Efficacy and Safety Outcomes With Odevixibat in Children With Progressive Familial Intrahepatic Cholestasis Due to Deficiencies in Multidrug Resistance Protein 3 (PFIC Type 3) or Myosin 5B (PFIC Type 6)

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INTRODUCTION

- Progressive familial intrahepatic cholestasis (PFIC) is a group of rare, inherited liver diseases characterized by impaired bile flow, high serum bile acids, intractable pruritus, impaired growth, and life-threatening progressive liver disease[1]
- PFIC results from mutations in genes encoding proteins with diverse functions, including familial intrahepatic cholestasis protein 1 (FIC1), bile salt export pump (BSEP), and multidrug resistance protein 3 (MDR3), corresponding with PFIC type 1 (PFIC1), PFIC type 2 (PFIC2), and PFIC type 3 (PFIC3), respectively[1-3]; initial descriptions of PFIC were primarily based on data from patients with PFIC1 or PFIC2[2]
  - Clinical data on other types of PFIC are currently limited
- Odevixibat, an ileal bile acid transporter inhibitor, is approved in the European Union and the United Kingdom for the treatment of PFIC in patients aged 6 months or older[4]
- In the phase 3, randomized, placebo-controlled PEDFIC 1 study, odevixibat treatment reduced serum bile acids, improved pruritus, and was generally well tolerated in patients with PFIC1 or PFIC2[5]
- The ongoing open-label, phase 3 PEDFIC 2 study is assessing the effects of odevixibat in patients with any type of PFIC[6]
- As of a data cutoff date of December 4, 2020, 6 patients with PFIC types other than PFIC1 or PFIC2 had enrolled in PEDFIC 2
  - Here, we describe efficacy and safety outcomes in this subset of patients, which comprises 5 patients with PFIC3 and 1 with PFIC type 6 (PFIC6, resulting from mutation of the gene encoding myosin 5B [MYO5B])

METHODS

PEDFIC 2 Patients and Study Design

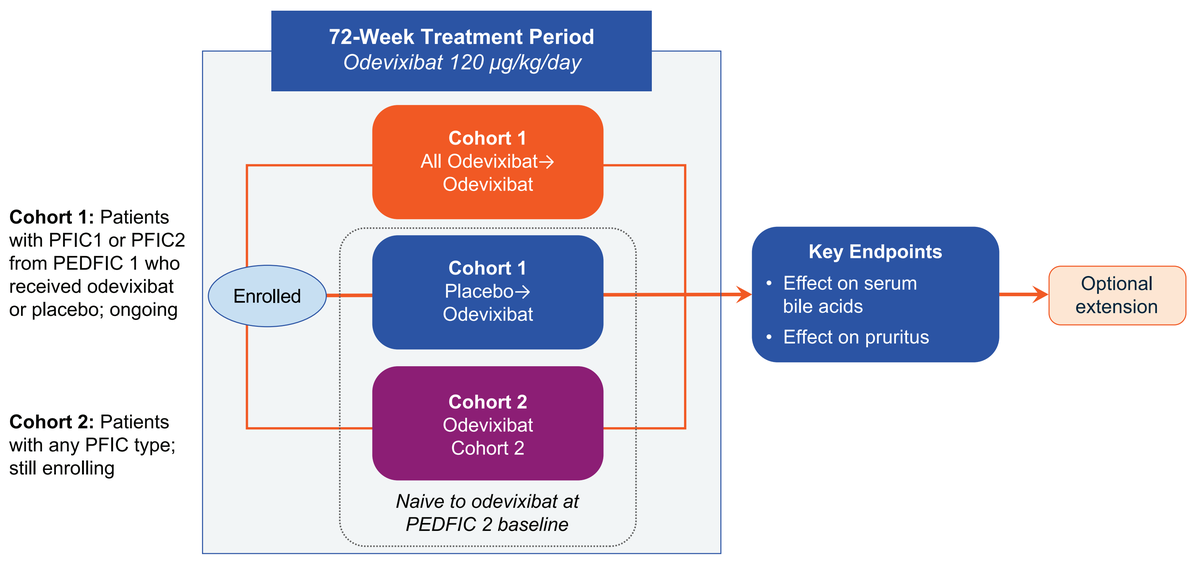
Patients

- In PEDFIC 2, eligible patients are enrolled into one of 2 cohorts, based on the following criteria:
  - Cohort 1: pediatric patients with PFIC1 or PFIC2 from PEDFIC 1
  - Cohort 2: patients of any age with any PFIC type; these are newly enrolled patients
- In both cohorts, eligible patients are those with genetically confirmed PFIC, elevated serum bile acids (≥100 µmol/L), and significant pruritus (ie, itching or scratching score of ≥2 per patient/caregiver report using the PRUCISION instrument)

Study Design

- PEDFIC 2 includes a 72-week treatment period (**Figure 1**) in which all patients receive oral, once-daily odevixibat 120 µg/kg

Figure 1. PEDFIC 2 Study Design Schematic



PFIC, progressive familial intrahepatic cholestasis.

Outcomes, Assessments, and Statistical Analysis

- The following outcomes were assessed in patients with PFIC3 or PFIC6:
  - Change from baseline in serum bile acids, pruritus, hepatic biochemical parameters, growth, and sleep
  - Serum bile acid response (ie, serum bile acids reduced ≥70% or levels ≤70 µmol/L)
  - Proportion of positive pruritus assessments (PPAs) at the patient level (ie, pruritus score ≤1 or a ≥1-point drop from baseline)
  - Treatment-emergent adverse events (TEAEs)
- Patient pruritus and sleep were evaluated twice daily by caregivers using the validated PRUCISION scale; pruritus responses range from 0 to 4, with higher scores indicating worse symptoms[7]

RESULTS

Patients

- A total of 5 patients with PFIC3 (age range, 3.7–13.3 years) and 1 patient with PFIC6 (aged 12.8 years) were enrolled (**Table 1**)
- Mean (range) exposure was 41 (34−54) weeks for the 5 PFIC3 patients and 54 weeks for the 1 PFIC6 patient
- All 6 patients were ongoing in the study at the data cutoff

Table 1. Patient Demographics, Baseline Characteristics, and Odevixibat Exposure

	Patient 1 (PFIC3)	Patient 2 (PFIC3)	Patient 3 (PFIC3)	Patient 4 (PFIC3)	Patient 5 (PFIC3)	Patient 6 (PFIC6)
Age, years	5.0	11.2	13.3	6.1	3.7	12.8
Sex	F	F	F	F	F	F
Serum bile acids, µmol/L	363	168	125	119	288	169
Pruritus score	4.0	3.0	2.3	3.0	2.4	2.1
Serum ALT, U/L	115	72	111	94	47	50
Total bilirubin, mg/dL	2.6	1.7	1.7	1.7	1.1	6.0
Odevixibat exposure, weeks	34	54	38	39	41	54

ALT, alanine aminotransferase; F, female; PFIC, progressive familial intrahepatic cholestasis.

Efficacy

- From baseline to week 36 of odevixibat treatment, mean improvements were observed in serum bile acids, pruritus scores, height and weight Z scores, and most sleep parameters in patients with PFIC3 and PFIC6; mean changes in alanine aminotransferase and total bilirubin were somewhat more variable (**Table 2**)

Table 2. Effects of Odevixibat Treatment in Patients With PFIC3 and PFIC6

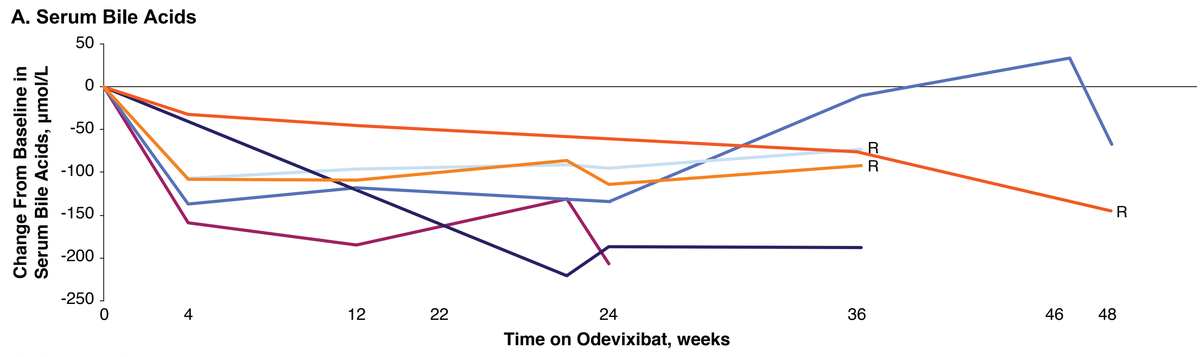
Parameter	Patients With PFIC Due to MDR3 Deficiency (PFIC3)		Patient With PFIC Due to MYO5B Deficiency (PFIC6)	
	Mean (SE) baseline value (n=5)	Mean (SE) change from baseline to week 36 (n=4)	Baseline value (n=1)	Change from baseline to week 36 (n=1)
Serum bile acids, µmol/L	212 (48)	–91 (37)	169	–78
Pruritus score	2.9 (0.3)	–1.6 (0.4)[a]	2.1	–1.8[a]
Serum ALT, U/L	88 (13)	67 (21)	50	89
Total bilirubin, µmol/L	30 (4)	18 (13)	102	–83
Height Z score	–2.0 (0.5)	0.2 (0.2)	–2.5	0.1
Weight Z score	–1.4 (0.6)	0.1 (0.4)	–1.0	0.5
% of days with bleeding associated with scratching	18 (14)	6 (6)[a]	0	0[a]
% of days needing help falling asleep	60 (21)	–29 (24)[a]	21	–21[a]
% of days needing soothing	59 (20)	–28 (21)[a]	36	–36[a]
% of days sleeping with caregiver	60 (21)	–27 (22)[a]	0	0[a]

[a]Mean change to weeks 34–36. ALT, alanine aminotransferase; MDR3, multidrug resistance protein 3; MYO5B, myosin 5B; PFIC, progressive familial intrahepatic cholestasis.

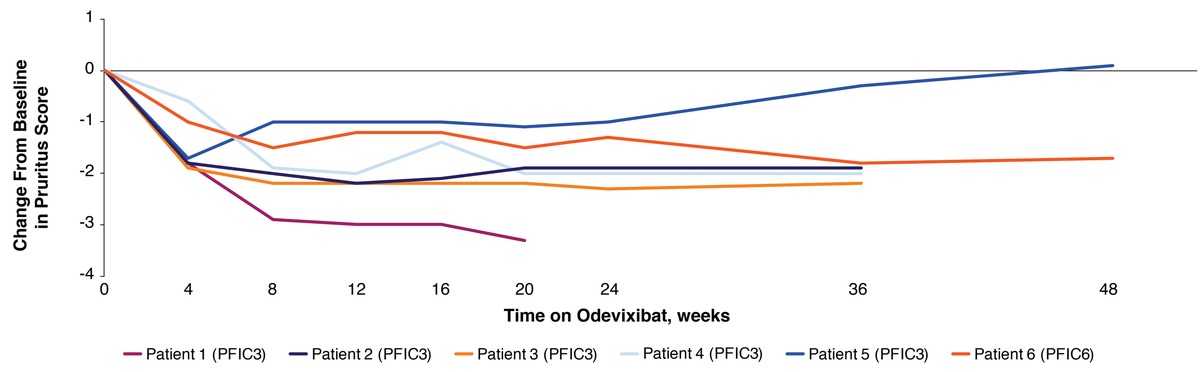
- From baseline to last assessment, all patients with PFIC3 or PFIC6 had reductions in serum bile acids and all but 1 patient (PFIC3) had reductions in pruritus score (**Figure 2**)
  - Three patients, including 2 with PFIC3 and 1 with PFIC6, met criteria for serum bile acid response at last assessment (**Figure 2**)

Figure 2. Change From Baseline in Serum Bile Acids and Pruritus Score in Patients With PFIC3 or PFIC6

A. Serum Bile Acids



B. Pruritus Score



PFIC, progressive familial intrahepatic cholestasis; R, serum bile acid responder (ie, patient with at least a 70% reduction in fasting serum bile acid concentration from baseline or reaching a level ≤70 µmol/L).

- Over the interval from weeks 0–36, PPAs in 5 patients with available data (4 with PFIC3, 1 with PFIC6) were ≥85%; in 1 additional patient with PFIC3 with data over the interval from weeks 0−22, PPAs were 99% (data not shown)

Safety

- Odevixibat was generally well tolerated up to the data cutoff in PEDFIC 2 in patients with PFIC3 or PFIC6
- Overall, 5 of 6 patients with PFIC3 or PFIC6 experienced any TEAE (**Table 3**)
  - Most TEAEs were mild or moderate in severity
  - There were no serious TEAEs, TEAEs leading to discontinuation, or deaths

Table 3. Summary of TEAEs in Patients With PFIC3 or PFIC6

	Patient 1 (PFIC3)	Patient 2 (PFIC3)	Patient 3 (PFIC3)	Patient 4 (PFIC3)	Patient 5 (PFIC3)	Patient 6 (PFIC6)
TEAEs	0	3	5	5	3	1
Mild	0	1	0	2	3	1
Moderate	0	2	4	0	0	0
Severe	0	0	1	3	0	0
Serious TEAEs	0	0	0	0	0	0
TEAEs leading to discontinuation	0	0	0	0	0	0
Common TEAEs (occurring in ≥2 patients with PFIC3 or PFIC6), by preferred term						
ALT increased	0	0	1	1	0	0
Total bilirubin increased	0	1	2	0	0	0
INR increased	0	1	1	0	0	0
Vitamin D deficiency	0	0	0	1	2	0

ALT, alanine aminotransferase; INR, international normalized ratio; PFIC, progressive familial intrahepatic cholestasis; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Patients with PFIC3 and PFIC6 experienced clinical benefits during up to 54 weeks of odevixibat treatment, including reductions in serum bile acids and improvement in pruritus symptoms, growth, and sleep parameters
- Odevixibat treatment was generally well tolerated in patients with PFIC3 and PFIC6

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AUTHOR DISCLOSURES

H. Özen: None. **E. Sokal:** Promethera Biosciences – Founder, chairman of the board of directors, and member of the executive committee. **F. Lacaille:** Alexion – Consultant. **B. Dalgic:** None. **Q. Ni, L. Kjems, P. Horn:** Albireo – Current or former employment

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