belgium
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