# Odevixibat treatment in progressive familial intrahepatic cholestasis: a randomised, placebo-controlled, phase 3 trial

*Richard J Thompson, Henrik Arnell, Reha Artan, Ulrich Baumann, Pier Luigi Calvo, Piotr Czubkowski, Buket Dalgic, Lorenzo D'Antiga, Özlem Durmaz, Björn Fischler, Emmanuel Gonzalès, Tassos Grammatikopoulos, Girish Gupte, Winita Hardikar, Roderick H J Houwen, Binita M Kamath, Saul J Karpen, Lise Kjems, Florence Lacaille, Alain Lachaux, Elke Lainka, Cara L Mack, Jan P Mattsson, Patrick McKiernan, Hasan Özen, Sanjay R Rajwal, Bertrand Roquelaure, Mohammad Shagrani, Eyal Shteyer, Nisreen Soufi, Ekkehard Sturm, Mary Elizabeth Tessier, Henkjan J Verkade, Patrick Horn*

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**Institute of Liver Studies, King's College London, London, UK** (Prof R J Thompson MD, PhD, T Grammatikopoulos MD); **Department of Women's and Children's Health** (H Arnell MD) **and Department of Paediatrics, CLINTEC** (B Fischler PhD), **Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; Department of Paediatric Gastroenterology, Akdeniz University, Antalya, Turkey** (Prof R Artan MD); **Paediatric Gastroenterology and Hepatology, Hannover Medical School, Hannover, Germany** (Prof U Baumann MD); **Paediatric Gastroenterology Unit, Regina Margherita Children's Hospital, Azienda Ospedaliera Città della Salute e della Scienza di Torino, Turin, Italy** (P L Calvo MD); **Department of Gastroenterology, Hepatology, Nutritional Disorders and Paediatrics, The Children's Memorial Health Institute, Warsaw, Poland** (P Czubkowski MD); **Department of Paediatric Gastroenterology, Gazi University Faculty of Medicine, Ankara, Turkey** (Prof B Dalgic MD); **Department of Paediatric Hepatology, Gastroenterology, and Transplantation, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy** (L D'Antiga MD); **Istanbul University Istanbul Faculty of Medicine, Department of Paediatric Gastroenterology and Hepatology, Istanbul, Turkey** (Prof Ö Durmaz MD); **Hépatologie et Transplantation Hépatique Pédiatriques, Centre de Référence de l'Atrésie des**

## Summary

**Background** Progressive familial intrahepatic cholestasis (PFIC) is a group of inherited paediatric liver diseases resulting from mutations in genes that impact bile secretion. We aimed to evaluate the effects of odevixibat, an ileal bile acid transporter inhibitor, versus placebo in children with PFIC.

**Methods** Patients eligible for this 24-week, randomised, double-blind, completed, phase 3 study were paediatric outpatients diagnosed with PFIC1 or PFIC2 who had pruritus and elevated serum bile acids at screening. Patients were randomly assigned (1:1:1) using an interactive web-based system to once a day oral placebo, odevixibat 40 µg/kg, or odevixibat 120 µg/kg. Randomisation was done in a block size of six and stratified by PFIC type and patient age; patients, clinicians, and study staff were blinded to treatment allocation. Patients were enrolled at one of 33 global sites. Two primary endpoints were evaluated: proportion of positive pruritus assessments (PPAs; ie, scratching score of ≤1 or ≥1-point decrease as assessed by caregivers using the Albireo observer-reported outcome [ObsRO] PRUCISION instrument) over 24 weeks, and proportion of patients with serum bile acid response (ie, serum bile acids reduced by ≥70% from baseline or concentrations of ≤70 µmol/L) at week 24. Efficacy and safety were analysed in randomly allocated patients who received one or more doses of study drug. This study is registered with ClinicalTrials.gov, NCT03566238.

**Findings** Between June 21, 2018, and Feb 10, 2020, 62 patients (median age 3·2 [range 0·5–15·9] years) were randomly allocated to placebo (n=20), odevixibat 40 µg/kg per day (n=23), or odevixibat 120 µg/kg per day (n=19). Model-adjusted (least squares) mean proportion of PPAs was significantly higher with odevixibat versus placebo (55% [SE 8] in the combined odevixibat group [58% in the 40 µg/kg per day group and 52% in the 120 µg/kg per day group] *vs* 30% [SE 9] in the placebo group; model-adjusted mean difference 25·0% [95% CI 8·5–41·5]; p=0·0038). The percentage of patients with serum bile acid response was also significantly higher with odevixibat versus placebo (14 [33%] of 42 patients in the combined odevixibat group [10 in the 40 µg/kg per day group and four in the 120 µg/kg per day group] *vs* none of 20 in the placebo group; adjusting for stratification factor [PFIC type], the proportion difference was 30·7% [95% CI 12·6–48·8; p=0·0030]). The most common treatment-emergent adverse events (TEAEs) were diarrhoea or frequent bowel movements (13 [31%] of 42 for odevixibat *vs* two [10%] of 20 for placebo) and fever (12 [29%] of 42 *vs* five [25%] of 20); serious TEAEs occurred in three (7%) of 42 odevixibat-treated patients and in five (25%) of 20 placebo-treated patients.

**Interpretation** In children with PFIC, odevixibat effectively reduced pruritus and serum bile acids versus placebo and was generally well tolerated. Odevixibat, administered as once a day oral capsules, is a non-surgical, pharmacological option to interrupt the enterohepatic circulation in patients with PFIC.

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## Introduction

Progressive familial intrahepatic cholestasis (PFIC) is a group of rare, inherited diseases of hepatocellular origin resulting in disrupted bile formation.[1] PFIC results from genetic variants in several genes,[2,3] including mutations in *ATP8B1* and *ABCB11* (designated PFIC type 1 [PFIC1] and PFIC type 2 [PFIC2], respectively).[4]

Severe pruritus is common in children diagnosed with PFIC,[5] and the need for relief is crucial given that pruritus can considerably reduce quality of life and can result in an indication for liver transplantation.[6,7] Retention of bile acids within the liver is a central component of the aetiopathogenesis of cholestasis in PFIC, a disease feature that can drive downstream complications such as increased risk of hepatocellular carcinoma and progression to cirrhosis and end-stage liver disease.[5,8] Secondary spill over of bile acids into the peripheral circulation is easily measured and forms a clinically useful marker of disease severity.[2,9]

## Research in context

### Evidence before this study

Progressive familial intrahepatic cholestasis (PFIC) is a group of paediatric cholestatic liver diseases characterised by disruption of bile production and transport (ie, cholestasis), elevated serum bile acids, fat-soluble vitamin deficiency and growth failure, intense pruritus, and progressive liver disease. Pruritus associated with PFIC can disrupt the patient's sleep, which can have a negative impact on the quality of life of patients and their families. Historically, initial treatments for PFIC were limited to nutritional supplementation and off-label agents aimed at increasing bile flow or reducing pruritus. PFIC can also be treated with surgical interventions, such as partial external biliary diversion and liver transplantation. However, these therapies might not be effective in all patients with PFIC or provide sustained relief.

The ileal bile acid transporter (IBAT), also known as the apical sodium-dependent bile acid transporter (ASBT), is a critical regulator of the enterohepatic circulation of bile acids, taking up bile acids in the distal intestine for return to the liver via the portal circulation. Small-molecule inhibition of IBAT has been investigated as a therapeutic approach to treat a number of disease states, including cholestatic liver diseases.

We searched ClinicalTrials.gov from database inception to April 6, 2021, for interventional studies categorised by "cholestasis" as the condition or disease and one of the following other terms: "IBAT inhibitor", "ASBT inhibitor", "odevixibat", "maralixibat", "volixibat", "GSK2330672", or "elobixibat". This search revealed four IBAT inhibitors in clinical development for cholestatic diseases such as PFIC, primary biliary cholangitis, Alagille syndrome, biliary atresia, intrahepatic cholestasis of pregnancy, and primary sclerosing cholangitis. The ClinicalTrials.gov identifiers of the studies found in the initial search (n=20) were then cross-referenced with published articles indexed on PubMed. There was no language or date restriction for the search. Of articles identified on PubMed, only one published manuscript included data from the patient population of interest (ie, those with PFIC). This was a phase 2 study of the IBAT inhibitor odevixibat that enrolled paediatric patients with cholestatic liver diseases including PFIC and who had pruritus. In addition, some phase 2 study results of the IBAT inhibitors odevixibat or maralixibat in patients with PFIC have been presented as congress proceedings. Published and presented results of phase 2 studies of IBAT inhibitors in PFIC have shown evidence of improvement in key features of PFIC, such as reduced serum bile acid concentrations and pruritus, but these studies had no placebo controls. These searches revealed that, to date, there have been no completed, published, placebo-controlled trials of an IBAT inhibitor in patients with PFIC.

### Added value of this study

The current study, called PEDFIC 1, is the first completed, phase 3 interventional trial in patients with PFIC. In children with PFIC type 1 or PFIC type 2, odevixibat effectively reduced pruritus and serum bile acids relative to placebo. These effects occurred rapidly and were sustained up to week 24. Overall, odevixibat was generally well tolerated, with similar safety profiles observed for both doses of odevixibat.

### Implications of all the available evidence

Study results from PEDFIC 1 indicated that odevixibat can reduce pruritus and lower serum bile acids in patients with PFIC, both of which might have long-term implications for patients (ie, potentially reduce the need for liver transplantation and delay disease progression, respectively). The findings from this study formed the basis for the approval of odevixibat for the treatment of pruritus in patients aged 3 months and older with PFIC in the USA and for the treatment of PFIC in patients aged 6 months and older in the EU. Odevixibat represents a non-surgical, pharmacological option to interrupt the enterohepatic circulation and could provide significant treatment benefits in PFIC, a disease with high unmet medical needs. The ongoing open-label extension study of odevixibat in PFIC, called PEDFIC 2, will provide long-term efficacy and safety information on odevixibat in patients with PFIC.

Historically, treatment options for patients with PFIC were limited to surgical interruption of bile acid enterohepatic circulation and off-label symptomatic medical therapies. Because such therapies might not provide adequate relief or prevent progression to end-stage liver disease, patients often require liver transplantation.[1,10,11]

The ileal bile acid transporter (IBAT), also called the apical sodium-dependent bile acid transporter (ASBT), is encoded by *SLC10A2* and located on the luminal surface of enterocytes in the terminal ileum; this transport protein mediates resorption of conjugated bile acids for recirculation back to the liver.[12] Inhibition of IBAT disrupts the enterohepatic circulation and leads to faecal elimination of bile acids similar to surgical interruption of the enterohepatic circulation.[13,14]

In the 24-week PEDFIC 1 study, the efficacy and safety of odevixibat, an orally administered, luminally restricted, potent, selective IBAT inhibitor, was evaluated versus placebo in children with PFIC1 or PFIC2. Odevixibat was approved in 2021 for the treatment of pruritus in patients aged 3 months and older with PFIC in the USA and for the treatment of PFIC in patients aged 6 months and older in the EU[15,16] based in part on the results of this pivotal study.

## Methods

### Study design and participants

PEDFIC 1 was a phase 3, randomised, double-blind, multicentre study conducted at 33 sites in the USA, Canada, Europe, Australia, and the Middle East, from May 16, 2018, to July 28, 2020. This outpatient study

**Voies Biliaires et des Cholestases Génétiques, FSMR FILFOIE, ERN RARE LIVER, Hôpital Bicêtre, AP-HP, Université Paris-Saclay, Hépatinov, Inserm U1193, Paris, France** (Prof E Gonzalès MD); **Paediatric Liver, GI and Nutrition Centre and MowatLabs, King's College Hospital NHS Trust, London, UK** (T Grammatikopoulos); **Liver Unit and Small Bowel Transplantation, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK** (G Gupte FRCPCH, Prof P McKiernan MD); **Department of Gastroenterology, Royal Children's Hospital, Melbourne, VIC, Australia** (Prof W Hardikar PhD); **Department of Paediatric Gastroenterology, Wilhelmina Children's Hospital and University Medical Centre, Utrecht, Netherlands** (Prof R H J Houwen MD); **Department of Gastroenterology, Hepatology and Nutrition, Hospital for Sick Children and the University of Toronto, Toronto, ON, Canada** (Prof B M Kamath MD); **Paediatrics Department, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, GA, USA** (Prof S J Karpen MD); **Albireo Pharma, Boston, MA, USA** (L Kjems MD, J P Mattsson PhD; P Horn MD); **Paediatric Gastroenterology–Hepatology–Nutrition Unit, Hôpital Universitaire Necker-Enfants Malades, Paris, France** (F Lacaille MD); **Hospices Civils de Lyon, Hôpital Femme-Mère-Enfant, Service D'hépatogastoentérologie et Nutrition Pédiatrique, Lyon, France** (Prof A Lachaux MD); **Children's Hospital, Department of Paediatric Gastroenterology, Hepatology, and Transplant Medicine, University Duisburg-Essen, Essen, Germany** (E Lainka MD); **Paediatrics Department, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA** (Prof C L Mack MD); **Division of Paediatric Gastroenterology, Hepatology, and Nutrition, Hacettepe University Faculty of Medicine, Ankara, Turkey** (Prof H Özen MD); **Children's Liver Unit, Leeds Teaching**

**Hospitals NHS Trust, Leeds Children's Hospital, Leeds, UK** (S R Rajwal MD)**; APHM, Service de Pédiatrie Multidisciplinaire, Hôpital de la Timone Enfants, Marseille, France** (B Roquelaure MD)**; Department of Liver and SB Transplant and Hepatobiliary–Paediatric Surgery, King Faisal Specialist Hospital and Research Centre–Organ Transplant Centre and College Of Medicine–Alfaisal University, Riyadh, Saudi Arabia** (M Shagrani MD)**; Faculty of Medicine, Hebrew University of Jerusalem, Juliet Keidan Department of Paediatric Gastroenterology, Shaare Zedek Medical Centre, Jerusalem, Israel** (Prof E Shteyer MD)**; Paediatrics Department, Children's Hospital Los Angeles, Los Angeles, CA, USA** (N Soufi MD)**; Paediatric Gastroenterology and Hepatology, University Children's Hospital Tübingen, Tübingen, Germany** (E Sturm MD)**; Department of Paediatrics, Section of Paediatric Gastroenterology, Hepatology, and Nutrition, Baylor College of Medicine–Texas Children's Hospital, Houston, TX, USA** (M E Tessier MD)**; Department of Paediatrics, University of Groningen, Beatrix Children's Hospital–University Medical Centre Groningen, Groningen, Netherlands** (Prof H J Verkade MD)

Correspondence to: Prof Richard J Thompson, Institute of Liver Studies, King's College Hospital, London SE5 9RS, UK
**richard.j.thompson@kcl.ac.uk**

See **Online** for appendix

For **study protocol** see https://clinicaltrials.gov/ProvidedDocs/38/NCT03566238/Prot_000.pdf

consisted of a screening phase and parallel-design treatment period (appendix p 4). The trial adhered to the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. Research protocols and amendments were approved by relevant institutional review boards or ethics committees, or both, at each site (see appendix pp 6–7 for additional details). The final study protocol is available to view online.

Children (aged 0·5 to 18 years) with a clinical diagnosis of PFIC1 or PFIC2 and genetic confirmation of biallelic pathogenic mutations in the *ATP8B1* (ie, PFIC1) or *ABCB11* (ie, PFIC2) genes, elevated serum bile acids (≥100 µmol/L), history of significant pruritus as determined by the investigator, and an average caregiver-reported observed scratching score of 2 or greater (calculated from daily electronic diary [eDiary] entries) in the 14 days preceding randomisation were eligible for inclusion. Additionally, caregivers or age-appropriate patients (≥8 years of age) agreed to use the eDiary device to record symptoms. Patients or their caregivers provided written informed consent before entering the study.

Patients with two mutations in *ABCB11* predicting a complete absence of functional bile salt export pump protein were excluded (appendix p 8). Patients were also excluded if they had a medical history or ongoing presence of other types of liver disease (eg, biliary atresia, benign recurrent intrahepatic cholestasis, liver cancer, histopathologic evidence of non-PFIC aetiology of cholestasis); diseases or conditions known to interfere with bile acid metabolism (eg, inflammatory bowel disease); chronic (>3 months) diarrhoea; active, clinically significant, acute or chronic infection or infection requiring hospitalisation or parenteral anti-infective treatment within 4 weeks of treatment start; or chronic kidney disease. Patients were also excluded from the study if they had biliary diversion surgery within the 6 months preceding the screening period; had a liver transplant or one planned within 6 months of randomisation; signs of decompensated liver disease (eg, ascites); or pruritus caused by any condition other than PFIC (eg, treatment-refractory atopic dermatitis, other primary pruritic skin disease).

Other exclusion criteria included exposure to an investigational drug, biologic agent, or medical device within 30 days preceding screening or five half-lives of the study agent, whichever was longer, and previous treatment with an IBAT inhibitor if there was no pruritus response to treatment. Patients with laboratory parameters of international normalised ratio greater than 1·4, serum alanine aminotransferase (ALT) greater than 10 times the upper limit of normal at screening, serum ALT greater than 15 times the upper limit of normal during the last 6 months, and total bilirubin greater than 10 times the upper limit of normal at screening were excluded.

From the first day of screening to the last day of the treatment period, medications with effects on bile acid concentrations in the gastrointestinal tract, drugs known to slow gastrointestinal motility, and other investigational products to treat PFIC were not allowed. Other drugs with possible effects on gastrointestinal motility were allowed provided the patient had stable usage of the drug from 4 or more weeks before enrolment until treatment discontinuation (appendix p 1). Treatment with ursodeoxycholic acid, rifampicin, or antihistamines was allowed provided the patient was on a stable dosage 4 weeks or more before enrolment and no dosage changes were planned during the study period.

### Randomisation and masking

After written informed consent was obtained, an eight-digit patient identification number was assigned by the interactive web response system (IWRS). The first two digits denoted country, followed by a three-digit site number, and a three-digit patient sequence number. The randomisation codes were computer generated by a biostatistician at ICON Clinical Research (Dublin, Ireland) and kept by an unblinded statistician at Firma Clinical Research (Chicago, IL, USA), independent from the project team. Patients deemed eligible for randomisation by study investigators were assigned a unique four-digit randomisation number by the IWRS that identified which treatment was allocated to the patient. Randomisation to odevixibat 40 µg/kg per day, odevixibat 120 µg/kg per day, or placebo was done in a block size of six and stratified according to PFIC type (1 or 2) and age group (6 months to 5 years, 6 to 12 years, and 13 to ≤18 years) to ensure approximate balance between dose schemes (1:1:1). Patients, clinicians, and study staff (except the statistician who generated the randomisation codes) were blinded to treatment allocation. A separate randomisation list was prepared for the patients who had taken part in the phase 2 study of odevixibat in paediatric patients with cholestasis (A4250-003); these patients were not stratified. Randomisation codes were assigned sequentially as patients became eligible for randomisation. The IWRS 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.

To ensure blinding of treatment assignment, study drug and matching placebo had the same shape, size, and colour, with labels on the study drug containers that did not identify the randomised treatment assignment. Dispensing of study drug was coordinated by IWRS.

### Procedures

Two on-site screening visits occurred: the first took place during the window of time from days 56 to 35 before the first dose of study drug and the second occurred during the window of time from days 28 to 7 before the first dose of study drug. Randomisation occurred on day 0, and patients took their first dose of study drug at home on day 1. Patients returned to the clinic for planned clinic

visits on weeks 4, 8, 12, 18, 22, and 24, with one telephone call at week 2 between the randomisation and week 4 visits. The double-blind treatment period lasted 24 weeks.

Patients who completed the treatment period either attended a follow-up visit 28 days after the last dose of study drug, or they could choose to continue into an optional 72-week open-label extension study (PEDFIC 2; ClinicalTrials.gov NCT03659916), in which all patients received odevixibat 120 µg/kg per day. Initially patients could withdraw from PEDFIC 1 due to intolerable symptoms after 12 or more weeks of treatment and enroll early into PEDFIC 2; however, this provision was removed with the last PEDFIC 1 protocol amendment on June 24, 2019.

From March 10, 2020, to Aug 28, 2020, study procedures for patients were affected by the COVID-19 pandemic due to missed or altered on-site study visits (eg, sites were closed per institutional or national guidelines, travel was restricted due to risk of infection). Several contingency measures were implemented during this time including frequent outreach to monitor safety, use of local laboratories, direct-to-patient shipment of study drug, and possible extension of the 24-week period to ensure that patients could attend an on-site end-of-treatment visit.

Placebo, odevixibat 40 µg/kg, or odevixibat 120 µg/kg were administered by patients or their caregivers once per day for up to 24 weeks. Treatment was dispensed during on-site clinic visits, and patients or caregivers were instructed to take or administer the study drug at home each morning, either as intact capsules (swallowed with a glass of water and with food) or sprinkled on soft, room-temperature food (eg, apple sauce), followed by water.

Patient pruritus was assessed twice daily, in the morning (AM) and the evening (PM), by caregivers using the Albireo observer-reported outcome (ObsRO) PRUCISION instrument on an eDiary device (Signant Health, Plymouth Meeting, PA, USA). PRUCISION responses range from 0 to 4, with higher scores indicating worse scratching or sleep disturbance (appendix p 5); a 1-point decrease in ObsRO pruritus score is considered a clinically meaningful change (details on the development and measurement characteristics of PRUCISION can be found in the appendix pp 1–2).[17]

Blood samples to measure fasting serum bile acids were drawn at all visits and were processed by a central laboratory using a validated commercial assay (Diazyme Laboratories; Poway, CA, USA). Patients were asked to fast for 4 h or longer before sample collection. Investigators, patients and caregivers, the sponsor, and the clinical research organisation were blinded to the serum bile acid values during treatment and the follow-up period. ALT, aspartate aminotransferase (AST), and total bilirubin were measured at screening, day 0, and weeks 4, 8, 12, 18, and 24, as well as at the week 28 follow-up visit.

Growth was measured at all visits and was based on Z scores for height and weight, with change in growth assessed by comparison with standard growth curves (ie, World Health Organization child growth standards for children <2 years of age and Centers for Disease Control and Prevention clinical growth charts for patients ≥2 years of age).

For more on **World Health Organization child growth standards** see https://www.who.int/tools/child-growth-standards

For more on **Centers for Disease Control and Prevention clinical growth charts** see https://www.cdc.gov/growthcharts/clinical_charts.htm

Blood samples for determining autotaxin and plasma 7α-hydroxy-4-cholesten-3-one (C4) concentrations were taken at day 0 and at weeks 4 and 24 in children who weighed more than 10 kg. An AST-to-platelet ratio index (APRI) score was used to measure liver fibrosis. The lower the APRI score (<0·5), the greater the negative predictive value (and ability to rule out cirrhosis), and the higher the value (>1·5), the greater the positive predictive value (and ability to rule in cirrhosis).[18,19] The Fibrosis-4 (FIB-4) score estimates the amount of scarring in the liver. A FIB-4 score of less than 1·45 has a negative predictive value of 90% for advanced fibrosis, while a score greater than 3·25 has a positive predictive value of 65% for advanced fibrosis.[20] Paediatric end-stage liver disease (PELD) score or the model for end-stage liver disease (MELD) score were used to estimate relative hepatic disease severity and the probability of survival for patients awaiting liver transplantation. The PELD score for patients younger than 12 years ranges from negative to positive values (eg, from –10 to 50) and takes into account the following variables: albumin, bilirubin, international normalised ratio, growth, and age. The MELD score for patients aged 12 years and older ranges from 6 to 40 and takes into account the following variables: serum creatinine, bilirubin, international normalised ratio, and serum sodium. Lower scores for each represent less severe hepatic disease.

The frequency and timing of other laboratory tests, such as other clinical chemistries and haematological parameters, are given in the appendix (p 4). Criteria for a patient to be removed from the study and criteria related to treatment interruption and possible dose reinitiation, as well as criteria related to liver disease monitoring that triggered further monitoring are described in the appendix (p 2). Briefly, treatment was to be interrupted if a patient developed diarrhoea plus at least one other concomitant sign or symptom (eg, grossly bloody stools or vomiting), and treatment could be restarted if symptoms resolved; criteria related to liver disease monitoring that triggered further monitoring and dose interruption included elevation of ALT, AST, total bilirubin, or international normalised ratio beyond designated threshold levels.

## Outcomes

This global study was designed, in part, to fulfil regulatory requirements for both the US Food and Drug Administration (FDA) and the European Medicines Agency. As such, two different primary endpoints were evaluated. The first was the proportion of a patient's positive pruritus assessments (defined as a scratching score ≤1 or at least a 1-point reduction from baseline on

the ObsRO PRUCISION instrument) over 24 weeks. Positive pruritus assessment was the terminology agreed upon with the US FDA to describe the pruritus primary endpoint for the study. The second primary endpoint was the proportion of patients with a serum bile acid response (defined as a ≥70% reduction from baseline in fasting serum bile acids or serum bile acids ≤70 µmol/L) at week 24. The primary endpoints were also evaluated in a prespecified subgroup analysis by PFIC type.

Prespecified secondary efficacy endpoints were: change from baseline to weeks 12 and 24 in fasting serum bile acids, serum ALT, and growth; the proportion of patients with a pruritus response at weeks 12 and 24 (ie, ≥1-point drop on the ObsRO pruritus measure); the number of patients undergoing surgical interruption of the enterohepatic circulation or liver transplantation; change from baseline in sleep parameters (ie, percentage of days requiring help falling asleep, requiring soothing, sleeping with the caregiver, seeing blood due to scratching, and taking medication to induce sleep based on ObsRO assessments as well as difficulty falling asleep and difficulty staying asleep based on patient-reported outcome [PRO] assessments) by 4-week intervals over the 24-week treatment period; the proportion of positive pruritus assessments (itch score ≤1, or at least a 1-point reduction from baseline) over 24 weeks at the patient level based on PRO assessments; proportion of positive pruritus assessments at the patient level based on AM, PM, and AM plus PM ObsRO scores over the intervals of 0–4 weeks, 0–8 weeks, 0–12 weeks, 0–18 weeks, 0–24 weeks, and in each 4-week interval; and number and percentage of patients who had a positive pruritus assessment more than 50% of the time during the 24-week treatment period. Although the secondary outcome of proportion of patients with pruritus response at weeks 12 and 24 based on the PRO instrument was specified in protocol, the small number of available PRO assessments precluded a determination of a threshold for clinically meaningful change in pruritus; therefore, this secondary outcome could not be assessed.

Exploratory endpoints included change from baseline to week 24 in total bilirubin, AST, and gamma glutamyltransferase (GGT); change from baseline in additional sleep parameters (ie, tiredness [ObsRO and PRO], number of awakenings [ObsRO], and percentage of days waking up [PRO]) by 4-week intervals over the 24-week treatment period; change from baseline in ObsRO pruritus score; change in select markers of bile acid synthesis (ie, autotaxin, C4); and change in liver disease severity scores (ie, APRI, FIB-4, and PELD or MELD). Changes in total bilirubin, AST, GGT, autotaxin, C4, and liver disease severity scores were also evaluated in post-hoc subgroup analyses by PFIC type.

The primary safety analysis for PEDFIC 1 was based on the incidence of treatment-emergent adverse events (TEAEs). TEAEs were categorised by causality, severity, and seriousness for odevixibat and placebo. Other safety assessments included physical examinations, vital signs, and abdominal ultrasounds (liver and spleen ultrasounds at day 0 and week 24).

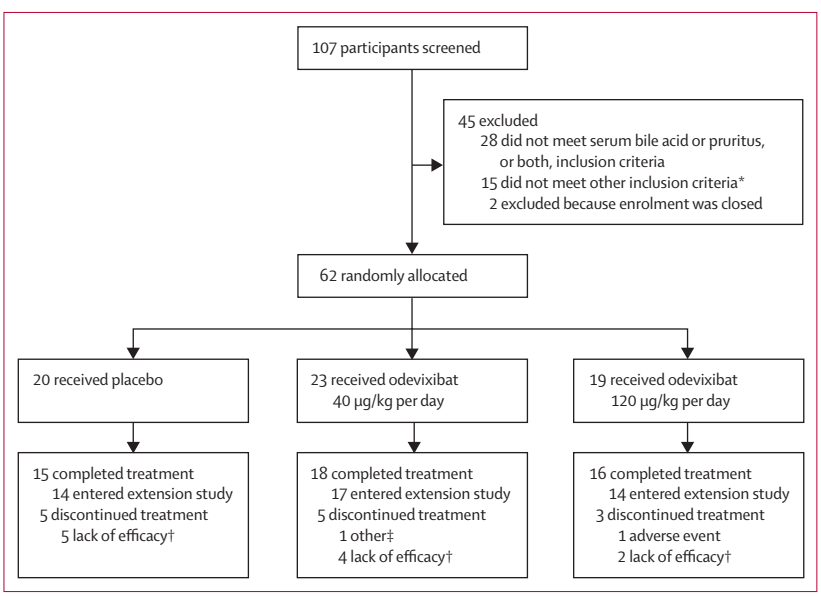



***Figure 1:*** **PEDFIC 1 trial profile**
*Not including serum bile acid or pruritus, or both, inclusion criteria. †Rolled over early to long-term extension study—there were 11 patients who rolled over early into the PEDFIC 2 open-label extension study: seven at week 12, one at week 14, and three at week 18. ‡Non-compliance and inability to travel to the clinic.

## Statistical analysis

The statistical analysis plan was finalised before database lock and analysis.

For the primary endpoint related to pruritus, the individual null hypothesis was that the average proportion of positive assessments would be the same between the active and placebo groups; the alternative hypothesis was that the average proportion would be larger in the active group. For the primary endpoint related to serum bile acids, the individual null hypothesis was that the odds ratio of the response in an active group versus placebo would be 1; the alternative hypothesis was that the odds ratio would be greater than 1. Since each active group was to be compared with placebo, there were two individual null hypotheses for each endpoint.

For each primary endpoint, simulations with 5000 iterations using 20 patients per group were conducted to estimate power after multiplicity adjustment based on a closed-testing procedure to control the one-sided overall type I error rate for two treatment comparisons versus placebo at the 0·025 level.

For the first primary endpoint of proportion of positive pruritus assessments, 20 patients per treatment group provided approximately 89%, 95%, and 83% power to claim significance for a particular odevixibat group, for at least one group, and for both groups, respectively, after multiplicity adjustment, assuming a mean

difference of –1 between each odevixibat group and placebo for change from baseline in scratching score, with standard deviation of 0·95 (ie, effect size of 1·0526). This effect size was used to estimate the power for the primary endpoint of proportion of positive pruritus assessments using simulation based on beta-binomial distribution.

For the second primary endpoint of proportion of patients with a serum bile acid response, 20 patients per treatment group provided approximately 94%, 99%, and 91% power to claim significance for a particular odevixibat group, for at least one group, and for both groups, respectively, after multiplicity adjustment, assuming 60% responders in each odevixibat group and 10% responders in the placebo group.

The full analysis set (FAS) consists of all randomly allocated patients who received one or more dose of study treatment. Patients were analysed as randomised. The FAS was the primary analysis set for efficacy analyses. The safety analysis set consisted of all randomised patients who received one or more dose of study drug. Patients were analysed according to the treatment they actually received. The safety analysis set was used for safety analyses. The FAS set and the safety analysis set included the same patients in this study.

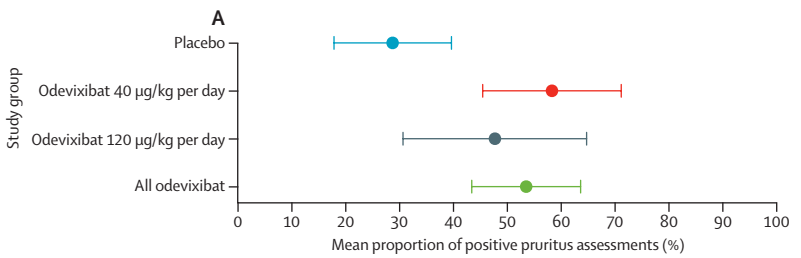
Detailed descriptions of analysis of efficacy outcomes can be found in the appendix (p 3). Briefly, for the primary efficacy variable of proportion of positive pruritus assessments at the patient level for the pooled odevixibat groups versus placebo over the 24-week treatment period, an ANCOVA model was used that included treatment group and rounded AM and PM baseline pruritus scores as covariates and treatment group and stratification factors as fixed effects. A prespecified supportive analysis of this primary endpoint was conducted for change from baseline in monthly pruritus score using a mixed-effects model for repeated measures, which included baseline score, treatment group, time, treatment-by-time interaction, and randomisation stratification factors as well as placebo-reference multiple imputation for missing data. For the primary efficacy variable of fasting serum bile acid response, a Cochran-Mantel-Haenszel test stratified by PFIC type was performed at the end of treatment to compare the two pooled odevixibat groups with placebo. For each primary endpoint, a closed-testing procedure was used to control for type I error as follows: the individual dose groups were pooled and compared with placebo first; if the one-sided p value was 0·025 or less, one-sided p values for low dose versus placebo and high dose versus placebo were calculated. The p values presented in the manuscript have been converted to two-sided p values as follows: for one-sided p values greater than 0·5, the two-sided p value equaled 2*(1 minus the one-sided p value); otherwise, two-sided p values were calculated by multiplying one-sided p values by 2.

| | Placebo (n=20) | Odevixibat 40 µg/kg per day (n=23) | Odevixibat 120 µg/kg per day (n=19) | Odevixibat, all doses (n=42) |
|---|---|---|---|---|
| Age, years | 2·8 (0·8–4·5) | 3·2 (1·0–6·1) | 4·9 (1·3–9·2) | 3·2 (1·3–6·1) |
| Age category, years | | | | |
| 0·5 to 5 | 16 (80%) | 17 (74%) | 14 (74%) | 31 (74%) |
| 6 to 12 | 3 (15%) | 5 (22%) | 4 (21%) | 9 (21%) |
| 13 to 18 | 1 (5%) | 1 (4%) | 1 (5%) | 2 (5%) |
| Sex | | | | |
| Female | 8 (40%) | 12 (52%) | 11 (58%) | 23 (55%) |
| Male | 12 (60%) | 11 (48%) | 8 (42%) | 19 (45%) |
| Race | | | | |
| White | 17 (85%) | 18 (78%) | 17 (90%) | 35 (83%) |
| Black | 0 | 2 (9%) | 0 | 2 (5%) |
| Asian | 1 (5%) | 0 | 1 (5%) | 1 (2%) |
| Other | 2 (10%) | 3 (13%) | 1 (5%) | 4 (10%) |
| Height, cm | 89·0 (24·4) | 92·3 (20·2) | 98·5 (22·8) | 95·1 (21·4) |
| Weight, kg | 14·5 (9·8) | 15·5 (9·8) | 17·6 (9·6) | 16·4 (9·6) |
| PFIC type | | | | |
| PFIC1 | 5 (25%) | 7 (30%) | 5 (26%) | 12 (29%) |
| PFIC2 | 15 (75%) | 16 (70%) | 14 (74%) | 30 (71%) |
| Use of UDCA at baseline | 18 (90%) | 19 (83%) | 13 (68%) | 32 (76%) |
| Use of rifampicin at baseline | 17 (85%) | 13 (57%) | 11 (58%) | 24 (57%) |
| Serum bile acids, µmol/L*† | 255 (168–329) | 228 (189–336) | 189 (154–363) | 221 (160–351) |
| Pruritus score‡ | 3·0 (2·7–3·3) | 3·0 (2·6–3·4) | 2·9 (2·3–3·1) | 3·0 (2·5–3·1) |
| Serum ALT, U/L§ | 56 (37–85) | 83 (40–109) | 59 (34–92) | 70 (39–105) |
| Total bilirubin, mg/dL¶ | 1·8 (0·6–4·3) | 2·8 (0·9–3·4) | 1·5 (0·7–3·3) | 2·2 (0·8–3·3) |

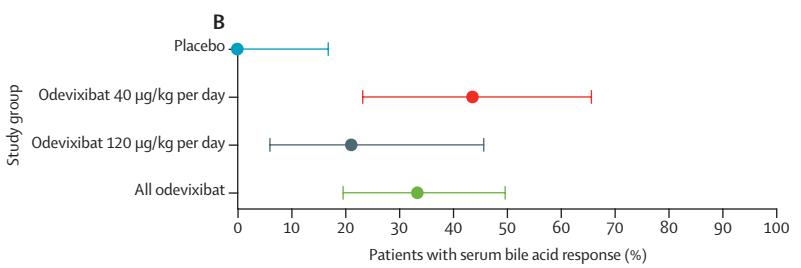
Data are n (%), median (IQR), or mean (SD). PFIC=progressive familial intrahepatic cholestasis. UDCA=ursodeoxycholic acid. ALT=alanine aminotransferase. *Normal reference range: 0 to 10 µmol/L. †Baseline measurements differed from criteria used to determine eligibility (ie, to be eligible, patients must have had a serum bile acid level of 100 µmol/L or more based on the average of two samples taken during screening visits; the baseline serum bile acid level was calculated by averaging the last two values before the first dose of study drug [value before treatment on day 1 and the second screening value]). ‡Baseline measurements differed from criteria used to determine eligibility (ie, to be eligible, patients' worst daily pruritus score as observed by caregivers had to be 2 or greater in the 2 weeks before randomisation; baseline pruritus score was calculated as the average of AM and PM scores in the 14 days before the first dose of study drug). §Normal reference range varies by age and sex, but typical values for paediatrics are in the range of 1 to 35 U/L. ¶Normal reference range: 1·2 mg/dL or lower.

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

The secondary endpoints of change from baseline in serum bile acids, ALT, and growth were analysed using a mixed-effects model for repeated measures, including terms for baseline, PFIC type, age category, treatment, visit, treatment-by-baseline interaction, and treatment-by-visit interaction. Post-hoc analyses of the exploratory endpoints of change from baseline in total bilirubin, AST, GGT, autotaxin, C4, APRI, FIB-4, and PELD or MELD were performed using an ANCOVA model with baseline level as a covariate and treatment group, PFIC type, and age category as fixed effects. Additional secondary endpoints (ie, proportion of patients with a pruritus response at weeks 12 and 24; number of patients undergoing surgical interruption of the enterohepatic




| | Model-adjusted mean (SE) proportion of positive pruritus assessments (%) | p value (odevixibat *vs* placebo) |
|---|---|---|
| Placebo | 30% (SE 9) | .. |
| Odevixibat 40 µg/kg per day | 58% (SE 9) | 0·0032 |
| Odevixibat 120 µg/kg per day | 52% (SE 9) | 0·033 |
| All odevixibat | 55% (SE 8) | 0·0038 |




| | Patients with serum bile acid response, n/N (%, 95% CI) | p value (odevixibat *vs* placebo) |
|---|---|---|
| Placebo | 0/20 (0%, 95% CI 0–17) | .. |
| Odevixibat 40 µg/kg per day | 10/23 (43%, 95% CI 23–66) | 0·0006 |
| Odevixibat 120 µg/kg per day | 4/19 (21%, 95% CI 6–46) | 0·035 |
| All odevixibat | 14/42 (33%, 95% CI 20–50) | 0·0030 |

***Figure 2:*** **Primary PEDFIC 1 endpoints**
Proportion of positive pruritus assessments over 24 weeks (A) and percentage with serum bile acid response at week 24 (B). p values in (A) were calculated on the basis of model-adjusted mean differences with rounded AM and PM baseline scores as covariates, and treatment group and stratification factors (PFIC type and age category) as fixed effects; p values in (B) were calculated using proportion differences adjusted for stratification factor (PFIC type). Error bars show 95% CIs (A) and Clopper-Pearson exact 95% CIs (B). ObsRO=observer-reported outcome. PFIC=progressive familial intrahepatic cholestasis.

circulation or liver transplantation; change from baseline in sleep parameters by 4-week intervals over the 24-week treatment period based on ObsRO and PRO assessments; proportion of positive pruritus assessments over 24 weeks at the patient level based on PRO assessments; proportion of positive pruritus assessments at the patient level based on AM, PM, and AM plus PM ObsRO scores over the intervals of 0–4 weeks, 0–8 weeks, 0–12 weeks, 0–18 weeks, 0–24 weeks, and in each 4-week interval; and number and percentage of patients who had a positive pruritus assessment more than 50% of the time during the 24-week treatment period), exploratory endpoints, all subgroup analyses, and safety data were summarised descriptively. All statistical analyses were performed using SAS version 9.4 or higher.

Adverse events were coded using Medical Dictionary for Regulatory Activities version 23.0. An independent data safety monitoring committee (ie, the DSMB) reviewed patient safety data. This study is registered with ClinicalTrials.gov: NCT03566238.

### Role of the funding source
The study funder, Albireo Pharma, had input into the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

## Results
The first patient was randomly allocated on June 21, 2018, and the last patient was randomly allocated on Feb 10, 2020; the last visit for the last enrolled patient occurred in July, 2020. In total, 45 patients were excluded during screening (figure 1) and 62 patients were randomly allocated to treatment (odevixibat 40 µg/kg per day, n=23 and odevixibat 120 µg/kg per day, n=19) or placebo (n=20). These randomly allocated patients comprised the population assessed for efficacy and safety analyses. Overall, 49 (79%) of 62 patients completed the 24-week treatment period (figure 1). 11 patients (placebo, n=5; odevixibat 40 µg/kg per day, n=4; odevixibat 120 µg/kg per day, n=2) discontinued treatment due to patient or caregiver judgment of no improvement or intolerable symptoms (ie, perceived lack of efficacy, as patients and clinicians were blinded to study outcomes until the last patient completed the study) and rolled over into the long-term extension study before completing 24 weeks of treatment. Additionally, one patient treated with odevixibat 40 µg/kg per day discontinued due to non-compliance and inability to travel to the clinic, and one patient treated with odevixibat 120 µg/kg per day discontinued early due to a TEAE of diarrhoea.

Patient demographics and baseline characteristics by treatment group are depicted in table 1. The median patient age in PEDFIC 1 was 3·2 years (ranging from 0·5 to 15·9 years; 47 [76%] of 62 were aged ≤5 years), and 31 (50%) of 62 of patients were female. Of all 62 patients, 17 (27%) had PFIC1 and 45 (73%) had PFIC2; overall median time since diagnosis was 1·5 years. Patient genotype information for all randomly allocated patients is provided in the appendix (pp 9–12). Median duration of exposure to study drug was 23·7 (IQR 19·9–23·9) weeks in placebo-treated patients and 23·9 (IQR 23·4–24·0) weeks in all patients who received odevixibat.

At study entry, most patients were receiving ursodeoxycholic acid (50 [81%] of 62) or rifampicin (41 [66%] of 62; table 1). Consistent with the potential for patients with PFIC to experience impaired growth,[14] median height-for-age and weight-for-age Z-scores were –1·7 and –1·0 at baseline, respectively. At baseline, median serum bile acids, serum ALT, and total bilirubin concentrations were considerably elevated above normal levels (table 1), indicating cholestasis.[21] There were some differences in certain characteristics at baseline between the placebo and odevixibat groups (eg, ALT concentrations, use of ursodeoxycholic acid or rifampicin), although these were not stratification factors used in randomisation.

The study met both primary endpoints. Treatment with odevixibat overall, and separately, at doses of 40 µg/kg

per day and 120 µg/kg per day, led to statistically significant improvements in pruritus compared with placebo over the 24-week treatment period based on the ObsRO instrument: the model-adjusted (least squares) mean proportion of positive pruritus assessments at the patient level was 55% for the all-odevixibat group (58% in the odevixibat 40 µg/kg per day group and 52% in the 120 µg/kg per day group) compared with 30% with placebo; the model-adjusted mean difference for the all-odevixibat group versus placebo was 25·0% (95% CI 8·5–41·5; p=0·0038; figure 2A). After 24 weeks of treatment, the percentage of patients with serum bile acid response was also significantly higher in the all-odevixibat group compared with placebo. Of all 42 patients who received odevixibat, 14 (33%) had a serum bile acid response (ten [43%] of 23 patients in the 40 µg/kg per day group and four [21%] of 19 in the 120 µg/kg per day group), whereas no patients (0 of 20) receiving placebo met this response threshold; the absolute proportion difference for the all-odevixibat group versus placebo was 33·3% (exact 95% CI 8·6–49·6; adjusting for stratification factor [PFIC type], this difference was 30·7% [12·6–48·8; p=0·0030]; figure 2B).

Improvement in pruritus based on mean monthly ObsRO scratching score among patients treated with odevixibat was observed by week 4 of treatment; the mean change from baseline to weeks 21 to 24 in ObsRO pruritus score was –1·11 (SD 1·20) in the all-odevixibat group versus –0·25 (0·78) with placebo (figure 3A; exploratory endpoint). The model-adjusted mean difference in ObsRO pruritus score changes from baseline for the all-odevixibat group versus placebo at weeks 21 to 24 was significant (–0·68 [95% CI –1·25 to –0·11]; p=0·020). Additionally, a greater proportion of patients treated with odevixibat had a clinically meaningful change in ObsRO pruritus at weeks 12 (appendix p 13) and 24 (figure 3B) based on mean monthly score versus patients treated with placebo (proportions at week 24: 18 [43%] of 42 *vs* two [11%] of 19, respectively; secondary endpoint). Additional pruritus outcomes (secondary endpoints) are summarised in the appendix (pp 13–14); briefly, mean proportions of positive pruritus assessments at the patient level were generally higher over time in the all-odevixibat group compared with placebo for the AM, PM, and AM plus PM ObsRO scores; the proportion of positive pruritus assessments at the patient level was greater over weeks 0–24 in the all-odevixibat group compared with the placebo group for PRO pruritus scores; and a larger proportion of patients

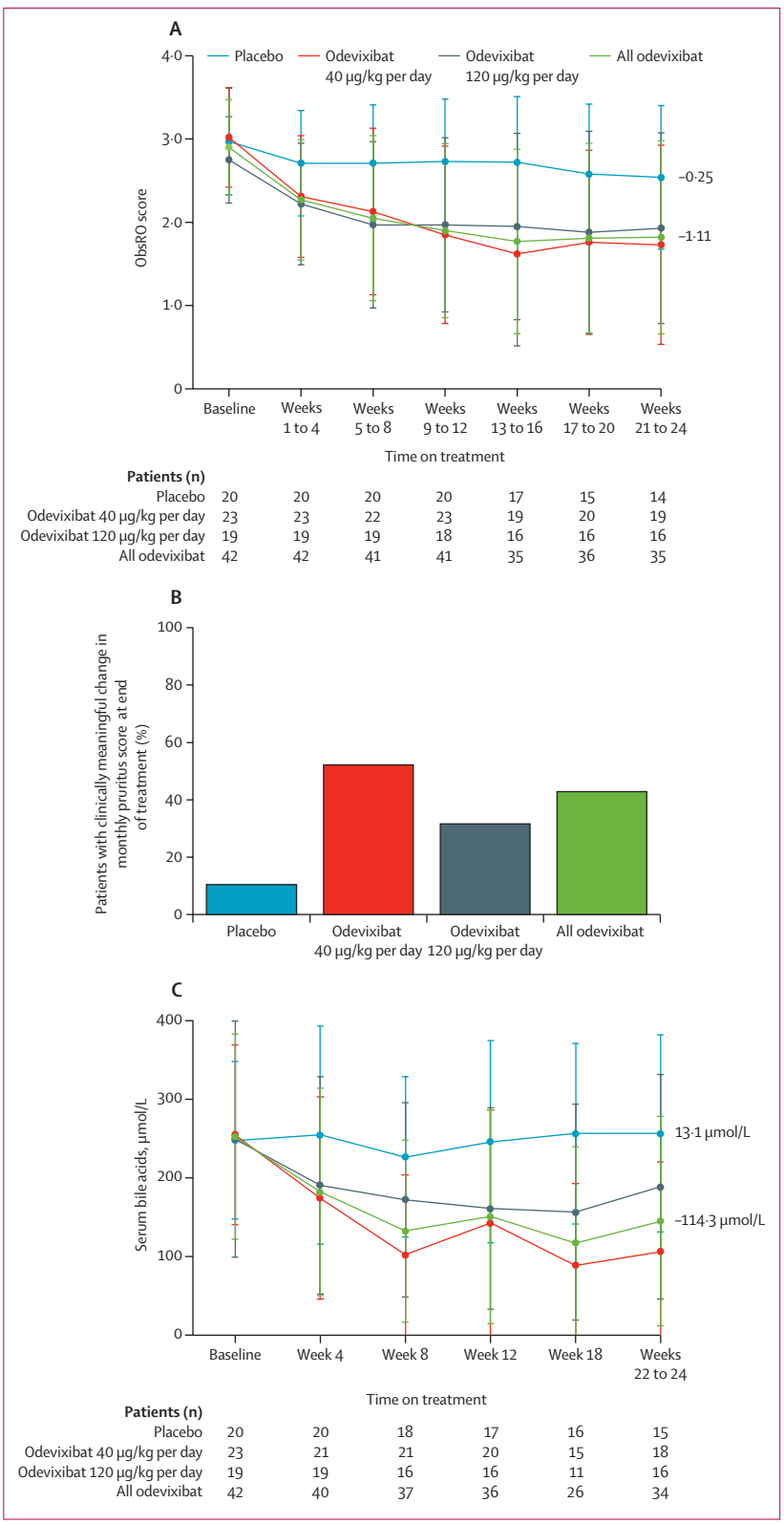



***Figure 3:*** **Additional efficacy outcomes**
Mean pruritus scores over time (A); proportion of patients with clinically meaningful change in monthly pruritus score at end of treatment (B); and mean fasting serum bile acid concentrations over time (C). The two values to the right in (A) and (C) depict the mean changes from baseline in the placebo and odevixibat groups at the last time point assessed. Error bars show SD. ObsRO=observer-reported outcome.

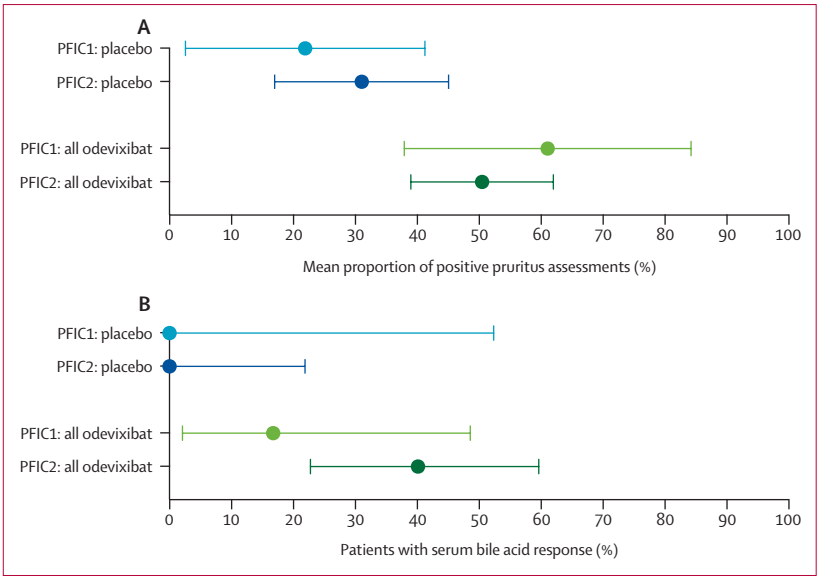



***Figure 4:*** **Treatment effects of odevixibat in patients with PFIC1 or PFIC2**
Proportion of positive pruritus assessments over 24 weeks (A) and serum bile acid response at week 24 (B; subgroup analyses of the primary endpoints). Error bars show 95% CIs (A) and Clopper-Pearson exact 95% CIs (B). PFIC=progressive familial intrahepatic cholestasis. ObsRO=observer-reported outcome.

in the all-odevixibat group achieved positive pruritus assessments more than 50% of the time relative to those in the placebo group based on either ObsRO or PRO pruritus scores. Changes from baseline in serum bile acids were observed from week 4 of odevixibat treatment (exploratory endpoint); at week 12 and weeks 22 to 24, mean serum bile acid concentrations decreased by 110·5 µmol/L (SD 165·3) and 114·3 µmol/L (173·9), respectively, in the all-odevixibat group and increased by 7·4 µmol/L (101·4) and 13·1 µmol/L (96·4), respectively, with placebo (figure 3C; secondary endpoint). The model-adjusted mean differences in serum bile acid level changes from baseline for the all-odevixibat group versus placebo were significant at week 12 (–106·7 µmol/L [95% CI –177·7 to –35·6]; p=0·0040) and at weeks 22 to 24 (–120·0 µmol/L [95% CI –194·3 to –45·7]; p=0·0022).

Prespecified subgroup analyses were performed to assess effects on serum bile acids and pruritus in patients with PFIC1 or PFIC2. The mean proportion of positive pruritus assessments in odevixibat-treated patients with PFIC1 during 24 weeks of treatment appeared to be higher than that in patients with PFIC1 treated with placebo; similar effects were observed for odevixibat-treated versus placebo-treated patients with PFIC2 (figure 4A; subgroup analysis based on one of the primary endpoints). The proportion of odevixibat-treated patients with PFIC1 who met serum bile acid response criteria at week 24 was 17% (two of 12) and for those with PFIC2 it was 40% (12 of 30), whereas no placebo-treated patients in either subgroup had a serum bile acid response (figure 4B; subgroup analysis based on one of the primary endpoints).

Treatment with odevixibat led to reductions from baseline in standard liver-associated tests: at week 12, mean changes in serum ALT were –20·5 U/L (SD 97·3) with odevixibat and 1·7 U/L (44·5) with placebo, and at week 24, these values were –26·7 U/L (79·1) and 3·7 U/L (16·4), respectively (secondary endpoints). The model-adjusted mean difference in change from baseline ALT concentrations for the all-odevixibat group versus placebo was not significant at week 12 (–2·1 U/L [95% CI –38·7 to 34·6]; p=0·91) or week 24 (–14·8 U/L [95% CI –45·1 to 15·4]; p=0·33). Changes in additional hepatic parameters, biochemical markers of bile acid synthesis, and measures of liver disease severity are presented in the appendix (pp 15–16; exploratory endpoints); post-hoc subgroup analyses of these endpoints in patients with PFIC1 or PFIC2 are also presented in the appendix (p 17). None of the 62 patients underwent surgical interruption of the enterohepatic circulation or liver transplantation during the study (secondary endpoint).

Mean change from baseline to week 12 in height Z-score was –0·02 (SD 0·46) for patients treated with odevixibat and –0·03 (0·54) for patients receiving placebo; by week 24, mean change from baseline in height Z-score was 0·03 (0·53) for patients treated with odevixibat and –0·16 (0·36) for patients receiving placebo (secondary endpoint). Mean change from baseline in weight Z-score was 0·12 (SD 0·39) and 0·13 (0·28) at week 12 and 0·22 (0·46) and 0·10 (0·35) at week 24 for patients receiving odevixibat and placebo, respectively (secondary endpoint). Model-adjusted mean differences in change from baseline height and weight Z-scores for the all-odevixibat group versus placebo were not significant at week 12 (height: 0·04 [95% CI –0·22 to 0·31], p=0·74; weight: 0·02 [95% CI –0·17 to 0·20], p=0·85) or week 24 (height: 0·24 [95% CI –0·05 to 0·53], p=0·10; weight: 0·18 [95% CI –0·08 to 0·44], p=0·17).

Treatment with odevixibat improved sleep parameters for patients based on caregiver-reported information (secondary endpoints). At baseline, patients typically needed help falling asleep (mean percentage of days: odevixibat overall, 82% [SD 33]; placebo, 74% [43]), needed soothing (84% [33]; 73% [44]), or slept with their caregiver (73% [40]; 58% [46]) based on caregiver report (appendix pp 18–20). During the treatment period, mean reductions from baseline in these sleep parameters were larger (ie, more improved) with odevixibat versus placebo; changes from baseline with placebo were minimal (appendix pp 18–20). For example, by weeks 21 to 24 of treatment, mean changes from baseline for odevixibat versus placebo were –43% (SD 51) versus –3% (11) for percentage of days needing help falling asleep; –44% (49) versus –8% (23) for percentage of days with soothing; and –42% (46) versus –5% (18) for percentage of days sleeping with the caregiver.

Caregivers rated patients' daytime tiredness using a 5-point scale that ranged from 0 ("not tired at all") to 4 ("very, very tired"; exploratory endpoint). At baseline, all

patients had moderate daytime tiredness (mean score: odevixibat overall, 2·3 [SD 1·0]; placebo, 2·7 [0·6]). A greater mean reduction (ie, improvement) from baseline to weeks 21 to 24 was observed with odevixibat compared with placebo (–0·99 [SD 1·23] *vs* –0·49 [0·95], respectively). On the sleep outcomes of percentage of days seeing blood associated with scratching (secondary endpoint), number of awakenings (exploratory endpoint), or percentage of days taking medications to induce sleep (secondary endpoint), no clear differences were noted between treatment groups. For these parameters, there was wide variability in both baseline and end-of-treatment values. Data from PROs for sleep parameters are presented in the appendix table (pp 19–20). Briefly, for the small number of patients with available PRO assessments, greater mean improvements from baseline were observed in patients treated with odevixibat compared with patients treated with placebo in difficulty falling asleep and difficulty staying asleep (secondary endpoints).

Overall, 35 (83%) of the 42 patients receiving odevixibat experienced any TEAE; a similar rate was observed in patients receiving placebo (17 [85%] of 20; table 2). The overall rate of TEAEs was similar between odevixibat dose groups. Most TEAEs were mild or moderate in severity. The most commonly reported TEAEs (occurring in ≥10% of patients overall) were diarrhoea or frequent bowel movements (13 [31%] of 42 odevixibat-treated patients *vs* two [10%] of 20 placebo-treated patients), fever (12 [29%] of 42 *vs* five [25%] of 20), upper respiratory tract infection (eight [19%] of 42 *vs* three [15%] of 20), vomiting (seven [17%] of 42 *vs* none of 20), increased ALT (six [14%] of 42 *vs* one [5%] of 20), and increased serum bilirubin (five [12%] of 42 *vs* two [10%] of 20).

In total, 14 (33%) of 42 odevixibat-treated patients and three (15%) of 20 placebo-treated patients had TEAEs considered to be related to the study drug by the investigator (table 2). Drug-related TEAEs of diarrhoea or frequent bowel movement occurred in four (10%) of 42 odevixibat-treated patients and in one (5%) of 20 placebo-treated patients. The drug-related TEAEs of increased ALT, AST, and total bilirubin in the placebo group all occurred in a single patient and did not result in a change in dosing. In the odevixibat 40 µg/kg per day group, one patient experienced drug-related TEAEs of increased ALT and AST, but these did not result in a change in dosing; a second patient in this group experienced two drug-related TEAEs of increased bilirubin that resulted in interruption of study drug; and a third patient experienced drug-related TEAEs of increased ALT, AST, and total bilirubin that also resulted in interruption of study drug. In the odevixibat 120 µg/kg per day group, one patient experienced a drug-related TEAE of increased ALT that did not result in a change in dosing; a second patient experienced drug-related TEAEs of increased ALT, AST, and total bilirubin that resulted in interruption of study drug; and a third patient experienced two drug-related TEAEs of increased bilirubin that resulted in interruption of study drug. All patients with drug-related TEAEs of increased ALT, AST, or bilirubin completed the study except for one patient in the odevixibat 40 µg/kg per day group who discontinued due to inability to travel to the clinic.

No patients in this study had dose reductions. One patient who had received odevixibat 120 µg/kg per

| | Placebo (n=20) | Odevixibat 40 µg/kg per day (n=23) | Odevixibat 120 µg/kg per day (n=19) | Odevixibat, all doses (n=42) |
|---|---|---|---|---|
| Any TEAE | 17 (85%) | 19 (83%) | 16 (84%) | 35 (83%) |
| Mild | 6 (30%) | 11 (48%) | 8 (42%) | 19 (45%) |
| Moderate | 9 (45%) | 7 (30%) | 6 (32%) | 13 (31%) |
| Severe | 2 (10%) | 1 (4%) | 2 (11%) | 3 (7%) |
| Serious TEAEs | 5 (25%) | 0 | 3 (16%) | 3 (7%) |
| TEAEs leading to discontinuation | 0 | 0 | 1 (5%) | 1 (2%) |
| Liver-related TEAEs* | 4 (20%) | 5 (22%) | 6 (32%) | 11 (26%) |
| TEAEs occurring in ≥5% of patients overall, by preferred term | | | | |
| Diarrhoea or frequent bowel movements | 2 (10%) | 9 (39%) | 4 (21%) | 13 (31%) |
| Pyrexia | 5 (25%) | 7 (30%) | 5 (26%) | 12 (29%) |
| Upper respiratory tract infection | 3 (15%) | 3 (13%) | 5 (26%) | 8 (19%) |
| Vomiting | 0 | 4 (17%) | 3 (16%) | 7 (17%) |
| ALT increased | 1 (5%) | 3 (13%) | 3 (16%) | 6 (14%) |
| Total bilirubin increased | 2 (10%) | 3 (13%) | 2 (11%) | 5 (12%) |
| Abdominal pain | 0 | 2 (9%) | 1 (5%) | 3 (7%) |
| AST increased | 1 (5%) | 2 (9%) | 1 (5%) | 3 (7%) |
| Blood ALP increased | 1 (5%) | 1 (4%) | 2 (11%) | 3 (7%) |
| Nasopharyngitis | 1 (5%) | 1 (4%) | 2 (11%) | 3 (7%) |
| Pruritus | 1 (5%) | 2 (9%) | 1 (5%) | 3 (7%) |
| Cough | 3 (15%) | 0 | 2 (11%) | 2 (5%) |
| Urinary tract infection | 3 (15%) | 1 (4%) | 1 (5%) | 2 (5%) |
| Epistaxis | 1 (5%) | 1 (4%) | 1 (5%) | 2 (5%) |
| Viral upper respiratory tract infection | 1 (5%) | 2 (9%) | 0 | 2 (5%) |
| Vitamin D deficiency | 1 (5%) | 0 | 2 (11%) | 2 (5%) |
| Blood creatine phosphokinase increased | 2 (10%) | 0 | 1 (5%) | 1 (2%) |
| Influenza | 2 (10%) | 0 | 1 (5%) | 1 (2%) |
| Scratch | 2 (10%) | 1 (4%) | 0 | 1 (2%) |
| Constipation | 4 (20%) | 0 | 0 | 0 |
| Rash | 3 (15%) | 0 | 0 | 0 |
| Drug-related TEAEs | 3 (15%) | 7 (30%) | 7 (37%) | 14 (33%) |
| Drug-related TEAEs occurring in ≥5% of patients overall, by preferred term | | | | |
| ALT increased | 1 (5%) | 2 (9%) | 2 (11%) | 4 (10%) |
| AST increased | 1 (5%) | 2 (9%) | 1 (5%) | 3 (7%) |
| Total bilirubin increased | 1 (5%) | 2 (9%) | 2 (11%) | 4 (10%) |
| Diarrhoea or frequent bowel movements | 1 (5%) | 2 (9%) | 2 (11%) | 4 (10%) |

Data are patients, n (%). TEAE=treatment-emergent adverse event. ALT=alanine aminotransferase. AST=aspartate aminotransferase. ALP=alkaline phosphatase. *Study investigators were asked to indicate which reported events were considered liver related; the most commonly reported liver-related TEAEs were increased ALT (7% [n=3/42] with odevixibat *vs* 0% [n=0/20] with placebo) and increased blood bilirubin (5% [n=2/42] with odevixibat *vs* 5% [n=1/20] with placebo).

***Table 2:*** **Summary of adverse events during the double-blind treatment period**

day discontinued due to a drug-related TEAE of diarrhoea. All severe and serious TEAEs observed during the study are shown in the appendix (p 21). No deaths, treatment-related serious adverse events, or TEAEs related to liver decompensation occurred.

Mean changes in clinical chemistry, haematology, and laboratory parameters were generally small and not considered clinically meaningful. In addition, there were only minimal changes in fat-soluble vitamins during treatment with odevixibat (appendix p 22), and no patients experienced new or worsening fat-soluble vitamin deficiency refractory to clinically recommended vitamin supplementation.

Most patients (34 [60%] of 57 with available assessments) had abnormal liver findings on abdominal ultrasound at baseline, primarily hepatomegaly. At week 24, most patients with assessments (19 [83%] of 23) had no change from baseline in liver findings. Clinically significant improvements from baseline in liver echogenicity were reported for three patients (two in the odevixibat 120 µg/kg per day group and one in the placebo group), and liver findings worsened for one patient in the odevixibat 40 µg/kg per day group. This one patient whose liver findings worsened had a clinically significant worsening in echogenicity pattern (from smooth homogeneous at baseline to heterogeneous at week 24). He was aged 1 year at baseline, had PFIC2 and a history of vitamin deficiency, and received concomitant treatments including ursodeoxycholic acid and vitamin supplementation during the study. Despite the worsened liver ultrasound finding, this patient was a serum bile acid responder at the end of treatment, and the patient's pruritus score changed from 3·00 at baseline to 2·02 at weeks 21–24.

Splenomegaly was noted at baseline in 35% of patients (13 of 37 with data available) in the overall odevixibat group and in 25% of patients (five of 20 patients) in the placebo group. At week 24, most patients with data available (ten of 19) had no change in spleen size. One patient on odevixibat 40 µg/kg per day had improved spleen findings, while eight patients (two on placebo and six on odevixibat) showed worsening. A thorough medical review was conducted in these eight patients; however, no trends relative to haematological or hepatic biochemical parameters or common aetiologies could be identified. Of the two patients in the placebo group with worse spleen findings (neither of whom were serum bile acid responders or pruritus responders), one had improvements in ALT and AST from baseline to week 24 and the other had increases of 8 U/L and 23 U/L in ALT and AST, respectively; this second patient also had a slightly decreased platelet count (change from baseline, $-1\times10^9$/L) and an APRI score increase of 0·4 at week 24. Of the six patients in the odevixibat group with worse spleen findings, three had improvements in ALT, AST, and APRI score from baseline to week 24 (changes from baseline to week 24 in APRI score ranged from –0·1 to –0·3); two of these three patients were both serum bile acid responders and pruritus responders, and one was a serum bile acid responder but not a pruritus responder. The other three patients in the odevixibat group with worse spleen findings had increases from baseline ranging from 16 to 51 U/L for ALT and 9 to 35 U/L for AST, and of the two of these patients who had APRI scores at week 24, both had increases (changes from baseline to week 24 in APRI score were 1·2 and 0·5, respectively); none of these three patients were serum bile acid or pruritus responders. In the five of these six patients in the odevixibat group with worse spleen findings who had haematology samples, platelet counts decreased from baseline (range of changes from baseline, $-34$ to $-172\times10^9$/L).

## Discussion

In this study, odevixibat 40 and 120 µg/kg per day effectively reduced pruritus and serum bile acids relative to placebo in children with PFIC1 or PFIC2, meeting both primary efficacy endpoints. These effects occurred rapidly and were sustained through week 24. Overall, there were no unexpected TEAEs observed, and odevixibat was generally well tolerated, with similar safety profiles observed for both doses of odevixibat.

Two potentially serious features of PFIC are cholestasis leading to progressive hepatic damage and unrelenting pruritus.[5] Excess retained intrahepatic bile acids (reflected in elevated serum bile acids) have been associated with, and are thought to contribute to, the progressive hepatic damage seen in these children.[22] Surgical interruption of the enterohepatic circulation can reduce serum bile acids and pruritus, as well as improve other clinical outcomes;[13,23] importantly, patients who had lower serum bile acids after diversion surgery have longer transplant-free survival.[24,25] However, the response to biliary diversion can wane over time, and many patients experience recurring cholestasis or pruritus after surgery.[26] Liver transplantation is considered when patients with PFIC have end-stage liver disease, hepatocellular carcinoma, or pruritus unresponsive to off-label medical therapy or biliary diversion surgery.[6,27] However, liver transplantation is not curative in all patients.[26,28]

In the present study, odevixibat-associated reductions in pruritus were clinically meaningful. Interestingly, odevixibat also reduced concentrations of autotaxin, a proposed pruritogen,[27] by approximately half with 24 weeks of treatment. Reductions in pruritus and serum bile acids might result in reduced need for diversion surgery in patients treated with odevixibat; avoidance of such surgery and the potentially associated consequences (eg, surgical complications; permanent stoma[29]) could lead to enhanced quality of life. In addition, to the extent that accumulation of bile acids contributes to ongoing liver damage, reduction of bile acid concentrations by odevixibat could also result in improved hepatic health and delay of liver transplantation; this potential is also

supported by the improvement in hepatic biochemical parameters observed in patients receiving odevixibat. Therefore, odevixibat might have the potential to delay, or perhaps even prevent, surgical interventions in this patient population.

The findings on pruritus should be considered in light of general limitations associated with subjective measures; however, these study results are strengthened by several factors, namely: inclusion of a placebo control and positive findings on two primary endpoints, with one based on subjective measurement of symptoms and the other based on a biological parameter. In addition, due to the study's eligibility criteria (ie, exclusion of patients with extreme perturbations in hepatic parameters), these study findings might not be fully generalisable to all patients with PFIC with these characteristics; thus, further research into these populations is warranted.

Although part of this study was conducted during the COVID-19 pandemic, no patient was lost to follow-up during this time. Overall, most patients (49 [79%] of 62) completed the treatment period, with 11 (18%) rolling over early to the ongoing long-term extension study, PEDFIC 2.

In conclusion, odevixibat, administered as once a day oral capsules, represents a non-surgical, pharmacological option to interrupt the enterohepatic circulation in patients with PFIC. Odevixibat has the potential to improve the standard of care in patients with PFIC and provide treatment benefits in a disease group with high unmet medical needs.

#### Contributors

RJT was the coordinating investigator of this trial, and PH worked as medical officer of this trial. RJT, LK, JPM, and HJV were responsible for conceptualisation. RJT, RHJH, HJV, LK, JPM, and PH provided feedback on the study design of the trial. RJT, HA, RA, UB, PLC, PC, BD, LD, ÖD, BF, EG, TG, GG, WH, RHJH, BMK, SJK, FL, AL, EL, CLM, PM, HÖ, SRR, BR, MS, ESh, NS, ESt, MET, and HJV were site investigators and participated in patient recruitment, treatment, data collection, and follow-up. RJT, HA, UB, EG, TG, WH, BMK, SJK, FL, CLM, PM, SRR, ESh, NS, ESt, and HJV provided critical review of the data. RJT, HA, UB, ÖD, TG, WH, BMK, SJK, LK, CLM, ESt, and PH verified the data and were involved in data curation and analysis. 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 the critical review, revision, and final approval of the manuscript.

#### Declaration of interests

RJT is a consultant at Albireo, Generation Bio, Mirum, and Rectify and is a stockholder at Generation Bio and Rectify. HA is an advisor at Mirum and receives honoraria from Baxter Healthcare. UB is a consultant at Albireo and Mirum. PC is an investigator with clinical trial contracts at Mirum and Albireo. LD is a consultant at Albireo. EG is a consultant at Albireo, CTRS Laboratories, Mirum, and Vivet; and advisory board member at Albireo and Mirum. BMK is a consultant at Albireo, Audentes and Mirum and receives unrestricted educational grants to SickKids Foundation from Albireo and Mirum. SJK is a consultant at Albireo, Intercept, and Mirum. LK is a former employee and stockholder at Albireo. EL is a treasurer of GPGE congress, receives honoraria for presentation from Albireo, and participated in the PEDFIC 1 clinical trial. JPM is an employee and stockholder at Albireo, and has a patent planned and pending at Albireo. ESt reports grants paid to institution from Albireo and Mirum; honoraria from Albireo (paid to institution), Mirum, Univar, and GMP Orphan; travel support from Albireo, Mirum, and Astellas; he is a consultant at Mirum and advisor at Albireo, and Mirum. HJV reports grants to institution from Albireo and Mirum; consultant fees paid to institution from Ausnutria BV, Albireo, Danone/Nutricia Research, Intercept, Mirum, Orphalan, and Vivet; advisor fees paid to institution from Albireo and Mirum; and unpaid leadership role at Medical Advisory Board PFIC Network. PH is a former employee and stockholder at Albireo. All other authors declare no competing interests.

#### Data sharing

Qualified academic investigators and researchers can request additional participant-level, de-identified clinical data and supporting documents (statistical analysis plan) pertaining to this study. For details regarding data availability, instructions for requesting information, and our data disclosure policy, please email us at medinfo@albireopharma.com.

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