Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study

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Summary

Background Alagille syndrome is a rare genetic disease that often presents with severe cholestasis and pruritus. There are no approved drugs for management. Maralixibat, an apical, sodium-dependent, bile acid transport inhibitor, prevents enterohepatic bile acid recirculation. We evaluated the safety and efficacy of maralixibat for children with cholestasis in Alagille syndrome.

Methods ICONIC was a placebo-controlled, randomised withdrawal period (RWD), phase 2b study with open-label extension in children (aged 1–18 years) with Alagille syndrome (NCT02160782). Eligible participants had more than three times the normal serum bile acid (sBA) levels and intractable pruritus. After 18 weeks of maralixibat 380 µg/kg once per day, participants were randomly assigned (1:1) to continue maralixibat or receive placebo for 4 weeks. Subsequently, all participants received open-label maralixibat until week 48. During the long-term extension (204 weeks reported), doses were increased up to 380 µg/kg twice per day. The primary endpoint was the mean sBA change during the RWD in participants with at least 50% sBA reduction by week 18. Cholestastic pruritus was assessed using observer-rated, patient-rated, and clinician-rated 0–4 scales. The safety population was defined as all participants who had received at least one dose of maralixibat. This trial was registered with ClinicalTrials.gov, NCT02160782, and is closed to recruitment.

Findings Between Oct 28, 2014, and Aug 14, 2015, 31 participants (mean age 5·4 years [SD 4·25]) were enrolled and 28 analysed at week 48. Of the 29 participants who entered the randomised drug withdrawal period, ten (34%) were female and 19 (66%) were male. In the RWD, participants switched to placebo had significant increases in sBA (94 µmol/L, 95% CI 23 to 164) and pruritus (1·7 points, 95% CI 1·2 to 2·2), whereas participants who continued maralixibat maintained treatment effect. This study met the primary endpoint (least square mean difference –117 µmol/L, 95% CI –232 to –2). From baseline to week 48, sBA (–96 µmol/L, –162 to –31) and pruritus (–1·6 pts, –2·1 to –1·1) improved. In participants who continued to week 204 (n=15) all improvements were maintained. Maralixibat was generally safe and well tolerated throughout. The most frequent adverse events were gastrointestinal related. Most adverse events were self-limiting in nature and mild-to-moderate in severity.

Interpretation In children with Alagille syndrome, maralixibat is, to our knowledge, the first agent to show durable and clinically meaningful improvements in cholestasis. Maralixibat might represent a new treatment paradigm for chronic cholestasis in Alagille syndrome.

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Introduction

Alagille syndrome is a rare, autosomal dominant, multisystem disorder caused by mutations in the *JAG1* and *NOTCH2* genes.[1–4] Alagille syndrome commonly presents in infancy and clinical diagnosis is established when at least three of the following are evident: chronic cholestasis (due to interlobular bile duct paucity); craniofacial dysmorphia; and ocular, skeletal, or cardiac malformations.[5] Additional organs, including the kidneys—a suggested sixth major criteria—and vascular system (Alagille syndrome was initially known as arteriohepatic dysplasia), might be involved. Growth delay is also frequently observed.[6] The reported incidence of Alagille syndrome is one in 30 000–50 000 livebirths, but this is probably an underestimate given an incomplete penetrance and highly variable expressivity.[6]

In the liver, Alagille syndrome might cause interlobular bile duct paucity, leading to chronic cholestasis, the accumulation of bile acids, and subsequent liver injury. Clinical presentation can range from no symptoms to severe chronic cholestasis manifesting as unrelenting pruritus, jaundice, and xanthomas (subcutaneous lipid deposits secondary to hypercholesterolaemia).[6] Serum bile acid (sBA) levels

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Research in context

Evidence before this study

Alagille syndrome is an autosomal dominant multisystem disorder and, in individuals with hepatic involvement, cholestasis is the defining clinical feature. In these patients, intractable pruritus is the most challenging symptom and frequently leads to liver transplantation. In a retrospective analysis of 293 children with Alagille syndrome, the estimated liver transplant-free survival at the age of 18·5 years was only 24%, demonstrating the previously underappreciated burden of liver disease in Alagille syndrome. There are no approved therapeutic agents for Alagille syndrome.

We conducted a PubMed search for research articles published from database inception until Dec 7, 2020, with no language restrictions, using the terms "Alagille" AND "clinical trial". We identified published clinical study data on three other agents being investigated for efficacy on pruritus, growth, and fat-soluble vitamin deficiency in Alagille syndrome. These studies had either no comparator or did not meet their primary endpoint. Two previous controlled studies in Alagille syndrome of maralixibat, an apical sodium-dependent bile acid transporter (ASBT) inhibitor, did not meet their primary endpoints.

Added value of this study

ICONIC is the first clinical study of an ASBT inhibitor in Alagille syndrome to meet its primary endpoint and demonstrate significant multiparameter clinical response, including pruritus, serum bile acid, xanthomas, improved quality of life, and growth. The ICONIC study assessed long-term efficacy and safety over 204 weeks of maralixibat treatment. The study design included higher doses than previous studies and a randomised withdrawal period to limit placebo response in the setting of patient-reported outcomes. Responses were durable across the 204-week period analysed, demonstrating long-term treatment potential. Maralixibat was generally well tolerated throughout.

Implications of all the available evidence

ICONIC presents, to our knowledge, the first conclusive data demonstrating therapeutic benefit with a pharmacological agent in Alagille syndrome. By inhibiting the enterohepatic circulation, maralixibat 380 µg/kg once per day improves pruritus or cholestasis, or both, in more than 80% of participants (at week 48, 26 of 31 participants had ≥1 Itch Reported Outcome [Observer] improvement and 24 of 29 participants had ≥20% serum bile acid reductions *vs* baseline). Maralixibat has been used in the setting of an international expanded access programme since 2020, and has recently been approved by the US Food and Drug Administration (Sept 29, 2021) for use in cholestatic pruritus in patients with Alagille syndrome aged 1 year and older. Our results suggest that maralixibat might extend transplant free survival in Alagille syndrome, and also that broader use of ASBT inhibitors, across paediatric and adult cholestasis settings might be of benefit.

are often highly elevated and hypothesised to contribute to pruritus and liver injury.[7,8]

Pruritus is the most burdensome symptom of cholestasis in Alagille syndrome. Intractable pruritus can lead to self-mutilation, scarring, sleep deprivation, and mood disturbance, severely reducing quality of life and often causing family disruption.[6,9,10] There are no approved drugs for the management of cholestasis or pruritus associated with Alagille syndrome. Instead, several agents, including ursodeoxycholic acid and rifampicin, are used off-label for their perceived anticholestatic and antipruritic properties.[8] Based on clinical findings, the efficacy of these agents is limited, and their adverse event profiles are a potential concern.[11]

In the absence of effective pharmacotherapy, cholestasis and pruritus are often managed by surgical interruption of the enterohepatic circulation of bile acids, including partial biliary diversion and ileal exclusion.[12] However, these interventions are not broadly recommended because efficacy is uncertain and the burden of a lifelong stoma is significant.[12,13] Consequently, children with Alagille syndrome frequently receive a liver transplant to address their cholestasis, pruritus, and xanthomas, even in the absence of liver failure or cirrhosis.[6,7,14,15] Native liver survival in Alagille syndrome has recently been reported as 24–41% at the age of 18·5 years.[15,16]

Inhibitors of the apical sodium-dependent bile acid transporter (ASBT), also known as ileal bile acid transporter inhibitors, are new agents that can pharmacologically interrupt the enterohepatic circulation of bile acids at the ileal enterocytes. This inhibition leads to increased faecal bile acid excretion and reduced levels of sBA and cholesterol.[8,17] Maralixibat is a minimally absorbed, selective ASBT inhibitor, that has shown the potential to reduce pruritus, sBA, and cholesterol in patients with Alagille syndrome in preliminary clinical studies.[8,17]

Here, we present data from ICONIC (LUM001–304; NCT02160782), a placebo-controlled, double-blind, randomised withdrawal period (RWD), phase 2b study with a long-term, open-label extension. ICONIC investigated the effect of maralixibat (formerly known as LUM001 and SHP625) on sBA and pruritus, as well as other biochemical and clinical markers of cholestasis, in children with Alagille syndrome.

Methods

Study design

ICONIC was an international, multicentre, phase 2b, double-blind, placebo-controlled, drug-withdrawal study

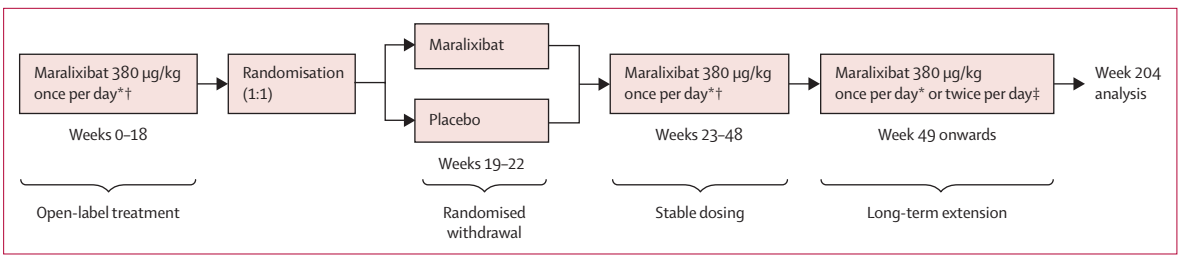

Figure 1: **Study design**
*Equivalent to maralixibat chloride 400 µg/kg. †Included a 6-week dose escalation period for all participants during the first 6 weeks of the open-label treatment period and for participants who received placebo during the randomised withdrawal period. ‡Twice per day dosing (started after week 100) was equivalent to maralixibat chloride 800 µg/kg.

with open-label extension of maralixibat in children with Alagille syndrome. The study was done across nine tertiary centres in Australia and Europe (Belgium, France, Poland, Spain, and UK).

From baseline to week 48, a prespecified core study had three primary components (figure 1): (1) an open-label run-in period from baseline to week 18 (6-week dose escalation and 12-week stable dosing) for all participants, with maralixibat doses up to 380 µg/kg once per day (equivalent to maralixibat chloride 400 µg/kg); (2) a 4-week double-blind, placebo-controlled RWD, from weeks 19 to 22, in which all participants were randomly assigned (1:1) to either remain on maralixibat at 380 µg/kg or receive placebo once per day; and (3) an open-label, stable-dosing period from weeks 23 to 48, with maralixibat at 380 µg/kg once per day for all participants (including an initial 6-week dose escalation for participants who previously received placebo).

After week 49 there was an optional open-label, long-term extension period. After week 100, to explore the efficacy and safety of higher maralixibat doses, participants with sBA levels of more than 8 µmol/L (upper limit of normal [ULN]) or pruritus (Itch Reported Outcome Observer [ItchRO(Obs)] ≥1·5) increased maralixibat dose to twice per day (to a maximum of 760 µg/kg per day).

Assessments reported herein were made up to week 204, because this timepoint maximised data availability and treatment duration.

The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and approved by institutional review boards and ethics committees in each country (Australia, Research Ethics and Governance, The Royal Children's Hospital Melbourne, VIC; Belgium, Comité d'Ethique des Cliniques Universitaires Saint-Luc and de l'UCL; France, CPP Ile de France VII; Poland, Komisja Bioetyczna przy instytucie Pomnik-Centrum Zdrowia Dziecka; Spain, Comité Ético de Investigación Clínica Hospital La Paz; UK, NRES Committee London—West London and GTAC, Nottingham REC Centre). Written informed consent (and assent) was obtained from the participant or their legal guardian.

Participants

ICONIC enrolled children aged 12 months to 18 years with a clinical diagnosis of Alagille syndrome,[5,18] sBA level more than three times the ULN and intractable pruritus (ItchRO[Obs] score >2 for two consecutive weeks). Exclusion criteria included surgical interruption of the enterohepatic circulation, liver transplantation, and decompensated liver cirrhosis.

Throughout, the coadministration of bile acid-binding resins was prohibited. Per protocol, from baseline to week 22, no new anti-pruritic medications were allowed, and pre-existing medications had to remain stable (ie, same dose except for weight adjustment).

Race and ethnicity data were not collected in this study.

Randomisation and masking

All participants were randomly assigned (1:1) in a blinded fashion to continue receiving the same dose of maralixibat or receive placebo for a period of 4 weeks (RWD; figure 1). Randomisation used a permuted block algorithm stratified by predefined response criteria (≥50% sBA reduction from baseline to week 12 or week 18) and with entire blocks (size 4) assigned by study site using SAS software (version 9.4) by an unblinded statistician not involved in the conduct of the trial or analysis of the data. The randomisation code was assigned to each participant in sequence in the order of enrolment, and then the participants received the investigational products labelled with the same code. Both maralixibat and placebo were identical in appearance. All participants, investigators, and laboratory staff were masked to treatment allocation.

Procedures

Participants received an oral, grape-flavoured solution containing maralixibat or matching placebo (during the RWD), 30 min before the morning meal. For twice per day doses, a dose 30 min before dinner was added. Doses were adjusted to bodyweight throughout. Pruritus was assessed each day, in the morning and evening, using the ItchRO scale—a validated tool designed to assess the impact of itching in children with cholestatic liver disease, including Alagille syndrome.[9] The Itch Reported Outcome (ItchRO)

score is a 0–4 scale, where 0 is none, 1 is mild, 2 is moderate, 3 is severe, and 4 is very severe. Changes in ItchRO score of 1·0 or more have been shown to be clinically meaningful.[19] ItchRO(Obs) was completed by caregivers and was the basis for the key pruritus endpoint.

See Online for appendix

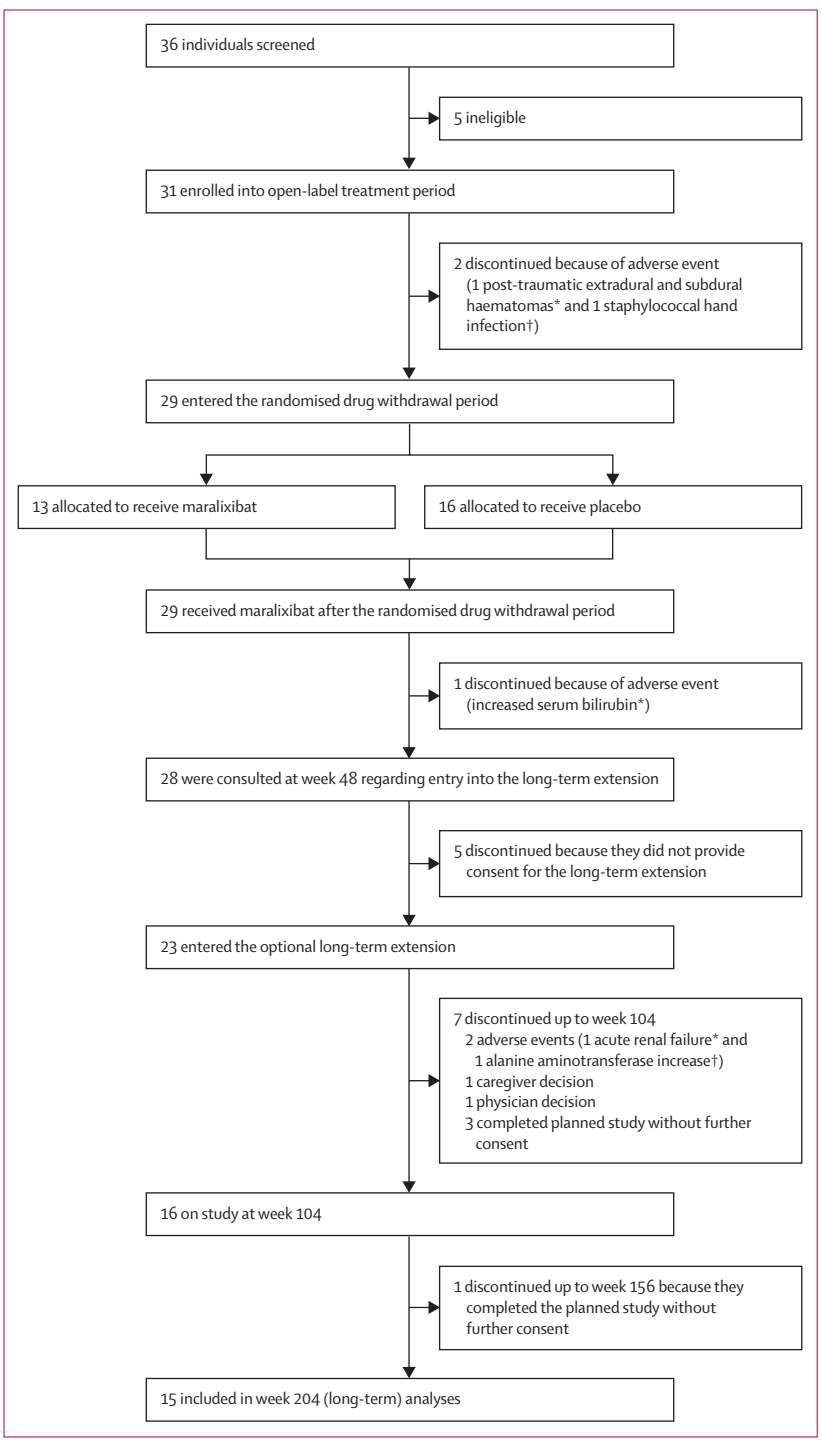

Figure 2: **Trial profile**
*Deemed unrelated to maralixibat by the investigator. †Deemed possibly related to maralixibat by the investigator.

The patient-rated ItchRO (ItchRO[Pt]) was completed independently by participants aged 9 years or older and with caregiver assistance for participants aged 5–8 years. Investigators assessed pruritus using the Clinician Scratch Scale (CSS; 0 is none, 1 is rubbing or mild scratching when undistracted, 2 is active scratching without abrasions, 3 is abrasions, and 4 is cutaneous mutilations, haemorrhage, scarring) and xanthomas using the Clinical Xanthoma Scale (CXS; 0–4 scale; appendix pp 2–3).[20,21] Quality of life was assessed using the Pediatric Quality of Life Inventory (PedsQL) Core (Parent) scale and fatigue using the PedsQL Multidimensional Fatigue Scale (appendix pp 2–3).[22,23]

Throughout the study, pharmacodynamic measurements, including sBA, were done using consistent central laboratories (appendix pp 2–3). Results were not provided to any study team personnel (study site, funder, or clinical research organisation) until after the week 48 analysis. The unblinded clinical research organisation statistician was segregated from both the clinical research organisation study team and the study sponsor, and the process was documented in the Interactive Web Response System Business Requirements Document (Premier IRT 1.0 platform).

Outcomes

The primary endpoint was the mean change in sBA levels during the RWD in participants who previously achieved an sBA reduction of at least 50% from baseline to week 12 or week 18.

To assess pruritus in the intention-to-treat population, the prespecified key pruritus endpoint was the difference in pruritus severity (measured by the weekly morning average ItchRO[Obs] score) between participants treated with maralixibat and participants treated with placebo during the placebo-controlled RWD, as well as the change from baseline to week 48. This analysis was done in all study participants and without the use of an enrichment strategy.

Key secondary endpoints were assessed in all study participants from baseline to weeks 18 and 48, and compared the maralixibat and placebo groups during the RWD, including sBA level and ItchRO(Pt) score. Other assessments included changes in CSS score, CXS score, height, weight, serum cholesterol, and 7α-C4. Changes in liver enzymes (alanine aminotransferase, gamma-glutamyl transferase, and alkaline phosphatase), total and direct bilirubin, and safety and tolerability (adverse events and serious adverse events), including severity and relatedness, as evaluated by the investigator, were also assessed.

Statistical analysis

Given the rarity of Alagille syndrome, a formal sample size calculation was not done. The planned sample size of 30 evaluable Alagille syndrome participants is based on practical considerations, rather than a desired power for a prespecified difference. Analyses were completed using

data from all participants, except for the primary endpoint, in which only participants who achieved the endpoint's criteria (≥50% sBA reduction from baseline to week 12 or week 18) were included. The safety population was defined as all participants who have received at least one dose of maralixibat. CI for the mean change using a normal approximation are presented. Analysis of covariance, using a mixed linear model with baseline value as a covariate, was used to assess least square mean statistical significance for between-group comparisons. All safety analyses were done in the overall treatment population and without inferential statistic tests. Week 204 analysis used data up to and including Dec 1, 2019. Statistical analyses were done using SAS, version 9.4. An independent data monitoring committee oversaw the safety of study participants.

Role of the funding source

This funder, Mirum Pharmaceuticals, was involved in data collection, analysis, and interpretation. Mirum Pharmaceuticals provided support for writing this manuscript.

Results

36 children with Alagille syndrome were screened between Oct 28, 2014, and Aug 14, 2015, after which the predefined sample size was filled (figure 2). Five children were excluded during the screening period. 31 participants were enrolled into the open-label period of the study, during which two discontinued due to serious adverse events not related to maralixibat.

From week 19, the remaining 29 participants received either ongoing maralixibat (n=13) or were switched to placebo (n=16) for the RWD. Participants had a mean age of 5·4 years (SD 4·25) at baseline, had clinically relevant pruritus (ItchRO[Obs] mean of the weekly average 2·9 points [SD 0·55]), raised mean sBA (283 µmol/L [SD 210·6]) and elevated mean alanine aminotransferase (181 µmol/L [SD 108·6]), mean aspartate aminotransferase µmol/L (168 [SD 75·9]), and mean total serum bilirubin (104·1 µmol/L [SD 98·82]). Of the 29 participants, ten (34%) were female and 19 (66%) were male. Characteristics at baseline were generally balanced between treatment groups (table 1; appendix p 11). Beyond week 48, consent was renewed for the 23 participants who continued treatment in the long-term extension, of which 15 remained on study at week 204 (figure 2). At baseline, 28 (90%) of 31 participants were receiving ursodeoxycholic acid or rifampicin, or both (table 1). At the time of publication, 13 participants

	All participants (N=31)	Maralixibat group* (n=13)	Maralixibat, placebo, maralixibat group* (n=16)
Age at baseline visit, years	5·4 (4·2); 5·0 (2·0–7·0)	5·5 (5·0); 4·0 (2·0–7·0)	5·8 (3·7); 5·0 (3·5–8·0)
Sex			
Female	12 (39%)	4 (31%)	6 (37%)
Male	19 (61%)	9 (69%)	10 (63%)
Genotyped mutation within *JAG1*	31 (100%)	13 (100%)	16 (100%)
History of receiving treatment for pruritus			
Any medication	29 (94%)	12 (92%)	15 (94%)
Ursodeoxycholic acid	25 (81%)	10 (77%)	13 (81%)
Rifampicin	23 (74%)	10 (77%)	12 (75%)
Naltrexone	1 (3%)	1 (8%)	0
Sertraline	1 (3%)	0	1 (6%)
Study parameter			
ItchRO(Obs) weekly morning average severity score†	2·9 (0·5); 3·0 (2·4–3·3)	2·9 (0·5); 2·8 (2·4–3·3)	2·9 (0·6); 3·0 (2·5–3·3)
CSS score	3·3 (0·9); 4·0 (3·0–4·0)	3·0 (1·1); 3·0 (3·0–4·0)	3·5 (0·7); 4·0 (3·0–4·0)
sBA, µmol/L	283 (211); 276 (79–479)	318 (234); 335 (79–412)	250 (197); 196 (79–460)
Alanine aminotransferase, U/L	181 (109); 171 (116–207)	218 (150); 196 (119–244)	147 (55); 144 (98–197)
Aspartate aminotransferase, U/L	168 (76); 161 (111–203)	172 (76); 183 (141–203)	147 (61); 135 (111–180)
GGT, U/L	508 (389); 419 (189–740)	614 (482); 463 (275–740)	404 (300); 311 (159–552)
Total bilirubin, µmol/L	104·2 (98·9); 78·7 (23·9–148·8)	111·5 (112·4); 78·7 (13·7–152·2)	82·6 (72·9); 48·7 (26·5–135·9)
Direct bilirubin, µmol/L	78·2 (62·7); 70·1 (13·7–138·5)	80·2 (64·9); 70·1 (13·7–138·5)	69·0 (61·4); 46·2 (12·8–123·1)
Cholesterol, mmol/L	13·3 (10·9); 8·5 (7·3–14·1)	14·4 (14·3); 8·4 (7·6–11·6)	11·9 (8·2); 9·1 (7·3–12·6)
7α-C4, nmol/L	25·8 (36·6); 11·3 (4·5–31·5)	36·9 (49·7); 19·0 (10·0–31·5)	16·3 (21·8); 7·3 (3·5–19·3)
FGF-19, pmol/L	27·4 (60·1); 8·4 (4·0–17·3)	30·5 (69·4); 9·4 (4·0–17·3)	26·1 (55·5); 7·7 (4·3–21·4)

Data are mean (SD); median (IQR), or n (%). CSS=Clinician Scratch Scale. FGF-19=fibroblast growth factor-19. GGT=gamma-glutamyl transferase. ItchRO(Obs)=Itch Reported Outcome (Observer). sBA=serum bile acid. 7α-C4=7α-hydroxy-4-cholesten-3-one. *The maralixibat, placebo, maralixibat group (n=16) received placebo during the randomised withdrawal period, whereas the maralixibat treatment group (n=13) continued to receive maralixibat. †Average ItchRO(Obs) scores are based on the 7 days before baseline visit.

Table 1: **Baseline demographics and characteristics**

	Change from baseline at week 18	Change during the randomised withdrawal window period (weeks 19–22)		Maralixibat–placebo comparison (week 22)	Change from baseline to week 48	Change from baseline to week 204
	Maralixibat (n=29)	Maralixibat (n=13)	Placebo (n=16)	NA	Maralixibat (n=27)	Maralixibat (n=15)
sBA, µmol/L	–88 (–133 to –42)*	–17 (–83 to 50)	94 (23 to 164)*	–114 (–213 to –15)*†	–96 (–162 to –31)*	–181 (–283 to –79)*
ItchRO(Obs) weekly morning average	–1·7 (–2·1 to –1·4)*	0·2 (–0·3 to 0·7)	1·7 (1·2 to 2·2)*	–1·5 (–2·1 to –0·8)*	–1·6 (–2·1 to –1·1)*	–2·3 (–2·9 to –1·7)*
ItchRO(Pt) weekly morning average‡	–2·1 (–2·6 to –1·5)*	–0·1 (–1·4 to 1·2)	1·8 (0·9 to 2·7)*	–2·0 (–3·0 to –1·0)*	–2·3 (–2·8 to –1·7)*	–2·4 (–3·5 to –1·3)*
CSS score	–1·8 (–2·3 to –1·2)*	0·4 (-0·4 to 1·1)	1·6 (0·7 to 2·4)*	–0·9 (–1·8 to –0·1)*	–1·8 (–2·3 to –1·3)*	–2·3 (–3·0 to –1·7)*
CXS score, with xanthoma at baseline (n=14)	–0·4 (–0·9 to 0·1)*	NA§	NA§	NA§	–0·9 (–1·3 to –0·5)*	–1·5 (–2·4 to –0·6)*
Quality of Life, PedsQL Core (parent)	11 (4 to 17)*	–8 (–17 to 1)	–8 (–17 to 0)	2 (–10 to 15)*	9 (2 to 16)*	9 (–2 to 21)
Fatigue, PedsQL Multidimensional Fatigue Scale	20 (9 to 32)*	–4 (–17 to 10)	–17 (–36 to 3)	14 (–3 to 31)	20 (9 to 32)*	17 (6 to 29)*
Growth (height), Z score	0·12 (–0·04 to 0·29)	NA§	NA§	NA§	0·18 (–0·02 to 0·37)	0·40 (0·12 to 0·69)*
Growth (weight), Z score	0·02 (–0·10 to 0·14)	NA§	NA§	NA§	0·02 (–0·15 to 0·18)	0·16 (–0·25 to 0·58)
Cholesterol, mmol/L	–2·3 (–3·6 to –0·9)*	0·3 (–0·5 to 1·0)	2 (0·3 to 3·4)*	–1·9 (–3·5 to –0·4)*	–1·6 (–2·7 to –0·5)*	–3·7 (–5·9 to –1·6)*
7α-C4, nmol/L	35·1 (12·1 to 58·1)*	–16·5 (–55·3 to 22·3)	–20·4 (–48·2 to 7·4)	31·1 (1·0 to 61·3)*	21·3 (–2·0 to 44·7)	40·9 (15·5 to 66·2)*
FGF-19, pmol/L	–19·9 (–40·2 to 0·4)	NA§	NA§	NA§	–16·1 (–38·7 to 6·6)	–9·5 (–17·2 to –1·8)*

Data are mean (95% CI). 7α-C4=7α-hydroxy-4-cholesten-3-one. CSS=Clinician Scratch Scale. CXS=Clinician Xanthoma Scale. FGF-19=fibroblast growth factor-19. ItchRO(Obs)=Itch Reported Outcome (Observer). ItchRO(Pt)=Itch Reported Outcome (Patient). NA=not applicable. PedsQL=Pediatric Quality of Life Inventory. sBA=serum bile acid. *Significant 95% CIs (that exclude 0). †The least square mean difference in sBA between the maralixibat and placebo groups in the 15 participants who achieved an sBA reduction of at least 50% from baseline to week 12 or 18 (the primary endpoint) was –117 µmol/L (SE 53; 95% CI –232 to –2). ‡Numbers for this row are as follows: change from baseline at week 18 (n=14), change during the randomised withdrawal window period (weeks 19–22; n=5), maralixibat–placebo comparison (week 22; n=9), change from baseline to week 48 (n=14), change from baseline to week 204 (n=6). §The duration of the time window was insufficient to generate clinically meaningful data. Values shown are for the overall study population, including but not limited to the 15 participants who achieved prespecified criteria for inclusion in the primary endpoint analyses. All analyses, with exception of the maralixibat–placebo comparison, were made based on within group comparisons. Mean difference and 95% CI are the least square mean difference from a repeated measures ANCOVA model that includes treatment group as a fixed effect and baseline value as a covariate. As a result, the least square mean difference is not equal to the difference of the individual treatment groups in the two columns to the left.

Table 2: **Efficacy data within the overall population from baseline to week 204**

are receiving maralixibat treatment in a roll-over extension study). Major protocol deviations are described in the appendix (p 4).

All efficacy endpoints, except for the primary endpoint, were assessed in the overall study population from baseline to week 204 (table 2). sBA level reduced significantly from baseline to week 12 (–108, 95% CI –166 to –50) and week 18 (–88, 95% CI –133 to –42; figure 3; table 2; appendix p 12). During the RWD, participants receiving maralixibat (n=13) maintained the sBA reductions observed in the first 18 weeks, whereas those randomly assigned to placebo (n=16) had significant sBA increases to levels similar to that of baseline. At the end of the RWD, sBA was significantly different between maralixibat and placebo groups (mean difference –114 µmol/L [SE 48], 95% CI –213 to –15; figure 3; table 2). The primary endpoint, evaluated per protocol in participants achieving an sBA reduction of at least 50% from baseline to week 12 or week 18 (n=15), was met with a significant least square mean difference in sBA between maralixibat and placebo groups during the RWD (–117 µmol/L [SE 53], 95% CI –232 to –2; figure 3). In this primary endpoint responder population, randomisation blocks assigned by study site led to more sBA responders being assigned to placebo (n=10) than maralixibat (n=5). All participants resumed maralixibat at the end of the RWD and had a significant sBA reduction from baseline to week 48 (–96, 95% CI –162 to –31; figure 3). These reductions were maintained in the 15 participants at week 204 (*vs* baseline, –181, 95% CI –283 to –79; table 2; appendix p 13). Reduction of sBA (≥50% at weeks 12 or 18) did not predict participant continuation at week 204 (post hoc). An sBA reduction of at least 20% was observed in 24 (83%) of 29 participants during the core 48-week period.

Pruritus was assessed using ItchRO[Obs], ItchRO[Pt], and CSS scales. ItchRO(Obs) improved significantly from baseline to week 12 (–1·6, 95% CI –1·9 to –1·2) and week 18 (–1·7, 95% CI –2·1 to –1·4; figure 4; table 2). At week 22, a significant increase (worsening) from week 18 in ItchRO(Obs) scores was observed in the placebo group (1·7, 95% CI 1·2 to 2·2; figure 4), with scores similar to those recorded at baseline. In the same period, the pruritus treatment effect was maintained in the group continuing maralixibat. At the end of the RWD, mean values were 1·4 (SD 0·9) in the maralixibat group and 2·8 (0·9) in the placebo group. The least square mean difference between the groups was statistically significant (–1·5 points [SE 0·3, 95% CI –2·1 to –0·8]; prespecified pruritus endpoint) and results were consistent across sensitivity analyses (figure 5). After the RWD, all participants again received maralixibat, and pruritus benefit was observed for participants who had been previously treated with

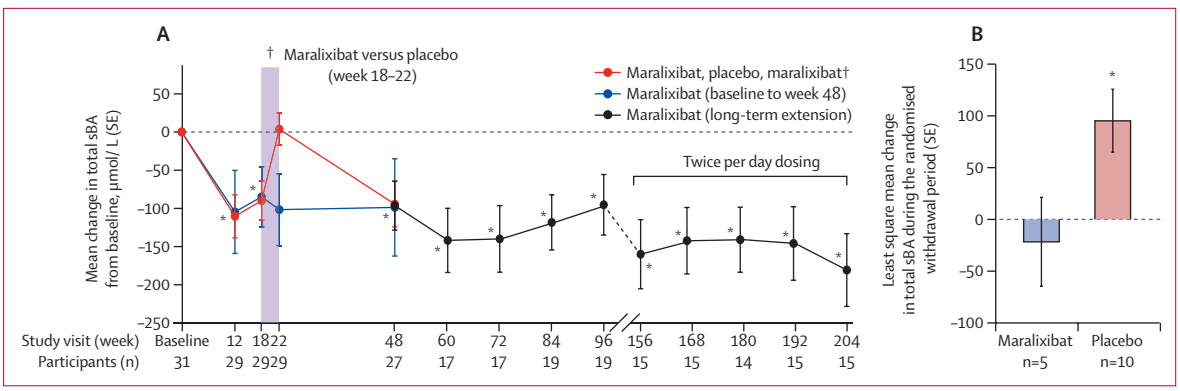

Figure 3: **Changes in sBA**
Changes in sBA from baseline to week 204 across all participants (A) and during the randomised withdrawal period in the primary endpoint responder analysis (B; n=15). (A) Dashed line represents data not shown between weeks 96 and 156. (B) Of the 15 participants assessed as part of the primary endpoint analysis (participants who had reductions in sBA of ≥50% from baseline to week 12 or 18), the placebo group (n=10) received placebo during the randomised withdrawal period, whereas the maralixibat treatment group (n=5) continued to receive maralixibat. 12 participants went to twice per day dosing on the basis of raised sBA in the open-label extension. sBA=serum bile acids. *95% CI excludes zero (compared with baseline, overall population; maralixibat treatment group *vs* placebo group). †The maralixibat, placebo, maralixibat group (n=16) received placebo during the randomised withdrawal period (purple-shaded area), whereas the maralixibat treatment group (n=13) continued to receive maralixibat.

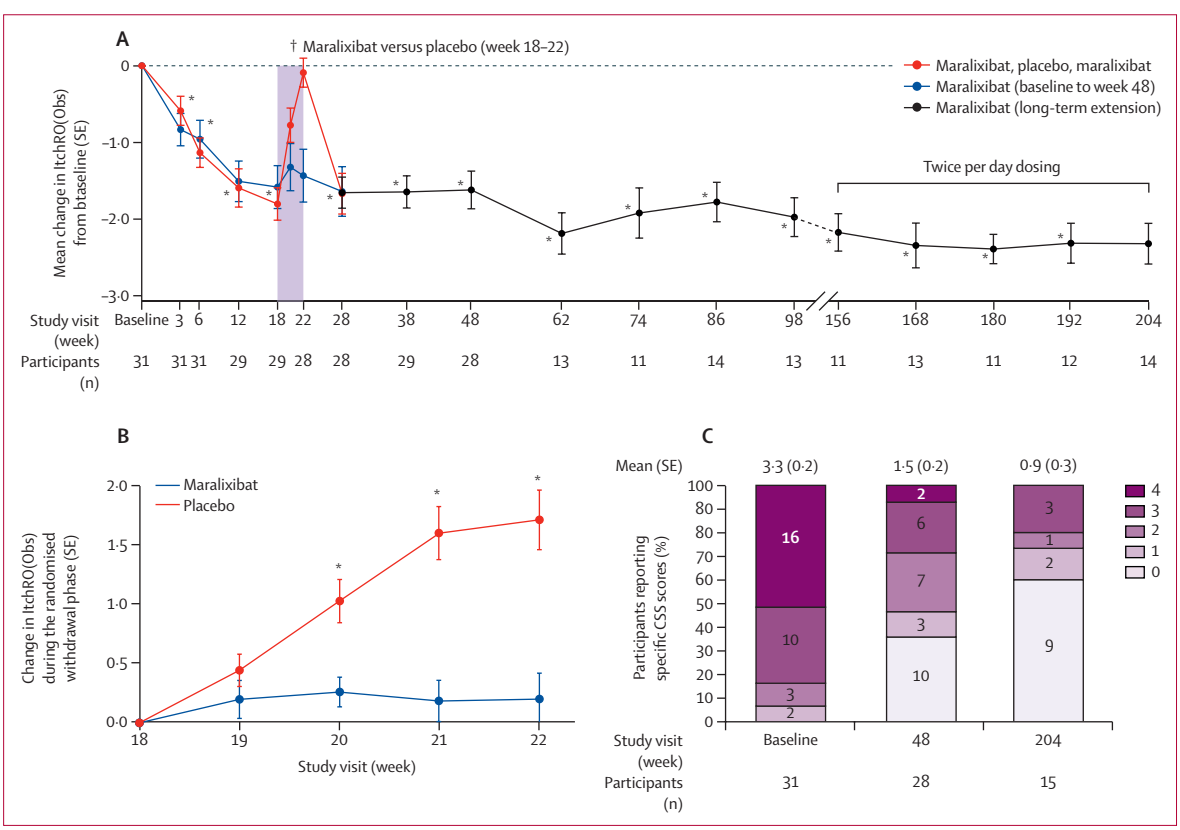

Figure 4: **Changes in pruritus**
Changes in pruritus from baseline to week 204 (ItchRO[Obs]; A), and during the randomised withdrawal period (prespecified pruritus endpoint; n=29; B). (C) Proportions of CSS scores at baseline, week 18, week 48, and week 204 (n=28 at week 48). Dashed lines in (A) represent data not shown between week 98 to week 156. Numbers in (C) represent the numbers of participants reporting each CSS score. Asterisks in represent paired *t* test comparing the change from baseline (testing if the change was equal to 0 or not). 12 participants went to twice per day dosing on the basis of raised sBA in the open-label extension. CSS=Clinical Scratch Scale. ItchRO(Obs)=Itch Reported outcomes (Observer). *95% CI excludes zero (compared with baseline, overall population). †The maralixibat, placebo, maralixibat group (n=16) received placebo during the randomised withdrawal period (purple-shaded area), whereas the maralixibat treatment group (n=13) continued to receive maralixibat.

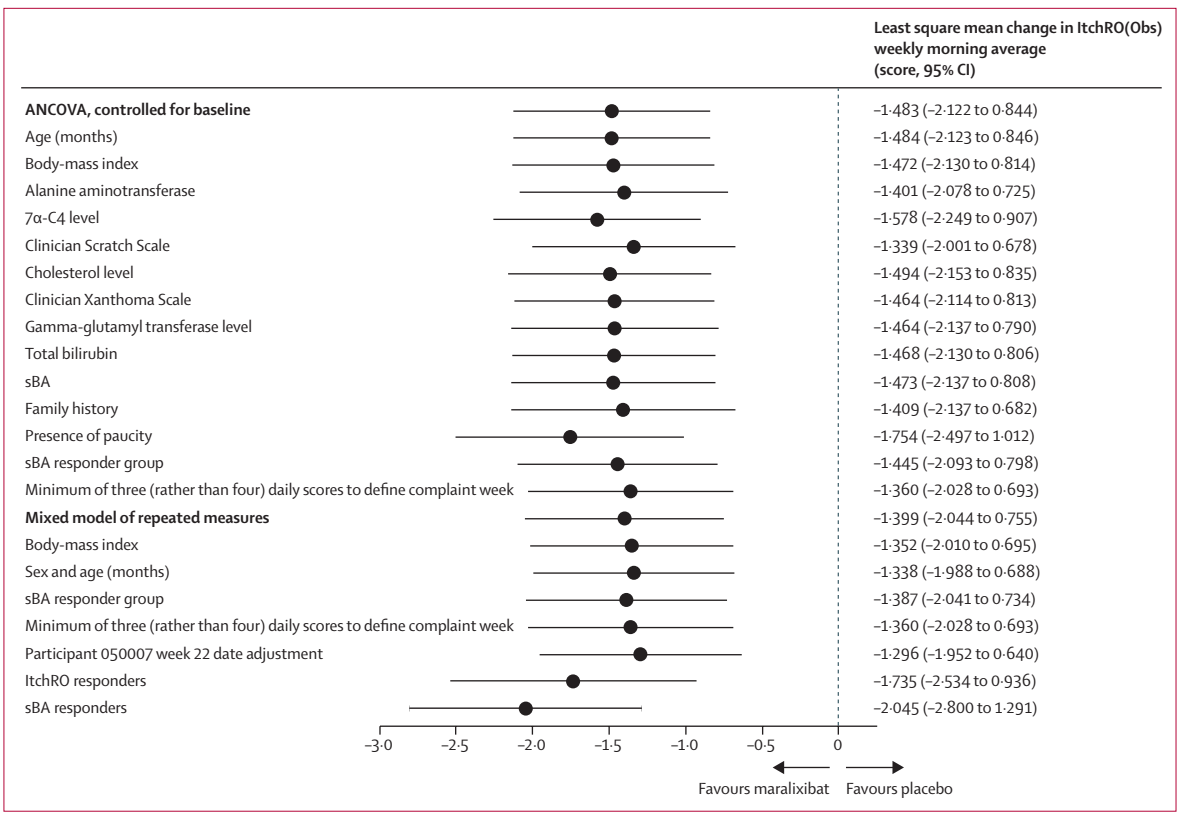

Figure 5: **Sensitivity analyses of ItchRO(Obs) weekly morning average score during the randomised withdrawal period**
Pruritus sensitivity analysis in the randomised withdrawal period (weeks 19–22) analysing treatment effect while controlling for potential confounding factors. Negative values represent improvements in pruritus with maralixibat treatment versus placebo. 7α-C4=7α-hydroxy-4-cholesten-3-one. sBA=serum bile acid. ItchRO=Itch Reported Outcome.

placebo (figure 4). ItchRO(Obs) improved significantly from baseline to week 48 in the overall population (–1·6, 95% CI –2·1 to –1·1). In the 15 participants who continued to week 204, maintenance of treatment effect on pruritus was demonstrated (–2·3, 95% CI –2·9 to –1·7; figure 4). Significant pruritus treatment effect was apparent at the first timepoint of assessment after baseline (week 3; –0·7, 95% CI –1·0 to –0·4), as well as within 2 weeks of randomisation between maralixibat-treated and placebo-treated groups (week 20; least square mean difference –0·8, 95% CI –1·3 to –0·3; figure 3). 26 (84%) of 31 participants experienced a clinically meaningful improvement (≥1-point decrease) at least once during the first 48 weeks. Among the 28 participants with week 48 ItchRO(Obs) scores, 21 (75%) reported a decrease of 1 point or more at week 48 (appendix p 12). Results from clinician-rated pruritus, as measured by the CSS, were similar to ItchRO(Obs), with a significant improvement from baseline to week 18 and week 48 that was maintained to week 204, and a clear separation between maralixibat-treated and placebo-treated groups during the RWD (table 2; figure 4). At week 18, 20 (69%) of 29 participants had low-rated to moderate-rated scores (0–2); this was also the case for 20 (71%) of 28 participants at week 48, and 12 (80%) of 15 participants at week 204. In the 15 participants who continued to week 204, ItchRO(Obs) significantly decreased in the twice per day versus the once per day period (–0·4, 95% CI –0·7 to –0·1; appendix p 13). ItchRO(Pt) results were consistent with both ItchRO(Obs) and CSS (table 2; appendix p 6).

In participants with xanthomas at baseline (n=14), CXS scores improved significantly from baseline to weeks 48 and 204 (table 2; appendix p 7). No participants developed new xanthomas while receiving maralixibat. These results are accompanied by significant reductions in total cholesterol from baseline to weeks 18, 48, and 204 and changes in 7α-C4 and FGF-19 (table 2; appendix p 8).

Mean values for serum gamma-glutamyl transferase, total and direct bilirubin, and other assessments of hepatic function, did not change from baseline to week 18 or week 48 (table 3; appendix p 14). In the 15 participants who continued long term, mean levels of total and direct bilirubin were lower from baseline to week 204, with direct bilirubin changing significantly (–19·6, 95% CI –37·6 to –1·7; table 3). There was no difference in alanine aminotransferase from baseline to week 18 (–1, 95% CI –33 to 31). During the RWD, mean alanine amino-transferase increased in the maralixibat-treated group (43, 95% CI 8 to 78; table 3). Participants with alanine

	Change from baseline at week 18	Change during the randomised withdrawal window period (weeks 19–22)		Change from baseline to week 48	Change from baseline to week 204
	Maralixibat (n=29)	Maralixibat (n=13)	Placebo (n=16)	Maralixibat (n=27)	Maralixibat (n=15)
Alanine aminotransferase, U/L	–1 (–33 to 31); 0 (–33 to 44)	43 (8 to 78)*; 35 (–1 to 80)*	13 (–12 to 37); 22 (–25 to 46)	18 (–15 to 50); 30 (–4 to 60)	71 (–4 to 147); 40 (3 to 143)*
Aspartate aminotransferase, U/L	–7 (–24 to 9); –1 (–33 to 21)	42 (11 to 73)*; 29 (–3 to 98)	37 (5 to 70)*; 14 (–4 to 64)	14 (–7 to 35); 23 (–18 to 36)	43 (–3 to 88); 48 (–30 to 73)
Gamma-glutamyl transferase, U/L	29 (–36 to 93); 22 (–18 to 129)	32 (–46 to 109); 26 (0 to 65)	–34 (–146 to 78); –13 (–155 to 114)	25 (–42 to 92); 6 (–49 to 99)	–7 (–123 to 109); –33 (–116 to 124)
Total bilirubin, µmol/L	–8·0 (–17·2 to 1·3); –1·7 (–15·4 to 0·0)	7·5 (–5·4 to 20·4); 1·7 (0·0 to 5·1)	6·1 (–1·4 to 13·6); 5·1 (0·0 to 10·3)	0·5 (–11·9 to 13·0); –0·9 (–11·1 to 2·6)	–18·1 (–37·9 to 1·6); –1·7 (–35·9 to 6·8)
Direct bilirubin, µmol/L	–8·6 (–15·3 to –1·9)*; –2·6 (–11·1 to 0·0)	1·9 (–5·9 to 9·6); 0·9 (0·0 to 6·0)	2·7 (–3·1 to 8·6); 1·7 (–3·4 to 6·8)	–4·1 (–9·7 to 1·5); 0·0 (–6·8 to 0·0)	–19·6 (–37·6 to –1·7)*; –6·8 (–35·9 to –1·7)*

Data are mean (95% CI); median (IQR). *Significant 95% CIs (that exclude 0).

Table 3: **Changes in liver parameters**

aminotransferase elevations during the RWD experienced later alanine aminotransferase reductions while continuing maralixibat treatment. There was no difference in alanine aminotransferase from baseline to week 48 in the overall group (18, 95% CI –15 to 50). Over the whole cohort, there was little change in alanine aminotransferase for approximately the first 120 weeks. After this period, a rise of approximately 50 U/L was identified.

Participant quality of life (mean PedsQL Core [Parent] score) improved significantly from baseline to weeks 18 and 48 (table 2). Fatigue (mean PedsQL Multidimensional Fatigue Scale) improved significantly from baseline to week 18 (20, 95% CI 9–32), week 48 (20, 9–32), and week 204 (17, 6–29; table 2).

Mean height Z score from baseline to week 48 was not increased significantly, but for the 15 participants who remained on treatment through week 204, height Z scores improved significantly from baseline (0·40, 95% CI 0·12 to 0·69; table 2; figure 6).

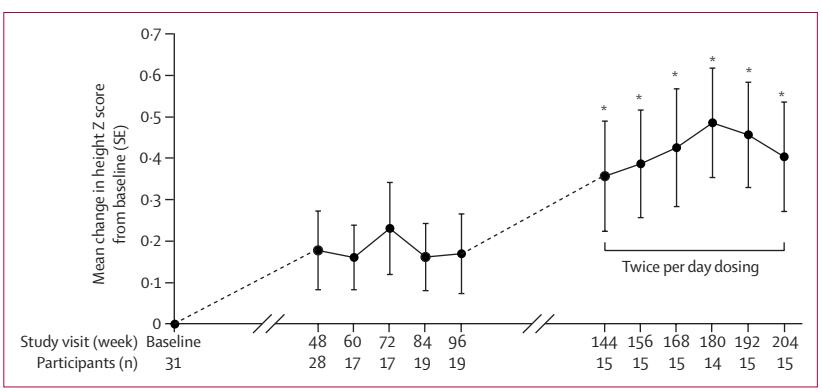

Figure 6: **Change in height Z scores**
From week 144 onwards the data from the same group of 15 participants are shown, with the exception of week 180, where one participant did not have available data. Dashed lines represent data not shown between baseline to week 48, and week 96 to week 144. *95% CI excludes zero (compared with baseline, overall population).

Mean duration of treatment was 2·6 years (135 weeks [range 5–228, IQR 49–218]). Maralixibat treatment was well tolerated throughout (table 4). Most adverse events were self-limiting in nature and mild to moderate in severity. Diarrhoea and abdominal pain were the most frequent adverse events, and occurred with a similar incidence between the maralixibat-treated and placebo-treated groups during the RWD (table 4; appendix p 15). There were no study discontinuations for gastrointestinal-related events. No deaths occurred during this study. Nine participants experienced serious adverse events from baseline to week 48; none were deemed related to maralixibat by the investigator (table 4). Six participants experienced serious adverse events during the long-term extension, all deemed unrelated to maralixibat (appendix pp 16–17).

Five participants had adverse events that led to study discontinuation from baseline to week 204 (appendix p 4). Two of these events were considered possibly related to study drug (one staphylococcal hand infection and one alanine aminotransferase elevation without raised serum bilirubin). The other three events were not considered related to study drug (acute renal failure, raised serum bilirubin, and combined extradural and subdural bleeding). The key treatment emergent adverse events were gastrointestinal disorders (appendix pp 15–16).

Over 204 weeks, dose reductions were made for two participants. One participant had elevations in alanine aminotransferase (at dose 380 µg/kg twice per day; deemed possibly related to maralixibat treatment) with no concomitant change in bilirubin, and one participant experienced intermittent diarrhoea (at dose 513 µg/kg per day split out into 380 µg/kg in the morning and 133 µg/kg in the afternoon). Neither participant experienced further complications or clinical sequelae, and each was able to continue maralixibat treatment. In those participants who continued long term, receiving maralixibat twice per day, alanine aminotransferase was numerically, but not statistically, increased versus baseline (table 3). No other markers of liver injury increased in this period, including bilirubin.

	Open-label period (baseline to week 18)	Randomised withdrawal window period (weeks 19–22)		Stable-dosing period (weeks 23–48)
	Maralixibat (n=31)	Maralixibat (n=13)	Placebo (n=16)	Maralixibat (n=29)
Participants with 1 or more treatment emergent adverse event	30 (97%)	7 (54%)	12 (75%)	25 (86%)
Treatment emergent adverse events potentially related to study drug*	12 (39%)	1 (8%)	3 (19)	1 (3%)
Treatment emergent adverse events leading to study drug discontinuation†	2 (7%)	0	0	1 (3%)
Serious adverse events	4 (13%)	1 (8%)	1 (6%)	5 (17%)
Serious adverse events potentially related to study drug*	0	0	0	0

Data are n (%). *Any treatment emergent or serious adverse event that was determined by an investigator as related or possibly related to the study drug is considered as potentially related to the study drug. †There were two discontinuations due to treatment emergent adverse events during the open-label period of the study; one participant discontinued for a serious adverse event deemed unrelated to maralixibat by the investigator (post-traumatic epidural and subdural haematomas), one participant discontinued for a treatment emergent adverse event deemed possibly related to maralixibat by the investigator (staphylococcal hand infection). During the stable dosing period, one participant discontinued due to a treatment emergent adverse event deemed unrelated to maralixibat by the investigator (increased serum bilirubin levels).

Table 4: **Safety data (from baseline to week 48)**

Fat-soluble vitamin supplements were available as standard of care throughout the study. No changes beyond standard of care in supplementation occurred during the study. 13 (42%) of 31 participants at baseline and eight (29%) of 28 participants at week 48 had deficiency in at least one fat-soluble vitamin. 11 (35%) of 31 participants at baseline and eight (29%) of 28 participants at week 48 had a vitamin D deficiency (appendix p 14). No fat-soluble vitamin-deficiency adverse events were assessed as related to maralixibat by study investigators.

Discussion

ICONIC is, to our knowledge, the first clinical trial studying an ASBT inhibitor to reach its primary efficacy endpoint in cholestatic disease. Maralixibat demonstrated significant improvements in sBA, pruritus, xanthomas, height, and quality of life, as well as other important disease measures in children with Alagille syndrome. Maralixibat might represent an important new treatment option for the management of underlying cholestasis in Alagille syndrome, improving pruritus, xanthomas, and height growth.

Pruritus is the main clinical expression of many paediatric and adult cholestatic diseases. In children with Alagille syndrome and progressive familial intrahepatic cholestasis (PFIC), as well as in adults with primary sclerosing cholangitis (PSC), and primary biliary cirrhosis (PBC), pruritus is a major burden and impacts quality of life. Elevated levels of sBA are a biological hallmark of these conditions and considered to contribute to pruritus, although the precise mechanism for this has not been fully elucidated.[7] In addition, the assessment of pruritus in clinical trials has been complicated by the symptom's subjective nature, the presence of placebo effect, and the absence of well validated tools or biomarkers.

By pharmacologically blocking the entry of bile acids into enterocytes, ASBT inhibitors inhibit the enterohepatic recirculation and increase the excretion of faecal bile acids, reducing the level of circulating sBA (appendix p 9). This reduces the activation of the farnesoid X receptor at both the ileal enterocytes (reducing FGF-19 portal circulation) and hepatocytes and contributes to an increase in the level of hepatic bile acid synthesis from cholesterol. Based on the above, ASBT inhibitors have been evaluated for the reduction of sBA and pruritus across a range of cholestatic conditions.[8,17] In adults with PSC and PBC, ASBT inhibition has led to improvements in cholestasis and pruritus and late-stage studies are now ongoing.[24,25] In children with PFIC, ASBT inhibitors, maralixibat, and odevixibat, have shown potential to reduce sBA, pruritus, and improve quality of life, whereas maralixibat has also demonstrated increased more than 5-year transplant-free survival.[26]

Although there has been limited study of other ASBT inhibitors in Alagille syndrome to date, two previous maralixibat studies in paediatric Alagille syndrome involved 13-week, parallel, placebo-controlled assessment of doses up to 266 µg/kg once per day and long-term extension (NCT02057692, NCT01903460, NCT02047318, and NCT02117713).[8,17] In these studies, trends in efficacy parameters consistent with the mechanism of action were documented, but the treatment effect did not reach statistical significance. In subsequent extension studies, clinically meaningful and statistically significant improvements in pruritus, quality of life, and growth have been observed.[19,27]

ICONIC used a longer treatment duration and higher doses of maralixibat (up to 380 µg/kg once or twice per day) than previous maralixibat Alagille syndrome studies. With this approach, clinically meaningful improvements in pruritus (ItchRO[Obs]) were achieved by week 3 of treatment, with mean ItchRO(Obs) reductions reaching –1·6 (95% CI –2·1 to –1·1) at week 48 and –2·3 (–2·9 to –1·7) in the 15 participants continuing to week 204. During the first 48 weeks, 21 (75%) of 28 participants reported an ItchRO(Obs) score of 1 or lower for at least one timepoint. The number of patients who had minimal to no itch (an absolute ItchRO[Obs] score 1 or lower) was 12 (43%) of 28 at week 48 and 14 (93%) of 15 at week 204. These observer-rated effects are supported by similar results collected from both participants (ItchRO[Pt]) and clinicians (CSS). In this study, the placebo effect observed in previous studies was controlled by the RWD, with those participants remaining on maralixibat in the placebo-controlled period experiencing no change in treatment effect.[25]

The pruritus results were mirrored by reductions in sBA levels, including a separation in sBA between the different treatment groups during the placebo-controlled RWD. Effects appear to be similar across participants identified as responders within the first 18 weeks (primary endpoint population) and the total study population. In line with the mechanism of action of maralixibat, xanthomas, which might impact quality of life in patients with Alagille syndrome,[6] were significantly improved over the course of the study, reducing the burden of a disfiguring, sometimes painful, and occasionally disabling hallmark of Alagille syndrome. This improvement is probably explained by the significant reduction in cholesterol secondary to increased primary bile acid synthesis (elevated sterol-C4) observed in this study. Although in previous cross-sectional analyses absolute sBA values have correlated poorly with absolute pruritus levels,[27] in this long-term prospective study the decrease in sBA was associated with a decrease in ItchRO(Obs).[28]

The treatment effects of maralixibat on pruritus, sBA, xanthomas, and quality of life was maintained during the 4-year observation period. The sustained benefit of maralixibat is meaningful for patients and families who suffer from debilitating pruritus, xanthomas, and impaired quality of life. There is also important benefit beyond this, because these symptoms are key drivers of liver transplantation, suggesting maralixibat might have the potential to delay or avoid liver transplantation in some patients or improve quality of life in individuals who cannot undergo transplantation because of severe cardiac or vascular malformations.[18]

Pruritus is the primary measure of patient benefit in ICONIC. 84% of participants saw clinically meaningful improvements in pruritus with once per day dosing. During the long-term extension, participants with insufficient pruritus response or sBA more than ULN were increased to twice per day maralixibat doses to explore the efficacy and safety of higher maralixibat doses. Our findings indicate that some participants had additional symptomatic improvement in the long-term extension. However, interpretations of the uncontrolled, open-label efficacy and safety data obtained during this period of twice per day dosing require caution and warrant additional study to adequately assess the risk–benefit balance.

Chronic use of maralixibat was generally safe and well tolerated. As expected for a minimally absorbed drug, the most common treatment emergent adverse events were diarrhoea, vomiting, and abdominal pain. These events resolved without any need for action; the majority occurred within the first 4 weeks of treatment and lasted less than 1 week. Long-term safety at higher total dosing (380 µg/kg twice per day) was well tolerated, suggesting a broad therapeutic margin in the sample of 15. Furthermore, unlike bile acid-binding resins,[29] Alagille syndrome-associated, fat-soluble vitamin deficiencies did not worsen during long-term maralixibat treatment.

Over the whole cohort, there was little change in alanine aminotransferase for approximately the first 120 weeks of ICONIC. After this period, a rise of approximately 50 U/L was identified. In the long-term extension, alanine aminotransferase elevations led one participant to discontinue maralixibat (due to prespecified stopping criteria) and two further participants to reduce dose (with no clinical sequelae). These elevations were isolated, asymptomatic, transient, and without indicators of drug-induced liver injury. Although we cannot exclude that these alanine aminotransferase changes might be related to treatment, the changes are within the range of fluctuations observed in the natural history of Alagille syndrome[15] and similar to changes described after biliary diversion surgery.[12,15,21] In ICONIC, isolated alanine aminotransferase fluctuations occurred while serum gamma-glutamyl transferase levels remained stable and total and direct measures of bilirubin decreased over time.

Limitations of this study include the duration of the placebo-controlled period, which was 4 weeks and limits the robustness of the placebo-controlled safety assessment, and the absence of adjustment for multiple comparisons. However, the 4-year treatment duration described here is supportive of maralixibat's safety and tolerability and includes no change in profile in those treated twice per day for more than 2 years. The efficacy of the twice per day dosing regimen could not be robustly assessed due to the open-label nature of the study, limited sample size, and known potential confounders (eg, previous treatment effect on once per day dosing and selection bias). Natural history data indicate that the sBA and pruritus reduction observed in this study do not usually occur spontaneously in Alagille syndrome.[8]

In conclusion, maralixibat is the first agent to demonstrate life-changing treatment benefit across a range of clinically relevant parameters in patients with Alagille syndrome. ICONIC demonstrated that maralixibat 380 µg/kg once per day safely improved the key burden of Alagille syndrome liver disease, including cholestasis (sBA), pruritus, xanthomas, growth, and quality of life. This response profile was durable over the 204-week period reported here. Patients with Alagille syndrome currently have no approved pharmacological treatment options and refractory pruritus is frequently addressed with liver transplantation. Maralixibat has the potential to provide a new treatment paradigm for patients with Alagille syndrome, with the potential to improve quality of life and delay or eliminate the need for liver transplantation. Future studies, including long-term evaluations or phase 3 trials, might further document the potential for long-term treatment benefit, including transplant-free survival.

Contributors

All authors contributed to data collection, analysis, interpretation, and the writing and review of the manuscript. EG, EJ, CK, and AD also contributed to the design of the study. EG, EJ, PV, AJW, WG, and JS had access to and verified the data, and were responsible for the decision to submit the manuscript. All authors confirm the fidelity of the study to the protocol, accuracy, and completeness of data, and approved

manuscript publication. The corresponding author had full access to study data and had final responsibility for manuscript submission.

Declaration of interests

EG has received consultancy fees from Mirum Pharmaceuticals, Albireo, and Laboratoires CTRS. AB has received grants and research support from Mirum Pharmaceuticals. ES has received consultancy fees from Mirum Pharmaceuticals and Albireo, and has received travel support from Albireo. KDRS has received consultancy fees from Retrophin and Sanitarium Health and Wellbeing Company and is a stockholder in Asklepion Pharmaceuticals, Ausio Pharmaceuticals, and Aliveris. CK and TJ are shareholders in Mirum Pharmaceuticals. NKD is a stockholder in and employee of Takeda. WG, PV, and AJW are stockholders in and employees of Mirum Pharmaceuticals. EJ has received consultancy fees from Laboratoires CTRS and Vivet Therapeutics. AD was an employee and stockholder of Lumina Pharmaceuticals and has received personal fees from Shire Pharmaceuticals. EMS has received grants from Mirum Pharmaceuticals. WH, MS, LH, FL, AL, DG, and JS declare no competing interests.

Data sharing

Beginning 6 months and ending 5 years after publication, de-identified participant data for data meta-analysis might be made available to investigators whose proposed use of the data has been approved by a review committee, including the primary authors as the study funder. The study protocol will also be available via weblink. Proposals should be directed to pvig@mirumpharma.com. Before being granted access, data requesters will be required to sign a data access agreement.

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