Odevixibat Therapy Improves Clinically Meaningful Endpoints in Children With Progressive Familial Intrahepatic Cholestasis: Data From the PEDFIC 1 and PEDFIC 2 Trials

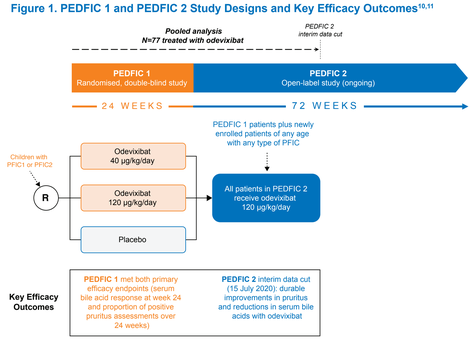
Richard J. Thompson[1], Lorenzo D'Antiga[2], Emmanuel Gonzalès[3], Saul J. Karpen[4], Patrick Horn[5], Kathleen M. Loomes[6], Cara L. Mack[7], Quanhong Ni[5], Henkjan J. Verkade[8], Lise Kjems[5]

[1]Institute of Liver Studies, King's College London, London, UK; [2]Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; [3]Hépatologie et Transplantation Hépatique Pédiatriques, Centre de Référence de l'Atrésie des Voies Biliaires et des Cholestases Génétiques, FSMR FILFOIE, ERN RARE LIVER, Hôpital Bicêtre, AP-HP, Université Paris-Saclay, Hépatinov, Inserm U 1193, Paris, France; [4]Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, GA, USA; [5]Albireo Pharma, Inc., Boston, MA, USA; [6]Children's Hospital of Philadelphia, Philadelphia, PA, USA; [7]Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA; [8]Department of Paediatrics, University of Groningen, Beatrix Children's Hospital/University Medical Centre Groningen, Groningen, the Netherlands

INTRODUCTION

- Progressive familial intrahepatic cholestasis (PFIC) is a group of rare cholestatic liver diseases resulting from mutations in proteins with diverse functions, including familial intrahepatic cholestasis protein 1 (FIC1; encoded by *ATP8B1*), bile salt export pump (BSEP; encoded by *ABCB11*), and multidrug resistance protein 3 (MDR3; encoded by *ABCB4*); corresponding with PFIC type 1 (PFIC1), PFIC2, and PFIC3, respectively[1]
- Children with PFIC may experience impaired bile flow, high serum bile acids, intractable pruritus, impaired growth, and life-threatening progressive liver disease[1]
  - Pruritus may be so severe as to cause sleep disturbance, negatively affect patients' and their families' quality of life, or necessitate liver transplant[2,3]
- Medications such as ursodeoxycholic acid (UDCA) and rifampicin are commonly used as initial treatments for PFIC, but these may not provide adequate relief or prevent disease progression in all patients[4,5]; however, a number of novel, targeted pharmacotherapies are in development[5]
- Currently, available effective, long-term treatment options are limited to surgical disruption of the enterohepatic circulation and liver transplantation[6]
- Thus, there is a need for non-invasive treatments that can alleviate the signs and symptoms of PFIC associated with negative long-term consequences (eg, pruritus and liver transplantation, elevated bile acids, and reduced native liver survival)[7,8]
- Odevixibat, an ileal bile acid transporter inhibitor, is in development to treat cholestatic liver diseases, including PFIC[9]
- Odevixibat has been investigated as treatment for PFIC in two phase 3 studies: PEDFIC 1 and PEDFIC 2 (**Figure 1**)[10,11]

Figure 1. PEDFIC 1 and PEDFIC 2 Study Designs and Key Efficacy Outcomes[10,11]



PFIC, progressive familial intrahepatic cholestasis; R, randomisation.

- Here, we describe key outcomes in children with PFIC
  - This analysis used pooled data from the PEDFIC 1 and PEDFIC 2 studies and assessed treatment effects in patients who received placebo in PEDFIC 1 and odevixibat in PEDFIC 1 and/or PEDFIC 2

METHODS

Study Designs

- PEDFIC 1 was a double-blind, randomised, placebo-controlled, multicentre, phase 3 study to investigate the efficacy and safety of odevixibat compared with placebo in children with PFIC (**Figure 1**)
  - Children aged ≥6 months to ≤18 years with a confirmed diagnosis of PFIC1 or PFIC2 were enrolled
  - Patients were randomly assigned 1:1:1 to receive odevixibat 40 or 120 µg/kg/day or matching placebo for 24 weeks
- PEDFIC 2 is an ongoing phase 3, multicentre, open-label extension study to investigate the long-term efficacy and safety of a once-daily 120 ug/kg dose of odevixibat in patients with PFIC (**Figure 1**)
  - Patients are enrolled in 1 of 2 cohorts
    - Cohort 1 included patients who enrolled from PEDFIC 1
    - Cohort 2 includes patients of any age with any type of PFIC who have elevated serum bile acids and cholestatic pruritus and who either did not meet eligibility criteria for PEDFIC 1 or were eligible for enrolment after recruitment had ended
  - The study includes a screening period (for cohort 2 only) and a 72-week treatment period

Pooling of Data and Assessments

- Data from PEDFIC 1 and PEDFIC 2 were pooled to allow for a more comprehensive evaluation of efficacy across a larger PFIC population with longer follow-up
  - This pooled analysis covers the period from the first-ever dose of odevixibat in PEDFIC 1 or PEDFIC 2 through the PEDFIC 2 interim data cut (15 July 2020)
  - This PEDFIC 2 interim analysis focuses on week 24, which represents approximately 48 weeks of cumulative odevixibat treatment for patients who received active treatment in the 24-week PEDFIC 1 study
  - Data for the placebo group are from patients who received placebo during PEDFIC 1
  - Baseline was defined as the last available assessment prior to first dose of odevixibat or placebo
- The following key endpoints were assessed in this pooled analysis in patients receiving placebo and any dose of odevixibat:
  - Change in serum bile acid levels
  - Change in observer-reported pruritus score (measured using the PRUCISION scale; range: 0–4)
  - Change in growth and sleep parameters
  - Safety monitoring
- This pooled analysis was exploratory, and all outcomes described below are summarized descriptively

RESULTS

Patients

- In this pooled analysis, 77 patients have received odevixibat
  - This includes 19 patients who received placebo in PEDFIC 1 and rolled into PEDFIC 2, where they initiated odevixibat;
  - 42 patients who received odevixibat in PEDFIC 1 (of these, 34 rolled into PEDFIC 2, where they continued odevixibat); and
  - 16 newly enrolled patients in PEDFIC 2, all of whom received odevixibat
- In all 77 patients, the median duration of exposure to odevixibat at the data cutoff date was 37 weeks; 31% of these patients had <24 weeks' exposure, 29% had ≥24–<48 weeks' exposure, and 40% had ≥48 weeks of exposure to odevixibat
  - At the data cutoff date, a majority of patients (68 of 77; 88%) who received odevixibat were continuing on treatment
- For all patients in the pooled analysis (**Table 1**)
  - More than half of the patients had PFIC2
  - Most patients were receiving UDCA and/or rifampicin at study entry
  - Almost all patients had a history of significant pruritus, and most had levels of serum bile acids >100 µmol/L within the past 6 months

Table 1. Patient Demographics and Baseline Characteristics in the Pooled Population

	Placebo (n=20)	Odevixibat, Any Dose (n=77)
Age, median (range), y	2.8 (0.5–15)	4.1 (0.6–19.5)
Female, n (%)	8 (40)	39 (51)
Race, n (%)		
White	17 (85)	66 (86)
Black	0	2 (3)
Asian	1 (5)	2 (3)
Height, mean (SD), cm	89.0 (24.4)	98.6 (23.9)
Height Z score, mean (SD)	−2.3 (1.5)	−1.9 (1.5)
Weight, mean (SD), kg	14.5 (9.8)	18.1 (12.1)
Weight Z score, mean (SD)	−1.5 (1.4)	−1.1 (1.4)
PFIC type, n (%)		
PFIC1	5 (25)	20 (26)
PFIC2	15 (75)	51 (66)
PFIC3	N/A	5 (6)
Other	N/A	1 (1)
UDCA at baseline, n (%)	18 (90)	62 (81)
Rifampicin at baseline, n (%)	17 (85)	48 (62)
Significant pruritus present per investigator report, n (%)	19 (95)	74 (96)
Serum bile acid levels >100 µmol/L in the 6 months prior to screening, n (%)	12 (60)	52 (68)

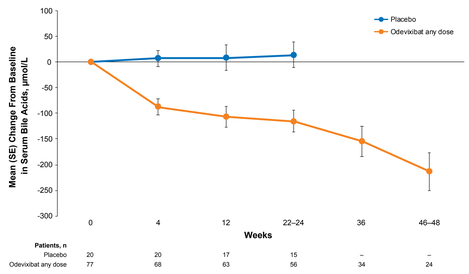
N/A, not applicable; PFIC, progressive familial intrahepatic cholestasis; SD, standard deviation, UDCA, ursodeoxycholic acid.

Efficacy

Serum Bile Acids

- At baseline, the mean (SE) serum bile acid level was 250 (15) µmol/L in the odevixibat group; mean (SE) serum bile acids decreased from baseline by 88 (16) µmol/L at week 4 after starting odevixibat and by 213 (37) µmol/L at week 48 (**Figure 2**)
- In patients treated with placebo, the mean (SE) baseline serum bile acid level was 248 (22) µmol/L, which increased by a mean (SE) of 13 (25) µmol/L at week 24

Figure 2. Mean (SE) Change From Baseline in Serum Bile Acid Concentration by Visit

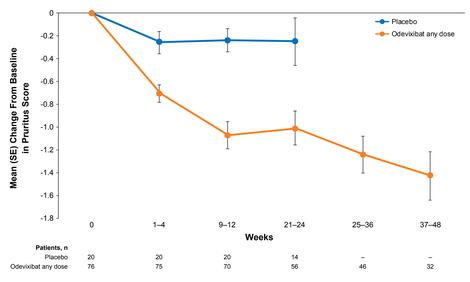


SE, standard error.

Pruritus

- At baseline, mean (SE) pruritus score in the odevixibat group was 2.9 (0.1); mean (SE) pruritus score decreased from baseline by 0.7 (0.1) points over weeks 1−4 after starting odevixibat and by 1.4 (0.2) points over weeks 37−48 (**Figure 3**)
- In patients treated with placebo, mean (SE) pruritus score at baseline was 3.0 (0.1), which decreased by a mean (SE) of 0.3 (0.2) points at week 24

Figure 3. Mean (SE) Change From Baseline in Scratching Severity Score Over Time



SE, standard error.

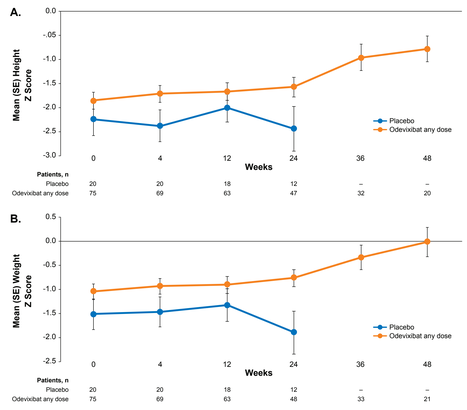
Growth

- In the odevixibat group, mean (SE) height Z scores improved from −1.9 (0.2) at baseline to −0.8 (0.3) at week 48 (**Figure 4A**), and mean (SE) weight Z scores improved from −1.1 (0.2) at baseline to 0.0 (0.3) at week 48 (**Figure 4B**)
- In patients treated with placebo, mean (SE) height Z scores were −2.3 (0.3) at baseline and −2.5 (0.5) at week 24; mean weight Z scores were −1.5 (0.3) at baseline and −1.9 (0.4) at week 24

Sleep

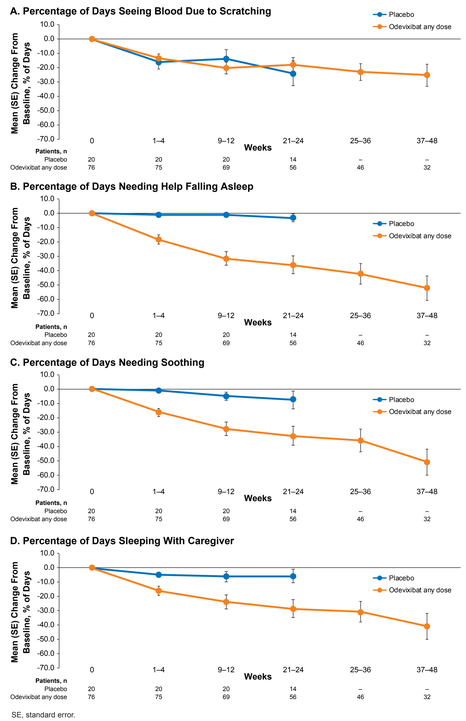
- Odevixibat-treated patients had reductions from baseline to weeks 37–48 in observer-reported percentage of days seeing blood due to scratching (39% to 14%), needing help falling asleep (77% to 32%), needing soothing (74% to 35%), and sleeping with caregiver (65% to 30%) (**Figure 5**)
  - In patients treated with placebo, baseline and weeks 21−24 percentage of days were: 50% to 24% for seeing blood due to scratching, 74% to 67% for needing help falling asleep, 73% to 61% for needing soothing, and 58% to 54% for sleeping with caregiver

Figure 4. Effects of Odevixibat on Height (A) and Weight (B) From Baseline Through Week 48



SE, standard error.

Figure 5. Mean Change From Baseline in Sleep Parameters Over Time



SE, standard error.

Safety

- The most commonly reported treatment-emergent adverse events (TEAEs; in ≥10%) among patients in the odevixibat group (n=77) were pyrexia (odevixibat vs placebo: 26% vs 25%), upper respiratory tract infection (25% vs 15%), diarrhoea (20% vs 5%), blood bilirubin increased (16% vs 10%), cough (16% vs 15%), vomiting (14% vs 0%), alanine aminotransferase increased (13% vs 5%), and pruritus (12% vs 5%)
- Overall, 61 of 77 (79%) patients receiving odevixibat experienced any TEAE, most of which were mild or moderate; a similar rate of any TEAEs was observed in patients receiving placebo during PEDFIC 1 (17/20 [85%])
- Drug-related TEAEs were reported in 32 of 77 (42%) patients receiving odevixibat and 3 of 20 (15%) patients who received placebo
- Four patients receiving odevixibat had TEAEs leading to discontinuation, but only 1 of these (a mild AE of diarrhoea in a patient receiving 120 µg/kg/day odevixibat during PEDFIC 1) was considered related to treatment
- For patients who received odevixibat, 7 serious TEAEs occurred; for those who received placebo, 5 serious TEAEs occurred; however, none of the serious TEAEs reported in either group were considered drug related
- No deaths occurred

CONCLUSIONS

- Patients with PFIC treated with odevixibat for up to 48 weeks experienced clinically meaningful effects on serum bile acids, pruritus, growth, and sleep parameters
  - The observed growth gains are consistent with those previously reported after surgical biliary diversion[12]
  - Pruritus improvements were mirrored by improvements in sleep characteristics and other aspects of cholestatic disease and may be particularly impactful
- Odevixibat treatment was generally well tolerated
- Future analyses will provide additional long-term data on the effects of odevixibat as patients continue on treatment

REFERENCES

1. Bull LN, Thompson RJ. *Clin Liver Dis.* 2018;22:657-69.
2. Torfgard K, et al. Presented at: Annual Meeting of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; October 25-28, 2018; Hollywood, FL.
3. Thebaut A, et al. *Clin Res Hepatol Gastroenterol.* 2018;42:103-9.
4. European Association for the Study of the Liver. *J Hepatol.* 2009;51:237-67.
5. Kamath BM, et al. *Liver Int.* 2020;40:1812-22.
6. Baker A, et al. *Clin Res Hepatol Gastroenterol.* 2019;43:20-36.
7. van Wessel DBE, et al. *Hepatology.* 2021;Mar 5 Online ahead of print.
8. Bjørnland K, et al. *Eur J Pediatr Surg.* 2020;Jul 24 Online ahead of print.
9. Graffner H, et al. *Aliment Pharmacol* Ther. 2016;43:303-10.
10. Thompson RJ, et al. Presented at: Annual Meeting of the American Association for the Study of Liver Diseases; November 13-16, 2020. [Abstract LO4].
11. Thompson RJ, et al. Presented at: Annual Meeting of the American Association for the Study of Liver Diseases; November 13-16, 2020. [Abstract LP19].
12. Bull LN, et al. *Hepatol Commun.* 2018;2:515-28.

AUTHOR DISCLOSURES

R.J. Thompson: Albireo, Alnylam, EVOX Therapeutics, Generation Bio, Mirum Pharma, Rectify Therapeutics, Retrophin, Qing Therapeutics, and Sana Biotechnology – Consultant
L. D'Antiga: Alexion, Mirum, Selecta, Vivet, and Spark – Consultant
E. Gonzalès: Laboratoires C.T.R.S., Mirum Pharma, and Albireo – Consultant
S.J. Karpen: Albireo, Intercept, LogicBio, and Mirum Pharma – Consultant
K.M. Loomes: Albireo, Mirum, Retrophin – Consultant
C.L. Mack: Albireo – Consultant
H.J. Verkade: Ausnutria BV, Albireo, Danone/Nutricia Research, Intercept, Mirum Pharma, Orphalan, and Vivet – Consultant
L. Kjems, Q. Ni and **P. Horn** are employees of Albireo Pharma, Inc.

ACKNOWLEDGMENTS

This study was sponsored by Albireo. Editorial and medical writing support was provided by Peloton Advantage, LLC, an OPEN Health company, and was funded by Albireo Pharma, Inc.

Presented at the International Liver Congress; June 23–26, 2021 (Virtual)