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Summary

Background In patients with Alagille syndrome, cholestasis-associated clinical features can include high serum bile acids and severe pruritus that can necessitate liver transplantation. We aimed to evaluate the efficacy and safety of the ileal bile acid transporter inhibitor odevixibat versus placebo in patients with Alagille syndrome.

Methods The ASSERT study was a phase 3, double-blind, randomised, placebo-controlled trial that enrolled patients at 21 medical centres or hospitals in ten countries (Belgium, France, Germany, Italy, Malaysia, the Netherlands, Poland, Türkiye, the UK, and the USA). Eligible patients had a genetically confirmed diagnosis of Alagille syndrome, a history of significant pruritus, and elevated serum bile acids. Patients were randomly assigned (2:1) to receive oral odevixibat 120 µg/kg per day or placebo for 24 weeks (in a block size of six and stratified by age: <10 years and ≥10 years to <18 years) via a web-based system. Patients, clinicians, study staff, and people analysing the data were masked to treatment allocation. The primary efficacy endpoint was change in caregiver-reported scratching score (on the PRUCISION instrument; range 0–4) from baseline to weeks 21–24. The prespecified key secondary efficacy endpoint was change in serum bile acid concentration from baseline to the average of weeks 20 and 24. Outcomes were analysed in patients who received at least one dose of study drug (the full analysis set for efficacy outcomes and the safety analysis set for safety outcomes). This trial is registered on ClinicalTrials.gov (NCT04674761) and EudraCT (2020-004011-28), and is completed.

Findings Between Feb 26, 2021, and Sept 9, 2022, 52 patients were randomly assigned to receive odevixibat (n=35) or placebo (n=17), all of whom were included in the analysis sets. The median age was 5·5 years (IQR 3·2 to 8·9). 27 (52%) of 52 patients were male and 25 (48%) were female. The mean scratching score was elevated at baseline in both groups (2·8 [SD 0·5] for odevixibat *vs* 3·0 [0·6] for placebo). Mean scratching scores at weeks 21–24 were 1·1 (0·9) for odevixibat and 2·2 (1·0) for placebo, representing a least-squares (LS) mean change of –1·7 (95% CI –2·0 to –1·3) for odevixibat and –0·8 (–1·3 to –0·3) for placebo, which was significantly greater for odevixibat than for placebo (difference in LS mean change from baseline –0·9 [95% CI –1·4 to –0·3]; p=0·0024). Odevixibat also resulted in significantly greater reductions in mean serum bile acids from baseline versus placebo (237 µmol/L [SD 115] with odevixibat *vs* 246 µmol/L [121] with placebo) to the average of weeks 20 and 24 (149 µmol/L [102] *vs* 271 µmol/L [167]; LS mean change –90 µmol/L [95% CI –133 to –48] with odevixibat *vs* 22 µmol/L [–35 to 80] with placebo; difference in LS mean change –113 µmol/L [95% CI –179 to –47]; p=0·0012). The most common treatment-emergent adverse events were diarrhoea (ten [29%] of 35 patients in the odevixibat group *vs* one [6%] of 17 in the placebo group) and pyrexia (eight [23%] *vs* four [24%]). Seven patients had serious treatment-emergent adverse events during the treatment period: five (14%) in the odevixibat group and two (12%) in the placebo group. No patients discontinued treatment and there were no deaths.

Interpretation Odevixibat could be an efficacious non-surgical intervention to improve pruritus, reduce serum bile acids, and enhance the standard of care in patients with Alagille syndrome. Longer-term safety and efficacy data of odevixibat in this population are awaited from the ongoing, open-label ASSERT-EXT study.

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Introduction

Alagille syndrome is a rare, autosomal dominant, multisystem disorder caused by defects in the Notch signalling pathway that can affect development of the liver, heart, eyes, face, bones, kidneys, and vasculature.[1,2] Most patients with Alagille syndrome (>90%) have mutations in *JAG1*; a smaller proportion of patients have mutations in *NOTCH2*.[1,3] Although early epidemiological

Research in context

Evidence before this study

Alagille syndrome is a rare multisystem disorder characterised by bile duct paucity, intrahepatic cholestasis, and intractable pruritus that frequently necessitates liver transplantation. Historically, treatment options for Alagille syndrome have been limited to off-label, supportive medical therapies with insufficient efficacy and surgical intervention (eg, liver transplantation or partial external biliary diversion). On April 5, 2023, we searched MEDLINE (PubMed) for clinical trials of Alagille syndrome using the search terms "Alagille syndrome" AND "trial". No date or language restrictions were applied. We found five peer-reviewed primary articles describing a total of six studies on the efficacy and safety of ileal bile acid transporter (IBAT) inhibitors in patients with Alagille syndrome. Five studies were phase 2/2b trials of maralixibat in children with Alagille syndrome, and one study was a phase 2 trial of odevixibat in children with pruritus due to chronic cholestatic disease (including Alagille syndrome). Two studies investigating maralixibat did not meet their primary endpoints; the study investigating odevixibat showed improvements in pruritus and serum bile acids with treatment. According to our search, there have been no published phase 3 studies of IBAT inhibitors, or any other pharmacological agents, in patients with Alagille syndrome.

Added value of this study

To the best of our knowledge, ASSERT is the first and only phase 3, double-blind, randomised, placebo-controlled trial conducted in patients with Alagille syndrome to date. Data from ASSERT indicate that odevixibat can improve pruritus and reduce serum bile acids in patients with Alagille syndrome. These effects on pruritus and serum bile acids occurred rapidly and were sustained up to week 24. Most treatment-emergent adverse events with odevixibat were mild or moderate in severity and non-serious.

Implications of all the available evidence

Data from ASSERT showing reductions in pruritus and serum bile acids with odevixibat treatment suggest that odevixibat could improve the standard of care for patients with Alagille syndrome as a non-surgical intervention. An ongoing, open-label extension study (ASSERT-EXT; NCT05035030) will provide longer-term efficacy and safety data. Exploratory analyses of ASSERT-EXT data will evaluate the potential effect of odevixibat on the need for biliary diversion or liver transplantation.

data estimated the incidence of Alagille syndrome to be one in every 70 000 births, more recent data based on molecular diagnostics suggest that the incidence might be closer to one in every 30 000–50 000 births.[2,4–6]

Patients with Alagille syndrome can have abnormal development of the intrahepatic bile ducts (eg, bile duct paucity), which can impair bile flow, lead to the accumulation of biliary components in the liver with secondary spillover into the systemic circulation, and cause unremitting pruritus and liver damage that can progress to end-stage liver disease.[2,7,8] Pruritus, which was reported in 761 (74%) of 1028 children with Alagille syndrome in the multicentre GALA cohort study, typically presents within the first 2 years of life and is commonly associated with skin excoriation, sleep problems, and mood disturbances.[2,9] Pruritus is one of the most common primary indications for liver transplantation in patients with Alagille syndrome; the LOGIC study, which investigates genetic causes of intrahepatic cholestasis, including Alagille syndrome, and the GALA study found that only 24–40% of patients with Alagille syndrome and a history of neonatal cholestasis reach adulthood with their native liver.[3,9]

The clinical presentation of Alagille syndrome is heterogeneous and varies in severity in individual patients.[1,8] In addition to cholestasis and pruritus, other presenting symptoms and characteristic features of Alagille syndrome include jaundice, elevated bile acids and hepatic biochemical parameters, cardiovascular abnormalities, xanthomas, and fat-soluble vitamin deficiencies.[1,8] Elevations in serum bile acids are likely to reflect increased hepatic bile acids due to bile flow impedance and might be a useful prognostic marker.[7,10,11] For example, in patients with cholestatic liver disease, reductions in serum bile acids after surgical intervention have been associated with prolonged native liver survival.[11–14]

Historically, pharmacological treatments for Alagille syndrome (eg, ursodeoxycholic acid, colestyramine, rifampicin, and naltrexone) have been prescribed off-label and targeted symptoms of disease (eg, pruritus).[15] As liver disease progresses and symptoms no longer respond to supportive therapies, patients can pursue surgical treatment options such as biliary diversion or liver transplantation.[7,16] However, these options are invasive, costly, and associated with postoperative complications and the need for lifelong immunosuppression.[7,17] Pruritus can also persist after surgery in some patients.[16,18,19]

Odevixibat is a potent, selective inhibitor of the ileal bile acid transporter (IBAT; also known as the apical sodium-dependent bile acid transporter [ASBT]) in development for the treatment of cholestatic liver diseases.[7] IBAT mediates reabsorption of intestinal bile acids from the ileum back to the liver; inhibition of IBAT interrupts the enterohepatic circulation and increases the faecal disposal of bile acids.[7,20] Accordingly, odevixibat has the potential to reduce systemic bile acid accumulation resulting from cholestasis and thus relieve pruritus, improve liver function, and modify the progression of liver disease in Alagille syndrome without surgical intervention.

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In 2021, odevixibat was approved in the USA for the treatment of pruritus in patients aged 3 months or older with progressive familial intrahepatic cholestasis and in the EU for the treatment of progressive familial intrahepatic cholestasis in patients aged 6 months or older.[21,22] In 2023, odevixibat was also approved in the USA for the treatment of cholestatic pruritus in patients aged 12 months or older with Alagille syndrome.[22] The approval of odevixibat in patients with Alagille syndrome was based on data from the 24-week pivotal study described herein, which aimed to evaluate the efficacy and safety of odevixibat for the treatment of pruritus in patients with Alagille syndrome.

Methods

Study design and participants

The Alagille Syndrome Safety and Efficacy Randomised Trial (ASSERT) was a phase 3, double-blind, randomised, placebo-controlled trial initiated at 32 medical centres or hospitals in ten countries: Belgium, France, Germany, Italy, Malaysia, the Netherlands, Poland, Türkiye, the UK, and the USA (see the appendix p 6 for the full list of investigators and study sites that enrolled patients; patients who were eligible as per the study inclusion and exclusion criteria were only enrolled from a total of 21 sites). The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation guidelines for Good Clinical Practice, and local requirements, as applicable. Research protocols and amendments were approved by relevant institutional review boards or ethics committees at each site. Patients (or their caregivers) provided written informed consent before enrolment. The protocol can be found online.

See Online for appendix

For the **protocol** see https://cdn.clinicaltrials.gov/large-docs/61/NCT04674761/Prot_000.pdf

Individuals of any age with a genetically confirmed diagnosis of Alagille syndrome (ie, a documented mutation in *JAG1* or *NOTCH2*), a history of significant pruritus as determined by the investigator, an average observer-reported scratching score or a patient-reported pruritus score for those aged 18 years and older (not reported since no patients aged ≥18 years were enrolled), of 2 or more, as measured by the PRUCISION instrument,[23] in the 14 days before randomisation, and elevated serum bile acid concentrations (ie, greater than the upper limit of normal [ULN] by patient age) at both screening visits were eligible for inclusion. The primary analysis population was prespecified to comprise patients younger than 18 years; the study protocol also allowed for inclusion of an exploratory cohort of patients aged at least 18 years, although no patients aged 18 years or older were enrolled.

We excluded patients with a past medical history or the ongoing presence of other types of liver diseases, including biliary atresia and progressive familial intrahepatic cholestasis. Patients with an international normalised ratio (INR) higher than 1·4 at screening (patients could be treated with vitamin K intravenously, and if their INR was ≤1·4 at resampling during screening, they could be randomly assigned), a serum alanine aminotransferase (ALT) greater than ten times the ULN at screening, a serum ALT greater than 15 times the ULN at any timepoint during the past 6 months (unless an alternative cause was confirmed), or a total bilirubin of more than 15 times the ULN at screening were excluded. Additional exclusion criteria are provided in the appendix (p 2).

Randomisation and masking

Site investigators screened patients for eligibility and enrolled patients at their respective medical centres or hospitals. Patients younger than 18 years were randomly assigned (2:1) to odevixibat or placebo by an interactive web response system. The randomisation codes were computer-generated by a masked biostatistician (Firma Clinical Research, Chicago, IL, USA) and kept by a second, unmasked biostatistician independent from the project team. Central randomisation was done in a block size of six and stratified according to patient age group (<10 years and ≥10 years to <18 years); this stratification factor was chosen because a higher prevalence and severity of pruritus have been shown in children younger than 10 years compared with older patients with Alagille syndrome.[3] Randomisation codes were assigned sequentially as patients became eligible for randomisation. Dispensing of the study drug was coordinated by the interactive web response system. Specifically, the interactive web response system assigned study drug numbers corresponding to the randomisation group at each dispensing visit. A five-digit study drug number identified study drug packs and was detailed on the study drug label. A separate randomisation scheme would be provided for the cohort of patients aged 18 years or older, who were also to be randomly assigned 2:1 to odevixibat or placebo.

Patients, clinicians, and study staff, including those analysing the data, were masked to treatment allocation, and masking was maintained until all patients had completed the study. To ensure masking of treatment assignment, the study drug and placebo were identical in appearance and filling weight.

Procedures

The study included a screening period of up to 56 days followed by a 24-week treatment period (figure 1A). Demographic information, including patient sex (male or female), was reported by caregivers or patients and collected during the screening period. Randomisation occurred on study day 1. Patients attended nine clinic visits during the study, including two visits during the screening period (screening visit 2 must have been separated by at least 7 days from screening visit 1 and must have occurred at least 14 days before study day 1) and visits at randomisation (study day 1), and weeks, 4, 8, 12, 16, 20, and 24. Additionally, a safety follow-up visit occurred 28 days after the week 24 visit or the date of last dose for patients who prematurely discontinued. Patients were also contacted in one scheduled telephone call on

study day 14 to review concomitant medications, monitor compliance with the electronic diary (eDiary), monitor adverse events, and complete a fat-soluble vitamin deficiency questionnaire. Patients who completed the treatment period could either enrol in the open-label extension study (ASSERT-EXT; NCT05035030) or attend the safety follow-up visit.

From the first day of screening to the last day of the treatment period, bile acid-binding or lipid-binding resins and medications that slow gastrointestinal motility were not permitted. Medications to treat pruritus, including ursodeoxycholic acid, rifampicin, or antihistamines, singularly or in combination, were allowed provided the patient was on a stable dose at least 4 weeks before enrolment and no dose change was planned during the treatment period. Patients received once-daily oral odevixibat 120 µg/kg or placebo for 24 weeks, and were instructed to take the study drug each morning as an intact capsule with water and food. For patients unable to swallow an intact capsule, the capsule could be opened and the contents sprinkled on soft, room-temperature food (eg, apple sauce); administration by this method was also to be followed by water. Selection of the odevixibat dose for this study was based on non-clinical and clinical data, including the results of a phase 1, first-in-human, dose-finding study conducted in healthy adults[24] and a phase 2 dose-finding study conducted in paediatric patients diagnosed with cholestatic pruritus.[25] In the phase 1 dose-finding study, odevixibat lowered serum bile acids in a dose-dependent manner, with a dose required to produce 50% of the maximum effect (ED_{50}) of 12·3 µg/kg and a dose required to produce 90% of the maximum effect (ED_{90}) of 111 µg/kg. In the phase 2 study, which included six patients with Alagille syndrome, there were no significant differences in the safety profiles of dose groups up to 200 µg/kg per day, and improvements in serum bile acids and pruritus were observed in most patients who received odevixibat for 4 weeks at doses of 30–200 µg/kg per day. To maximise potential for clinical efficacy in ASSERT, a dose (120 µg/kg per day [approximate ED_{90}]) was selected that was halfway between 30 µg/kg per day and 200 µg/kg per day.

Pruritus was assessed with the validated PRUCISION instrument.[23] Responses were captured twice daily (morning and evening) during the screening period and the 24-week treatment period in an eDiary, which included observer-reported outcome (ObsRO) items for observed scratching, sleep disturbance, and tiredness, and patient-reported outcome (PRO) items for itching, sleep disturbance, and tiredness (appendix pp 4–5). The ObsRO and PRO scratching, itching, and tiredness items use pictorial response scales ranging from 0 to 4; higher scores indicate worse symptoms.[23] For example, scratching severity ratings were as follows: 0=no scratching; 1=a little scratching; 2=medium scratching; 3=a lot of scratching; and 4=worst possible scratching. Caregivers of all patients completed ObsRO assessments; patients aged 8 years or older also completed PRO assessments. Caregivers and patients were instructed on use of the eDiary during screening visit 1, and daily recording of pruritus was begun at that time to confirm the magnitude of baseline pruritus symptoms. During screening visit 2, eDiary compliance was confirmed and retraining was provided if needed.

Blood samples for analysis of serum bile acid concentrations were taken at all clinic visits, including

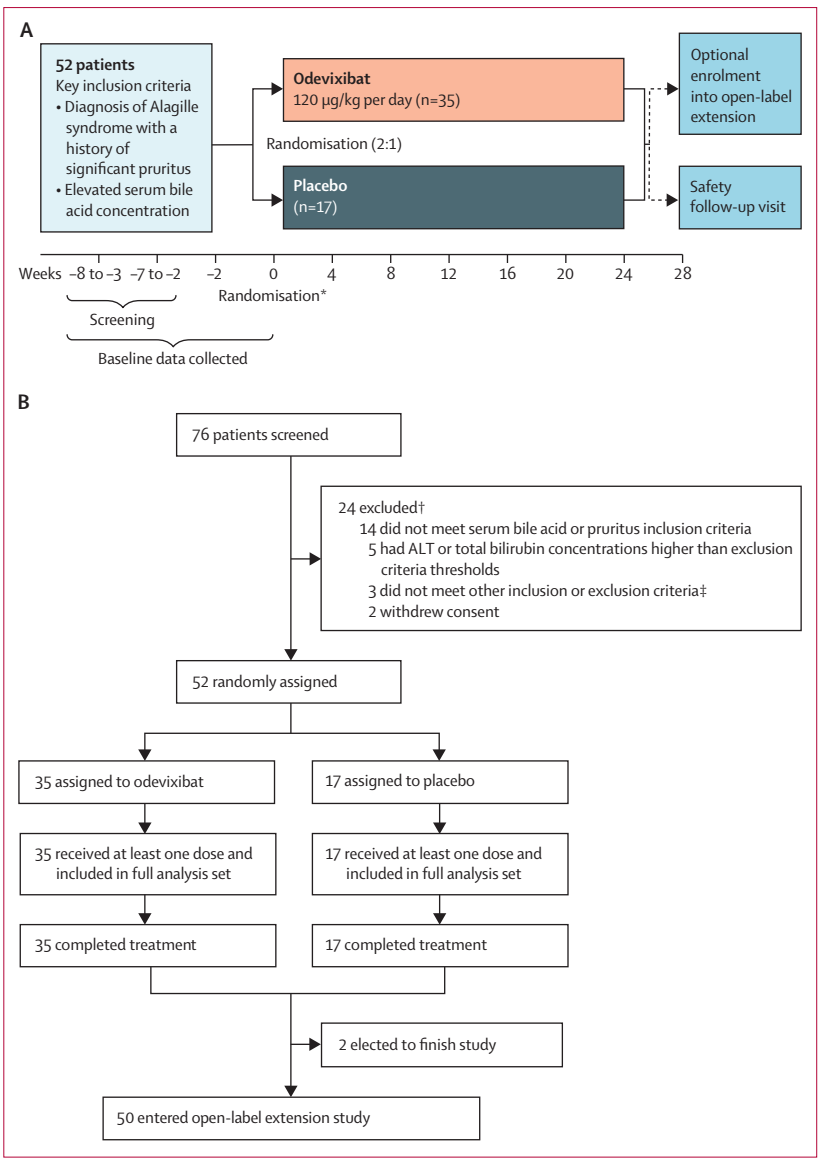

Figure 1: **ASSERT study design and trial profile**
(A) Study design. (B) Trial profile. ALT=alanine aminotransferase. *Randomisation occurred on study day 1 during week 0. †There were 27 screening failure events overall, resulting in 24 excluded patients. One patient did not successfully complete screening twice due to chronic kidney disease with a glomerular filtration rate of less than 70 mL/min per 1·73 m^2 (first screening) and failure to meet pruritus inclusion criteria (second screening); this patient subsequently met eligibility criteria (third screening) and was randomly assigned. Another patient with an ALT concentration exceeding the exclusion threshold during the first screening subsequently met eligibility criteria during a second screening and was randomly assigned. ‡Comprising issues with the electronic diary, absence of genetically confirmed diagnosis, and screening period exceeded (n=1 for each).

the safety follow-up visit, and processed by a central laboratory (PPD Global Central Labs, Highland Heights, KY, USA) with a validated commercial enzyme cycling assay (Diazyme Laboratories, Poway, CA, USA). Patients were asked to fast for at least 4 h before sample collection. Clinical laboratory parameters (eg, ALT, aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], total bilirubin, and total cholesterol) were measured at screening; at randomisation; at weeks 4, 8, 12, 16, 20, and 24; and at the safety follow-up visit. Blood samples to measure autotaxin and plasma 7α-hydroxy-4-cholesten-3-one (C4) concentrations were taken at randomisation and at weeks 12 and 24 in patients with a bodyweight of more than 10 kg.

Health-related quality of life was assessed by patients aged 5 years or older and by caregivers of patients aged 2 years or older at randomisation and at weeks 12 and 24 with the Paediatric Quality of Life Inventory (PedsQL), version 4.0. Patients aged 8 years or older, caregivers, and clinicians completed the Global Impression of Change (PGIC, CaGIC, and CGIC, respectively) and Global Impression of Symptoms (PGIS, CaGIS, and CGIS, respectively) questionnaires at randomisation (GIS items only) and at weeks 4, 12, and 24 (both GIS and GIC items). The GIC items were used to assess change in itch (PGIC), scratching (CaGIC, CGIC), and sleep (all versions) since starting the study by use of a 7-point scale ranging from 1 (very much better) to 7 (very much worse). The GIS items were used to assess the severity of itch (PGIS), scratching (CaGIS, CGIS), and sleep (all versions) in the past week by use of a 5-point scale ranging from 1 (none) to 5 (very bad or very severe). At the week 24 assessment, an exit interview was conducted with patients aged 8 years or older and caregivers. The exit interview included two yes or no questions and an open-ended question (appendix p 7).

Clinicians completed the Clinician Xanthoma Scale at randomisation and at weeks 12 and 24. This instrument assesses xanthomatosis on a 5-point scale (0 denotes no evidence of xanthomatosis; 1 denotes fewer than 20 scattered individual lesions that do not interfere with or limit activities; 2 denotes more than 20 lesions that do not interfere with or limit activities; 3 denotes large number of lesions that cause distortion of the face or limbs due to excess size or number; 4 denotes xanthomas that interfere with function [eg, hand use and ability to walk] because of excess size or number).

Safety assessments included monitoring of adverse events (monitored from the first dose of the study drug) and serious adverse events (monitored from signing of informed consent) until the last planned study visit or 28 calendar days after the last dose of the study drug, whichever occurred later. Other safety assessments included physical examinations, vital signs, laboratory test results, and ultrasound of the liver and spleen.

Per the clinical opinion of the investigator, the dose of study drug could be reduced to 40 μg/kg per day to manage adverse events. Treatment was to be interrupted if a patient developed clinically significant diarrhoea, defined as diarrhoea with at least one of the following: grossly bloody stools; vomiting; dehydration requiring treatment with oral or intravenous rehydration or for electrolyte imbalances, or both; fever (≥38°C); or if the diarrhoea persisted for 7 or more days. If the symptoms resolved, the patient could restart treatment. If clinically significant diarrhoea reoccurred within 1 week with no alternative cause, the dose of study drug could be reduced to 40 μg/kg per day; if clinically significant diarrhoea persisted at the lower dose, the patient would be discontinued from the study, with follow-up by the investigator until resolution or stabilisation of the event. There were six liver monitoring criteria triggering drug interruption (appendix p 2). If the study drug was interrupted for any liver-related criterion, a patient received additional monitoring, including assessment for drug-induced liver injury (see the appendix p 3 for more details on review of any cases of suspected drug-induced liver injury).

Patients could be removed from the study in the following circumstances: patient or caregiver desire for withdrawal for any reason; loss to follow-up; a safety or tolerability issue (ie, an adverse event that, in the opinion of the investigator, necessitated treatment discontinuation; a grade 3 or higher event deemed possibly or probably related to the study drug by the investigator; a grade 4 event regardless of attribution of study drug; or patient or caregiver estimation of intolerable symptoms); safety, behaviour, or non-compliance with study procedures; treatment unblinding; or an investigator's opinion that continuing the patient in the study was no longer appropriate.

Outcomes

The primary efficacy endpoint was change from baseline to month 6 (ie, weeks 21–24) in averaged morning and evening ObsRO caregiver scratching scores. The key secondary efficacy endpoint was change from baseline to the average of weeks 20 and 24 in serum bile acid concentrations. Data related to both outcomes were centrally assessed.

Additional secondary endpoints were the proportion of patients with a clinically meaningful decrease in ObsRO scratching score; change from baseline to weeks 21–24 in PRO itching score; change from baseline to week 24 in ObsRO scratching and PRO itching scores for morning and evening assessments overall and by patient age group (0 to <8 years, 8 to <12 years, 12 to <18 years, and ≥18 years); change from baseline to weeks 21–24 in sleep parameters (eg, tiredness, number of awakenings; measured by ObsRO and PRO instruments); assessment of GIS items from baseline to weeks 4, 12, and 24, and assessment of GIC items at weeks 4, 12, and 24; change

from baseline to week 24 in PedsQL subdomain scores, xanthomatosis (Clinician Xanthoma Scale), and hepatic parameters (ALT, AST, GGT, and total bilirubin); change from baseline through to week 24 in serum bile acid concentrations; change from baseline to week 24 in biochemical markers and measures of bile acid synthesis (autotaxin and C4, in patients with a bodyweight of >10 kg only) and total cholesterol; and patient impression of treatment effect as recorded during exit interviews. As the number of patients who completed the exit survey was relatively low, we added a post-hoc outcome of caregiver impression of treatment effect, as recorded by the exit interview. Although the secondary outcome of the proportion of patients with a clinically meaningful decrease in PRO itching score was also specified in the protocol, the small number of available PRO itching assessments precluded ascertainment of a threshold for clinically meaningful change; therefore, this secondary outcome could not be assessed (appendix p 2).

Safety analyses were based on the incidence of treatment-emergent adverse events. Treatment-emergent adverse events were categorised by causality, severity (Common Terminology Criteria for Adverse Events version 5.0), and seriousness for odevixibat and placebo.

Statistical analysis

The initial target sample size was 45 patients younger than 18 years to yield approximately 36 completers, assuming a dropout rate of 20%. At a one-sided significance level of 0·025, assuming a pooled SD of 1·0 and a difference between the treatment groups of 1·2 in mean change from baseline in ObsRO scratching score (favouring the experimental treatment), the power of the study was 0·909, using the exact method. The key secondary endpoint was also powered for a standardised treatment effect of 1·2.

A planned sample size re-estimation was performed by an independent masked statistician after 18 patients (17 patients with non-missing values) had completed the week 16 visit. Based on blinded data, the observed SD of the change from baseline to weeks 13–16 and weeks 21–24 (pooled data) in average monthly ObsRO scratching score was 1·11, and the sample size was increased to yield approximately 48 completers. Given the low actual dropout rate at that time (0%), the assumed study dropout rate was reduced to approximately 8% and the target sample size was increased by seven patients to total 52 patients. The number of patients aged 18 years or older was not to exceed 18 in total.

The full analysis set was the primary analysis set for efficacy analyses and comprised all randomly assigned patients who received at least one dose of study drug; patients in the full analysis set were analysed in the treatment group that they were randomly assigned, even if they received the incorrect study drug. The safety analysis set comprised all patients who received at least one dose of study drug; patients in the safety analysis set were analysed according to the treatment they actually received at first dose.

The primary efficacy endpoint and key secondary efficacy endpoint were analysed with a mixed-effects model for repeated measures (MMRM), with baseline data as a covariate (ie, scratching score or serum bile acid concentration), baseline age stratification, baseline direct bilirubin (for scratching score only), treatment group, time (in months), and treatment-by-time interaction as fixed effects and an unstructured covariance matrix between timepoints. MMRM was used to compare treatment effects at month 6 (weeks 21–24) and at each 1-week or 4-week interval up to month 6. For the primary endpoint (scratching score), the primary analysis was the difference in the least-squares (LS) mean change from baseline to month 6 (weeks 21–24) between odevixibat and placebo. For the key secondary endpoint (serum bile acid concentration), the primary analysis was the treatment difference in LS mean change from baseline to the average of week 20 and week 24. Statistical testing of the primary endpoint was done with a one-sided type I error rate of 0·025; the key secondary endpoint was to be assessed for significance only if the primary endpoint was met. All p values reported herein are two-sided. Prespecified sensitivity, supplementary, and subgroup (by baseline demographics and clinical characteristics) analyses were conducted for the primary and key secondary endpoints (appendix p 3). A Pearson correlation analysis was used to evaluate the relationship between the primary endpoint and the key secondary endpoint.

Baseline pruritus scores were calculated by averaging the two baseline morning weekly scores, the two baseline evening weekly scores, or the average of the morning and evening weekly scores in the 14 days preceding the start of treatment. Post-baseline monthly (28 days) morning, evening, or overall (average of morning and evening) scores were calculated by averaging the four weekly scores within the 4-week interval (eg, for the primary endpoint, weeks 21–24). Weekly scores were calculated by averaging the average of morning scores and the average of evening scores in a week.

MMRM was used as the primary analysis methodology for additional efficacy variables for which change from baseline was assessed; these models included the baseline value of the response variable, baseline age stratification, baseline direct bilirubin (for change in itching and scratching scores), treatment group, visit or time (in weeks or months), and treatment-by-visit interaction as fixed effects. The proportion of patients with a clinically meaningful decrease in ObsRO scratching score at weeks 21–24 (ie, pruritus response; defined in a blinded psychometric analysis as a 1·5-point decrease [primary analysis] or a 1-point decrease [sensitivity analysis] in ObsRO scratching score; appendix p 2) was analysed with Cochran–Mantel–Haenszel tests stratified by baseline age stratum. The proportion of patients with a clinically meaningful decrease using the 1-point threshold from

baseline in average weekly pruritus score during any week within the 24-week treatment period was computed for each treatment group in a post-hoc analysis. Changes in pruritus and sleep based on the GIC considered three categories (better, no change, or worse) and were analysed with a proportional odds model, with baseline GIS score and treatment group as covariates. When testing the additional secondary efficacy variables, no alpha adjustments were done for multiple comparisons.

The estimand strategy for efficacy endpoints was to include all data collected through to the end of the study except for those collected following intercurrent events of surgical biliary diversion or liver transplantation.

	Placebo (n=17)	Odevixibat (n=35)
Median age, years	4·2 (1·5–9·2)	6·1 (3·4–8·8)
Age category 1		
<2 years	5 (29%)	3 (9%)
≥2 to <12 years	11 (65%)	28 (80%)
≥12 to <18 years	1 (6%)	4 (11%)
Age category 2 (stratification groups)		
<10 years	13 (76%)	29 (83%)
≥10 to <18 years	4 (24%)	6 (17%)
Sex		
Male	6 (35%)	21 (60%)
Female	11 (65%)	14 (40%)
Race		
White	13 (76%)	30 (86%)
Black or African American	2 (12%)	2 (6%)
Asian	1 (6%)	2 (6%)
Other	1 (6%)	1 (3%)
Ethnicity		
Hispanic or Latinx	1 (6%)	1 (3%)
Not Hispanic or Latinx	14 (82%)	30 (86%)
Not reported	2 (12%)	4 (11%)
Genetic testing		
JAG1 mutation	16 (94%)	32 (91%)
NOTCH2 mutation	1 (6%)	3 (9%)
Use of UDCA	16 (94%)	30 (86%)
Use of antipruritic medication	17 (100%)	34 (97%)
Mean serum bile acids, µmol/L	246 (121)	237 (115)
Mean scratching score	3·0 (0·6)	2·8 (0·5)
Mean serum ALT, U/L	149 (84)	186 (83)
Mean serum AST, U/L	161 (91)	170 (81)
Mean total serum bilirubin, µmol/L	62 (57)	52 (43)
Mean cholesterol, mmol/L	9·2 (4·8)	8·0 (2·0)
Presence of xanthomas	2 (12%)*	9 (26%)†

Data are median (IQR), mean (SD), or n (%). Additional baseline values are provided in the appendix (pp 13–17, 19, 21). ALT=alanine aminotransferase. AST=aspartate aminotransferase. UDCA=ursodeoxycholic acid. *Including two patients with Clinician Xanthoma Scale scores of 2 and 3, respectively. †Including seven patients with Clinician Xanthoma Scale scores of 1, one patient with a score of 2, and one patient with a score of 3.

Table 1: **Patient demographics and baseline characteristics**

Safety data were summarised descriptively. Treatment-emergent adverse events were coded with the Medical Dictionary for Regulatory Activities (version 25.0). A data and safety monitoring board periodically reviewed study data to make recommendations about patient safety, and an independent Hepatic Safety Adjudication Committee was formed to review any hepatic events that occurred during the study (appendix p 3).

The statistical analysis plan was finalised before database lock and analysis. All statistical analyses were done with SAS, version 9.4 or higher. This study is registered with ClinicalTrials.gov (NCT04674761) and EudraCT (2020-004011-28).

Role of the funding source

Albireo Pharma, an Ipsen company, had input into the study design, data collection, data analysis, data interpretation, writing of the report, and in the decision to submit for publication.

Results

Between Feb 26, 2021, and Sept 9, 2022, 52 patients were randomly assigned to receive odevixibat 120 µg/kg per day (n=35) or placebo (n=17; figure 1B). All 52 (100%) patients received their assigned treatment and completed the 24-week treatment period, meaning all 52 patients were included in the full analysis and safety analysis sets (the same for this study). Overall, 50 (96%) of the 52 patients chose to enter the open-label extension study.

Patient demographics and baseline characteristics were generally similar across treatment groups (table 1). The median age was 5·5 years (IQR 3·2–8·9); a smaller proportion of patients in the odevixibat group were younger than 2 years (three [9%] of 35) compared with the placebo group (five [29%] of 17). Mean baseline values for serum bile acids, liver enzymes, total bilirubin, and cholesterol were elevated in both treatment groups, consistent with cholestasis. Most patients in both treatment groups were receiving ursodeoxycholic acid, other antipruritic medications, or both, at baseline; the mean per-patient average daily dose of ursodeoxycholic acid at baseline was 321 mg/day (SD 167) in the odevixibat group and 340 mg/day (193) in the placebo group. No patients had previously received treatment with an IBAT inhibitor. Only one patient (age at baseline 8·8 years) had previously received surgical biliary diversion; this patient was randomly assigned to odevixibat and had undergone surgical biliary diversion 6·6 years before the study.

Among the nine patients in the odevixibat group and four patients in the placebo group who had protocol deviations related to concomitant or prohibited medications, only one patient in the odevixibat group had a protocol deviation related to a prohibited antipruritic medication. This patient was receiving colestyramine (a bile acid-binding resin) at a stable dose for 11 months before study entry that was not reported before

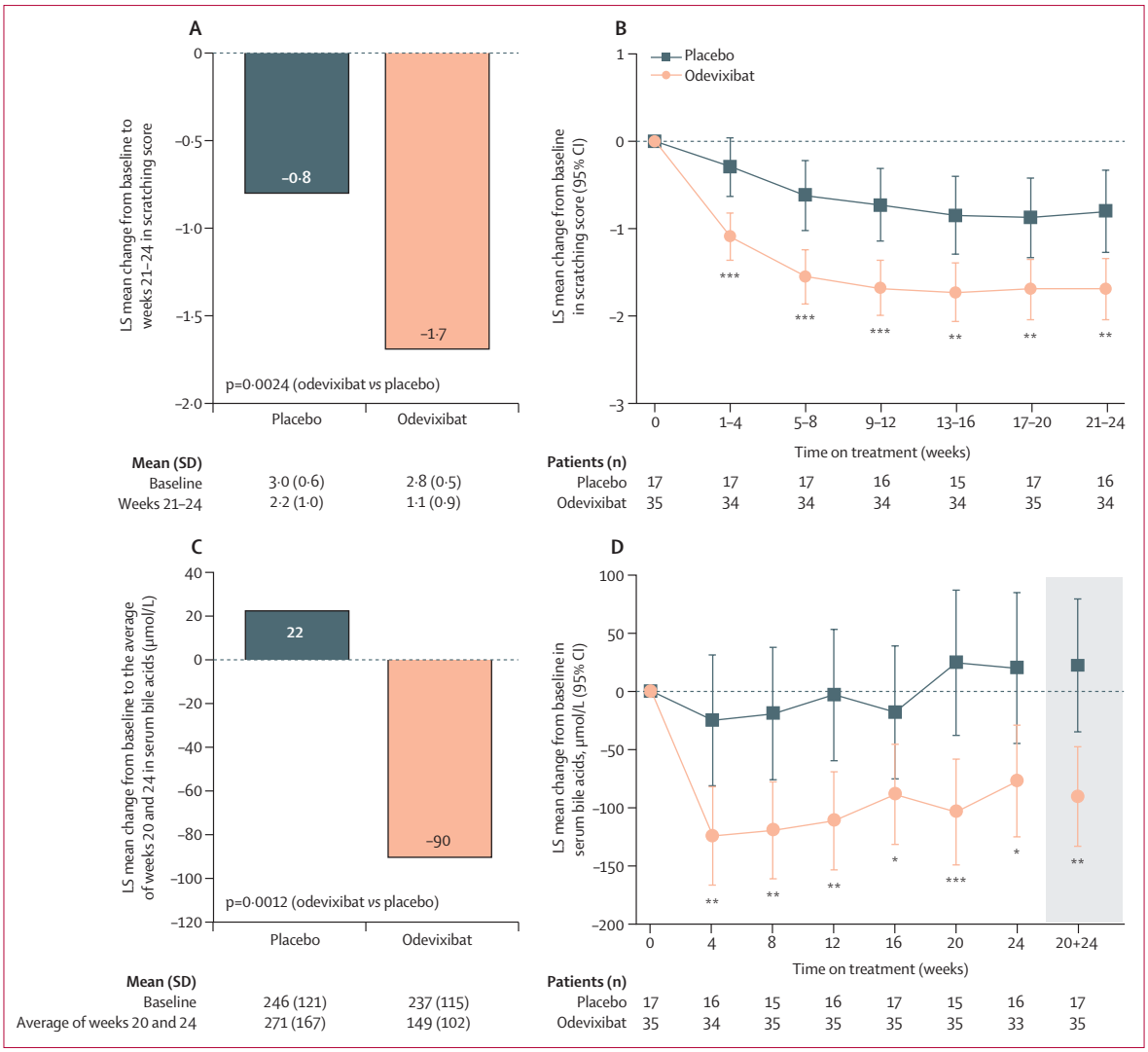

Figure 2: **ObsRO scratching score and serum bile acids**
Effect of odevixibat treatment on ObsRO scratching score (A, B) and serum bile acid concentrations (C, D). The corresponding error bars for panels A and C are shown on the last data points in panels B and D. p value comparison is for the difference in LS mean change from baseline between groups at each timepoint. LS=least-squares. ObsRO=observer-reported outcome. *p>0·01 and ≤0·05. **p>0·001 and ≤0·01. ***p≤0·001.

randomisation. Because this patient met all other entry criteria, the patient was permitted to remain in the study, and the dose of colestyramine was stable throughout the treatment period (the full list of concomitant medications in each treatment group is provided in the appendix pp 8–10).

The study met its primary and key secondary endpoints. Treatment with odevixibat for 24 weeks led to a significant improvement in pruritus based on the PRUCISION instrument: the LS mean change from baseline to weeks 21–24 in ObsRO scratching score was –1·7 (95% CI –2·0 to –1·3) with odevixibat compared with –0·8 (–1·3 to –0·3) with placebo. The difference in LS mean change from baseline to weeks 21–24 between groups was in favour of odevixibat (–0·9 [95% CI –1·4 to –0·3]; p=0·0024; figure 2A). Significant reductions in serum bile acid concentrations were also observed at the end of treatment with odevixibat versus placebo. The LS mean change from baseline to the average of weeks 20 and 24 in serum bile acid concentrations was –90 µmol/L (95% CI –133 to –48) with odevixibat compared with 22 µmol/L (–35 to 80) with placebo; the difference in LS mean change from baseline between groups was in favour of odevixibat (–113 µmol/L [95% CI –179 to –47]; p=0·0012; figure 2C). All prespecified sensitivity and supplementary analyses of the primary and key secondary endpoints confirmed these observed results (data not shown). In subgroup analyses of the primary and key secondary endpoints based on demographic characteristics (including sex; see appendix p 3 for more details), a similar efficacy of odevixibat was generally observed across patient subgroups (data not shown).

Improvements in ObsRO scratching score occurred rapidly in odevixibat-treated patients, with a non-significant difference between the odevixibat and placebo groups observed by week 1 of treatment (appendix p 11) and significant effects observed by weeks 1–4 that were sustained at each monthly interval up to weeks 21–24 (figure 2B). Serum bile acid concentrations were also significantly reduced in the odevixibat versus placebo groups by week 4 and this effect was sustained to week 24 (figure 2D). According to an analysis using a 1·5-point or greater decrease from baseline to weeks 21–24 in ObsRO scratching score as the threshold for a clinically meaningful change, a significantly higher proportion of odevixibat-treated patients had a clinically meaningful change than did patients receiving placebo (19 [54%] of 35 patients *vs* three [18%] of 17 patients, p=0·014; see appendix p 12 for results with a ≥1·0-point threshold). Furthermore, a post-hoc analysis found that 32 (91%) of 35 odevixibat-treated patients had a 1·0-point or greater decrease in scratching score from baseline at any timepoint during the study; in the placebo group, 12 (71%) of 17 patients had this decrease at any timepoint. Additional prespecified analyses of pruritus outcomes indicated that results were consistent when morning and evening assessments were considered separately, when PRO outcomes were examined in patients aged 8 years or older (although changes in PRO itching scores were not significantly different in patients receiving odevixibat compared with those receiving placebo for the small number of patients who completed PRO pruritus assessments; ie, 11 patients in the odevixibat group and five patients in the placebo group), when weekly or monthly scores were analysed, and when results were analysed in different patient age groups (appendix pp 13–14).

The correlation between ObsRO scratching scores (change from baseline to weeks 21–24) and serum bile acid concentrations (change from baseline to the average of weeks 20 and 24) was found to be low (Pearson correlation coefficient: odevixibat, *r*=0·18; placebo, *r*=0·11).

Consistent with the improvements observed in pruritus, treatment with odevixibat led to significant improvements in multiple ObsRO sleep parameters. At baseline, patients in both groups had difficulty with sleep. From baseline to weeks 21–24, LS mean change was significantly greater with odevixibat versus placebo for the proportion of days sleeping with a caregiver (odevixibat −35 percentage points [95% CI −45 to −24]; placebo −8 [−23 to 6]; difference −26 [−43 to −9]; p=0·0034), the proportion of days needing help falling asleep (odevixibat −43 [−57 to −30]; placebo −10 [−29 to 8]; difference −33 [−55 to −12]; p=0·0032), the proportion of days needing soothing (odevixibat −47 [−58 to −35]; placebo −6 [−22 to 10]; difference −40 [−59 to −22]; p<0·0001), and daytime tiredness score (odevixibat −1·1 points [95% CI −1·4 to −0·8]; placebo −0·5 [−0·9 to −0·1]; difference −0·6 [−1·1 to −0·1]; p=0·012; figure 3; appendix pp 15–16). Differences between groups in LS mean changes from baseline to weeks 21–24 were not significant for the proportion of days seeing blood due to scratching, the proportion of days taking medications to induce sleep, or the number of awakenings (figure 3; appendix pp 15–16). Additional data for ObsRO and PRO sleep parameters are presented in the appendix (pp 15–16).

Instruments assessing quality of life (ie, PedsQL) and global symptom relief (ie, GIC and GIS) also supported the efficacy of odevixibat, although changes in PedsQL total and domain scores were not significantly different in patients receiving odevixibat compared with those receiving placebo (appendix pp 17–19). For example, caregivers completing the CaGIC indicated that a higher proportion of odevixibat-treated patients had improved pruritus and sleep at week 24 relative to patients receiving placebo (pruritus: 28 [88%] of 32 patients on odevixibat *vs* six [35%] of 17 patients on placebo; sleep: 25 [78%] of 32 *vs* five [29%] of 17; appendix p 18). Based on these data, the odds of improvement versus no change or worsening in scratching at week 24 were 15 times higher for odevixibat-treated patients compared with patients receiving placebo (odds ratio [OR] 15 [95% CI 3–68]; p=0·0006). Similarly, the odds of improvement in sleep at week 24 were nine times higher for odevixibat-treated patients relative to patients receiving placebo (9 [2–35]; p=0·0016). According to a post-hoc analysis of the exit survey administered at the completion of the study, a higher proportion of caregivers in the odevixibat group reported meaningful change in the patient since the start of treatment (25 [78%] of 32 on odevixibat *vs* four [27%] of 15 on placebo; OR 10 [95% CI 2–48]; p=0·0009; appendix p 20). Although the number of patients who completed the exit survey was relatively low, patient-reported responses were consistent with caregiver-reported responses (nine [75%] of 12 patients in the odevixibat group *vs* two [50%] of four patients in the placebo group reported meaningful change since the start of treatment [OR 2·8 [95% CI 0·1–50·7]; p=0·39]; appendix p 20).

In the odevixibat group, 27 (77%) of 35 patients had no change from baseline to week 24 in xanthomas, including 25 patients who had no xanthomas at any timepoint during the study. An additional seven (20%) of 35 patients showed improvements in xanthomas with odevixibat, and one (3%) patient had an increase from 0 to 1 in the Clinician Xanthoma Scale score. In the placebo group, 14 (82%) of 17 patients had no change from baseline to week 24 in xanthomas, with all 14 having no xanthomas at any timepoint. Two (12%) of 17 patients in the placebo group showed improvements in xanthomas (the score decreased from 2 to 1 in one patient and 3 to 1 in another patient) and one (6%) patient showed worsening (the score increased from 0 to 3). Additional secondary outcomes (eg, change from baseline in hepatic parameters, biochemical markers, and markers of bile acid synthesis) are reported in the appendix (p 21).

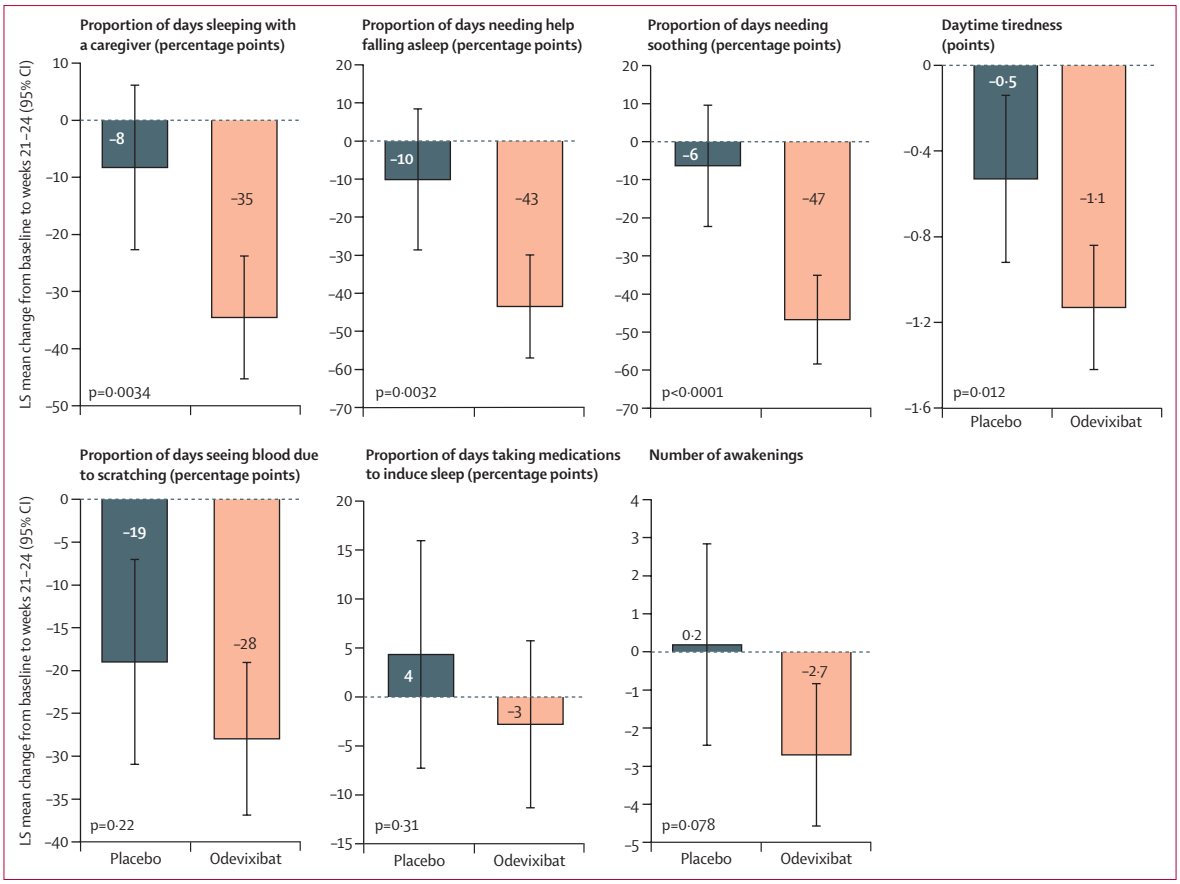

Figure 3: **Caregiver-reported change from baseline to weeks 21–24 in sleep parameters**
Baseline was calculated by averaging the two baseline weekly average scores in the 14 days preceding the start of treatment. The monthly (28-day) average score was calculated by averaging the four weekly scores within the 4-week interval. Tiredness severity ratings were as follows: 0=not tired at all; 1=a little tired; 2=medium tired; 3=very tired; and 4=very, very tired. LS=least-squares.

None of the 52 patients underwent surgical biliary diversion or liver transplantation during the study.

Overall, 26 (74%) of 35 odevixibat-treated patients had at least one treatment-emergent adverse event; a similar rate was observed in patients who received placebo (12 [71%] of 17 patients; table 2). Most treatment-emergent adverse events were mild or moderate in severity and non-serious. The most commonly reported treatment-emergent adverse events (ie, those reported in at least four odevixibat-treated patients) were diarrhoea (ten [29%] of 35 patients on odevixibat *vs* one [6%] of 17 patients on placebo), pyrexia (eight [23%] *vs* four [24%]), COVID-19 (five [14%] *vs* four [24%]), and abdominal pain (four [11%] *vs* one [6%]). All reports of diarrhoea were grade 1 in severity and non-serious; none led to treatment interruption or discontinuation. Seven patients had serious treatment-emergent adverse events during the treatment period: five (14%) of 35 in the odevixibat group and two (12%) of 17 in the placebo group (table 2). None of the serious treatment-emergent adverse events led to discontinuation of treatment or dose reductions.

A temporary dose reduction from 120 µg/kg per day to 40 µg/kg per day was reported in one patient in the odevixibat group. On the second day of treatment, this patient had non-serious, grade 1 treatment-emergent adverse events of nausea and vomiting, and the odevixibat dose was reduced to 40 µg/kg per day. On day 57, the odevixibat dose was increased to 120 µg/kg per day, which the patient received until week 24 without recurrence of nausea and vomiting.

Three (9%) of 35 odevixibat-treated patients had a treatment-emergent adverse event of haematoma; all were considered to be due to trauma and assessed as being unrelated to the study drug by investigators. Two (6%) odevixibat-treated patients had a treatment-emergent adverse event of decreased bodyweight; these events were considered mild in severity and resolved without changes in odevixibat dosing or interruption in treatment. Both patients with decreased bodyweight were enrolled at the study site in Malaysia and had a 0·2 kg decrease in bodyweight (from 11·6 kg [Z score −1·8] at baseline to 11·4 kg [−2·0] at week 4 in one patient and from 13·6 kg [−1·9] at baseline to 13·4 kg [−2·5] at week 20 in the other patient). At week 24, both had gained bodyweight relative to baseline (weighing 12·6 kg [Z score −1·5] and 14·0 kg [−2·1], respectively).

	Placebo (n=17)	Odevixibat (n=35)
Any treatment-emergent adverse event	12 (71%)	26 (74%)
Mild (grade 1)	7 (41%)	11 (31%)
Moderate (grade 2)	3 (18%)	10 (29%)
Severe (grade 3)	2 (12%)	5 (14%)
Drug-related treatment-emergent adverse events	3 (18%)	8 (23%)
Serious treatment-emergent adverse events	2 (12%)	5 (14%)
Drug-related serious treatment-emergent adverse events	0	1 (3%)
Treatment-emergent adverse events leading to discontinuation	0	0
Treatment-emergent adverse events occurring in ≥2 patients in either group, by preferred term		
Diarrhoea*	1 (6%)	10 (29%)
Pyrexia†	4 (24%)	8 (23%)
COVID-19‡	4 (24%)	5 (14%)
Abdominal pain*	1 (6%)	4 (11%)
Upper respiratory tract infection‡	2 (12%)	3 (9%)
Cough§	1 (6%)	3 (9%)
Respiratory tract infection‡	1 (6%)	3 (9%)
Bronchitis‡	0	3 (9%)
Haematoma¶	0	3 (9%)
Vomiting*	1 (6%)	2 (6%)
Asthenia†	0	2 (6%)
Conjunctivitis‡	0	2 (6%)
Gastroenteritis‡	0	2 (6%)
Nasopharyngitis‡	1 (6%)	2 (6%)
Decreased bodyweight‖	0	2 (6%)
Increased INR‖	2 (12%)	1 (3%)
Epistaxis§	2 (12%)	0
Drug-related treatment-emergent adverse events, by preferred term		
Diarrhoea*	1 (6%)	4 (11%)
Vomiting*	0	2 (6%)
Abdominal pain*	1 (6%)	1 (3%)
Increased hepatic enzymes‖	1 (6%)	1 (3%)
Increased INR‖	1 (6%)	1 (3%)
Upper abdominal pain *	0	1 (3%)
Faeces discoloured*	0	1 (3%)
Frequent bowel movements*	0	1 (3%)
Haematemesis*	0	1 (3%)
Nausea*	0	1 (3%)
Increased blood triglycerides‖	0	1 (3%)
Decreased bodyweight‖	0	1 (3%)

Data are n (%). Serious treatment-emergent adverse events with odevixibat were rhinovirus infection, pneumonia, and tonsilitis (n=1 patient each); abdominal pain and constipation (n=1); haematemesis and increased INR (n=1); and with placebo these were pyrexia (n=1) and subcutaneous abscess, cerumen impaction, chronic otitis media, and adenoidal hypertrophy (n=1). INR=international normalised ratio. MedDRA=Medical Dictionary for Regulatory Activities (version 25.0). *Gastrointestinal disorders MedDRA system organ class. †General disorders and administration-site conditions MedDRA system organ class. ‡Infections and infestations MedDRA system organ class. §Respiratory, thoracic, and mediastinal disorders MedDRA system organ class. ¶Vascular disorders MedDRA system organ class. ‖Investigations MedDRA system organ class.

Table 2: **Treatment-emergent adverse events**

Eight (23%) of 35 odevixibat-treated patients and three (18%) of 17 patients receiving placebo had treatment-emergent adverse events that were considered to be related to the study drug by the investigator (table 2). Drug-related treatment-emergent adverse events in the gastrointestinal disorders system organ class were reported more in odevixibat-treated patients than in those receiving placebo; the most common drug-related treatment-emergent adverse events in this system organ class were diarrhoea (four [11%] of 35 on odevixibat *vs* one [6%] of 17 on placebo), vomiting (two [6%] *vs* zero [0%]), and abdominal pain (one [3%] *vs* one [6%]). There were no reported treatment-emergent adverse events leading to discontinuation, treatment-emergent adverse events of liver decompensation, or treatment-emergent adverse events leading to death. There were no deaths in the study. Across both treatment groups, only one patient had drug-related serious treatment-emergent adverse events, per investigator report. The patient was female, aged 3 years, treated with odevixibat, and had enteroviral gastroenteritis on day 102 of treatment. Enteroviral gastroenteritis led to vomiting and a Mallory–Weiss tear, causing grade 3 serious treatment-emergent adverse events of haematemesis and increased INR (1·7) assessed as being related to the treatment by the investigator. The treatment-emergent adverse events were responsive to vitamin K administration and resolved after 2 days with no changes to the odevixibat dose.

Two odevixibat-treated patients and one patient receiving placebo had ALT elevations of at least three times higher than baseline values without concurrent (ie, within 30 days) elevations in total bilirubin of at least two times higher than baseline. Of the two odevixibat-treated patients, one had elevated ALT and AST concentrations at baseline, and the other had normal ALT and AST concentrations at baseline but elevated concentrations during the screening period. One of these odevixibat-treated patients interrupted the study drug for 40 days because of a treatment-emergent adverse event of increased hepatic enzymes and had a return to baseline concentrations when off treatment; after restarting treatment, the patient had fluctuating aminotransferase concentrations, but all were lower than the peak observed previously and the patient had no further treatment interruptions. For the other odevixibat-treated patient, ALT and AST concentrations improved while the patient continued odevixibat without interruption, and no treatment-emergent adverse events were reported. Overall, review of the pertinent clinical and diagnostic information for the two odevixibat-treated patients suggested the occurrence of drug-induced liver injury was unlikely, and both patients completed the treatment period. The patient who received placebo had elevated ALT and AST at baseline that became elevated further during the study; concentrations were lower than baseline at the final study assessment, and treatment was not interrupted. This patient reported a

treatment-emergent adverse event of Bell's palsy during days 56 to 63 of the study.

Dose interruptions due to treatment-emergent adverse events were reported in three (9%) of 35 patients who received odevixibat. In addition to the patient described above who interrupted due to a treatment-emergent adverse event of increased hepatic enzymes, one patient in the odevixibat group interrupted treatment for 2 days due to a treatment-emergent adverse event of rhinovirus infection, and one patient interrupted treatment for 18 days due to treatment-emergent adverse events of platelet count decreased and anaemic macrocytic. None of the 17 patients who received placebo had treatment-emergent adverse events leading to treatment interruption.

Changes from baseline in vital signs were similar in the odevixibat and placebo groups. Additionally, review of haematology, coagulation, clinical chemistry, and urinalysis data did not reveal any clinically meaningful changes from baseline, with similar results observed in odevixibat-treated and placebo-treated patients. Any clinically meaningful changes in physical examination and liver and spleen ultrasound were reported as adverse events.

Discussion

To the best of our knowledge, ASSERT is the first and only phase 3, double-blind, randomised, placebo-controlled trial to be completed in patients with Alagille syndrome. In this study, odevixibat significantly improved pruritus and reduced serum bile acid concentrations relative to placebo. Consistent with these results, improvements in multiple sleep parameters were observed with odevixibat treatment. Over the 24-week treatment period, the overall incidence of treatment-emergent adverse events with odevixibat was similar to that with placebo. The treatment-emergent adverse event of diarrhoea was reported in ten (29%) of 35 patients who received odevixibat and in one (6%) of 17 patients who received placebo; all cases were mild in severity and no cases of diarrhoea led to treatment interruption or discontinuation. All patients completed the study, and 96% chose to enter into the open-label extension study.

Pruritus due to chronic cholestasis is one of the most common and debilitating symptoms of Alagille syndrome.[2,26] The results of our study showing low correlation between scratching scores and serum bile acid concentrations in both treatment groups are consistent with published work indicating that the mechanism of pruritus in cholestatic liver diseases, in particular Alagille syndrome, remains poorly understood.[27] Nevertheless, according to the multicentre, natural history GALA study, pruritus is present in 74% of children with Alagille syndrome and, along with other complications of persistent cholestasis, is one of the leading indications for liver transplantation.[9] Although liver transplantation is associated with considerable morbidity and mortality, the procedure is performed in approximately 27% of patients with Alagille syndrome by 5 years of age and in 50% of patients by 18 years of age.[9,28] The wide-ranging effects of pruritus also include poor sleep and impaired quality of life in patients and caregivers alike.[2,26,29] Based on these findings, pruritus is both an obvious therapeutic target and a measure of direct treatment benefit.

In the present study, odevixibat-associated reductions in ObsRO pruritus severity were significant and clinically meaningful. Although PRO itching score also improved from baseline, the difference in change from baseline between treatment groups was not significant, probably due to the small sample size eligible for PRO assessments (ie, patients aged ≥8 years). In addition to the ObsRO pruritus responder analysis, data from the ObsRO sleep items, caregiver and clinician versions of the GIC, and exit interviews all support the clinical efficacy of odevixibat. As pruritus is a major driver of liver transplantation in patients with Alagille syndrome, these results suggest that odevixibat could have the potential to delay or prevent liver transplantation.

Another IBAT inhibitor, maralixibat, has been evaluated in a phase 2b study (ICONIC) of patients with Alagille syndrome.[30] However, a direct comparison of odevixibat and maralixibat in patients with Alagille syndrome is complicated by differences in study design and endpoints across the two studies. Whereas ASSERT was a phase 3, double-blind, randomised, placebo-controlled study with a symptom-based primary endpoint (ie, change from baseline to weeks 21–24 in ObsRO scratching score), ICONIC was a phase 2, drug-withdrawal study with an 18-week open-label run-in phase followed by a 4-week randomised withdrawal phase and a biologically based primary endpoint (ie, change in serum bile acids during the randomised withdrawal phase in the enriched subset of patients who previously had a serum bile acid reduction of at least 50% from baseline to week 12 or 18).[30] Additionally, instruments used to assess pruritus varied across studies (PRUCISION for ASSERT and Itch-Reported Outcome Observer [known as ItchRO] for ICONIC).[30]

Limitations of the current study include the subjective nature of the caregiver-reported and patient-reported pruritus assessments. Factors mitigating this concern, however, include the placebo-controlled study design and converging evidence from a biologically based endpoint (ie, serum bile acids). The exclusion of patients with extreme perturbations in hepatic parameters at baseline also precludes full generalisability of the results, as substantial inter-patient and intra-patient variation exists in hepatic parameters in patients with Alagille syndrome;[3] however, the proportion of patients who were excluded during screening due to elevations in hepatic biochemical parameters was low, at 7% (five of 76 screened patients). Additional data on odevixibat treatment are needed in patients with more advanced disease who might not have met the eligibility criteria for ASSERT.

In conclusion, odevixibat could be an efficacious, non-surgical option to reduce the systemic accumulation of bile acids that results from cholestasis, lessen the severity of pruritus, and ultimately improve the standard of care in patients with Alagille syndrome. Given the 24-week timeframe and the small sample size of the current study, additional studies are needed to investigate both the short-term and longer-term safety and efficacy of odevixibat and establish this drug as a potential first-line treatment in patients with Alagille syndrome. Longer-term data are being collected in the ongoing, open-label ASSERT-EXT study. Exploratory analyses of ASSERT-EXT data will evaluate the potential effect of odevixibat on the need for biliary diversion or liver transplantation.

For **Ipsen's data sharing criteria** see https://vivli.org/members/ourmembers/

Contributors

NO was the principal investigator and SM worked as medical officer of this trial. CC, SM, JR, and JPM were involved in the design, conduct, and oversight of the clinical trial. MA, AB, UB, PB, MC, PC, ÖD, RF, GI, WWK, FL, WSL, GM, NO, PR, MR, ESo, ESt, WvdW, HJV, and AW were site investigators and participated in recruitment of patients, treatment, data collection, and follow-up. QN and QY performed the statistical analyses. SM and NO accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors contributed to data analysis and interpretation and to the critical review, revision, and final approval of the manuscript.

Declaration of interests

NO has received research support to their institution from Albireo Pharma (an Ipsen company) and Mirum, and consulting fees from Albireo Pharma (an Ipsen company). UB has received grants or contracts and consulting fees from Mirum, Albireo Pharma (an Ipsen company), and Alexion. PB has received an unrestricted research grant from Albireo Pharma (an Ipsen company) and payment or honoraria for lectures, presentations, speakers bureaus, or educational events from Mirum; and has participated on a data safety monitoring or advisory board for Albireo Pharma (an Ipsen company) and Mirum. MC has received payment or honoraria for lectures, presentations, speakers bureaus, or educational events from Albireo Pharma (an Ipsen company) and has participated on a data safety monitoring or advisory board for Albireo Pharma (an Ipsen company) and Mirum. RF has received payments or honoraria for lectures, presentations, speakers bureaus, or educational events from Albireo Pharma (an Ipsen company) and Mirum, and has participated on a data safety monitoring or advisory board for Albireo Pharma (an Ipsen company). GI has participated on a data safety monitoring or advisory board for Albireo Pharma (an Ipsen company), Mirum, and Kedrion Pharma. PR has received research support to their institution from Albireo Pharma (an Ipsen company); grants or contracts from AbbVie, Arrowhead, Gilead, Merck, Mirum, Takeda, and Travere; consulting fees from Albireo Pharma (an Ipsen company), Ambys, Audentes, BioMarin, Dicerna, Encoded, Gilead, MedinCell, Mirum, RNAV8, Takeda, and Travere; and payment or honoraria for speakers bureaus from Mirum. MR has received consulting fees from Albireo Pharma (an Ipsen company), Grifols, Mirum, and Takeda; payment or honoraria for lectures, presentations, speakers bureaus, or educational events from Mirum and Takeda; and support for attending meetings or travel, or both, from Mirum and Albireo Pharma (an Ipsen company). ESt has received unrestricted grants from Albireo Pharma (an Ipsen company) and Mirum; consulting fees from Albireo Pharma (an Ipsen company) and Mirum; and payment or honoraria to their institution for lectures, presentations, speakers bureaus, or educational events from Albireo Pharma (an Ipsen company) and Mirum. WvdW has received consulting fees from Mirum. HJV has received grants or contracts to their institution from Albireo Pharma (an Ipsen company), Mirum, and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition; and consulting fees paid to their institution from Albireo Pharma (an Ipsen company) and Mirum. AW has received research support from Albireo Pharma (an Ipsen company), and has participated on a data safety monitoring or advisory board for Mirum. QY was previously employed at Albireo Pharma (an Ipsen company). CC, JPM, and SM were previously employed at Albireo Pharma (an Ipsen company) and received salary and stock options. JPM also held patents with and received support for attending meetings or travel, or both, from Albireo Pharma (an Ipsen company). QN and JR are current employees of Ipsen and receive salary or stock options (or both). MA, PC, ÖD, WSL, AB, WWK, FL, GM, and ESo declare no competing interests.

Data sharing

Qualified researchers can request access to patient-level study data that underlie the results reported in this Article. Additional relevant study documents, including the clinical study report, study protocol with any amendments, annotated case report form, statistical analysis plan, and dataset specifications can also be made available. Patient-level data will be anonymised, and study documents will be redacted to protect the privacy of study participants. Where applicable, data from eligible studies are available 6 months after the studied medicine and indication have been approved in the USA and EU or after the primary manuscript describing the results has been accepted for publication, whichever occurs later. Further details of Ipsen's data sharing criteria, eligible studies, and process for sharing are available online. Any requests should be submitted to https://vivli.org for assessment by an independent scientific review board.

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