Effects on Serum Bile Acids, Pruritus, and Safety With Up to 72 Weeks of Odevixibat Treatment: Pooled Data From the PEDFIC 1 and PEDFIC 2 Studies in Children With Progressive Familial Intrahepatic Cholestasis

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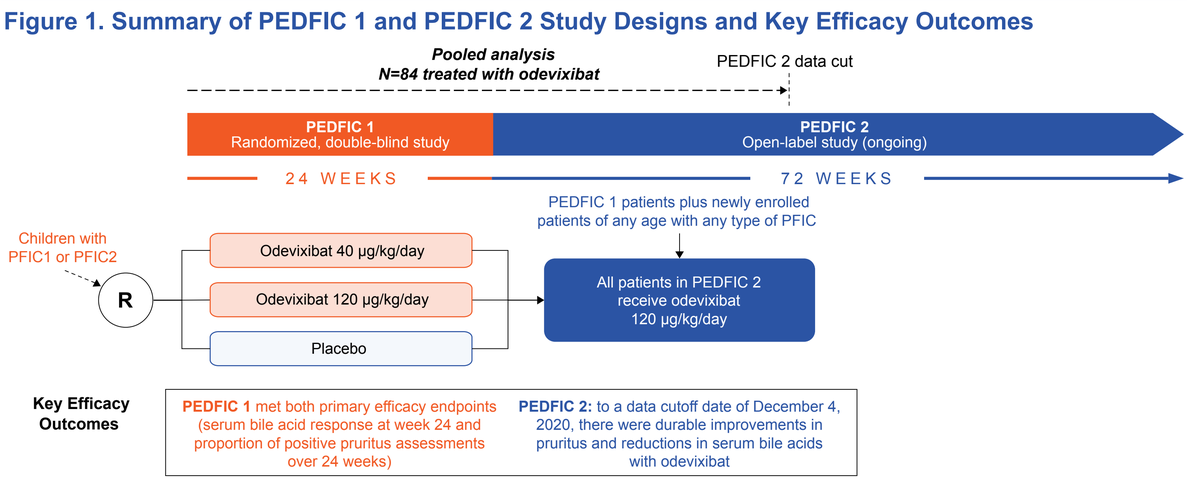
INTRODUCTION

- Progressive familial intrahepatic cholestasis (PFIC) is a group of rare cholestatic liver diseases of hepatocellular origin[1,2]
  - Children with PFIC may experience impaired bile flow, high serum bile acid levels, intractable pruritus, impaired growth, and life-threatening progressive liver disease[1,3]
- Historically, initial medical treatments for PFIC were limited; PFIC may also be treated with surgical interventions[4]
- 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[5]
- The phase 3 PEDFIC 1 and PEDFIC 2 studies evaluated the efficacy and safety of odevixibat in patients with PFIC (**Figure 1**)[6,7]
- Using pooled data from these studies, we analyzed changes in serum bile acids and pruritus and report the safety profile in patients treated for up to 72 weeks, comparing those who responded to odevixibat treatment with nonresponders

Figure 1. Summary of PEDFIC 1 and PEDFIC 2 Study Designs and Key Efficacy Outcomes



PFIC, progressive familial intrahepatic cholestasis; R, randomization.

METHODS

Data Pooling

- Patients eligible for PEDFIC 1 and PEDFIC 2 had PFIC, elevated serum bile acids, and significant pruritus
- Data from PEDFIC 1 and PEDFIC 2 were pooled for this analysis (**Figure 1**)
  - The pooled analysis period spans from the first-ever odevixibat dose in PEDFIC 1 or PEDFIC 2 through a data cutoff date of December 4, 2020

Assessments and Data Analysis

- In both PEDFIC 1 and PEDFIC 2, key efficacy outcomes were related to the effects of odevixibat on serum bile acids and pruritus
  - Blinded serum bile acid measurements were taken at all study visits
  - Pruritus was scored from 0 to 4 by caregivers using a validated scale; higher scores indicate worse symptoms, and a decrease of ≥1 point from baseline is clinically meaningful[8]
- Definitions of treatment response
  1. **Serum Bile Acid Response:** ≥70% reduction in serum bile acids or serum bile acids ≤70 µmol/L (baseline level had to be >70 µmol/L for this analysis) at last available assessment up to week 72
  2. **Serum Bile Acid and/or Pruritus Response:** Serum bile acid response at last available assessment and/or pruritus score reduction of ≥1 point from baseline based on last available monthly or 12-week interval score up to week 72

RESULTS

Patients

- Overall, 84 patients received odevixibat during the pooled analysis period, and the overall median (range) exposure from the first dose of odevixibat was 53 (3−128) weeks
- Patient demographics and baseline characteristics for all patients with odevixibat exposure as of the data cut-off date and for treatment responders and nonresponders are depicted in **Table 1**

Table 1. Patient Demographics and Baseline Characteristics

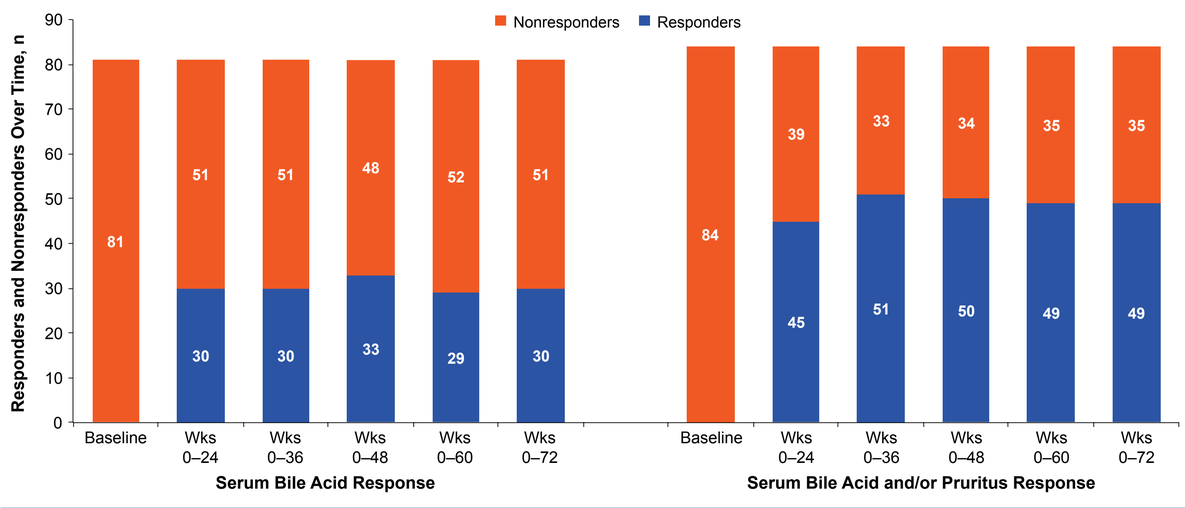
		Serum Bile Acid Response (≥70% reduction in serum bile acids or serum bile acids ≤70 µmol/L)		Serum Bile Acid and/or Pruritus Response (pruritus score reduction of ≥1 point from baseline)	
	All Odevixibat N=84	Responder n=30	Nonresponder n=51	Responder n=49	Nonresponder n=35
Age, mean (SD), years	5.0 (4.8)	4.3 (4.5)	5.8 (5.0)	4.8 (4.5)	5.5 (5.2)
Female, n (%)	41 (49)	20 (67)	21 (41)	28 (57)	13 (37)
PFIC type, n (%)					
PFIC1 (FIC1 deficiency)	22 (26)	3 (10)	19 (37)	11 (22)	11 (31)
PFIC2 (BSEP deficiency)	56 (67)	24 (80)	29 (57)	34 (69)	22 (63)
PFIC3 (MDR3 deficiency)	5 (6)	2 (7)	3 (6)	3 (6)	2 (6)
Other (MYO5B deficiency)	1 (1)	1 (3)	0	1 (2)	0
Pruritus score, mean (SE)	2.8 (0.1)	2.8 (0.1)	2.9 (0.1)	2.8 (0.1)	2.8 (0.1)
Serum bile acids, mean (SE)	246 (14)	226 (26)	261 (17)	237 (20)	259 (20)
UDCA at baseline, n (%)	64 (76)	24 (80)	39 (77)	38 (78)	26 (74)
Rifampicin at baseline, n (%)	51 (61)	14 (47)	35 (69)	27 (55)	24 (69)
ALT, mean (SD), U/L	92 (104)	113 (147)	81 (70)	105 (126)	75 (58)
AST, mean (SD), U/L	97 (67)	91 (55)	102 (74)	100 (66)	94 (68)
Total bilirubin, mean (SD), mg/dL	2.9 (3.5)	1.6 (2.0)	3.8 (4.0)	2.2 (2.1)	4.0 (4.7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSEP, bile salt export protein; FIC, familial intrahepatic cholestasis; MDR3, multidrug resistance protein 3; MYO5B, myosin 5B; PFIC, progressive familial intrahepatic cholestasis; SD, standard deviation; SE, standard error; UDCA, ursodeoxycholic acid.

Treatment Response

- Approximately 40% of patients met criteria for serum bile acid response during odevixibat treatment (**Figure 2**)
- When treatment response was defined by serum bile acid and/or pruritus criteria, approximately 60% of patients treated with odevixibat achieved a treatment response (**Figure 2**)

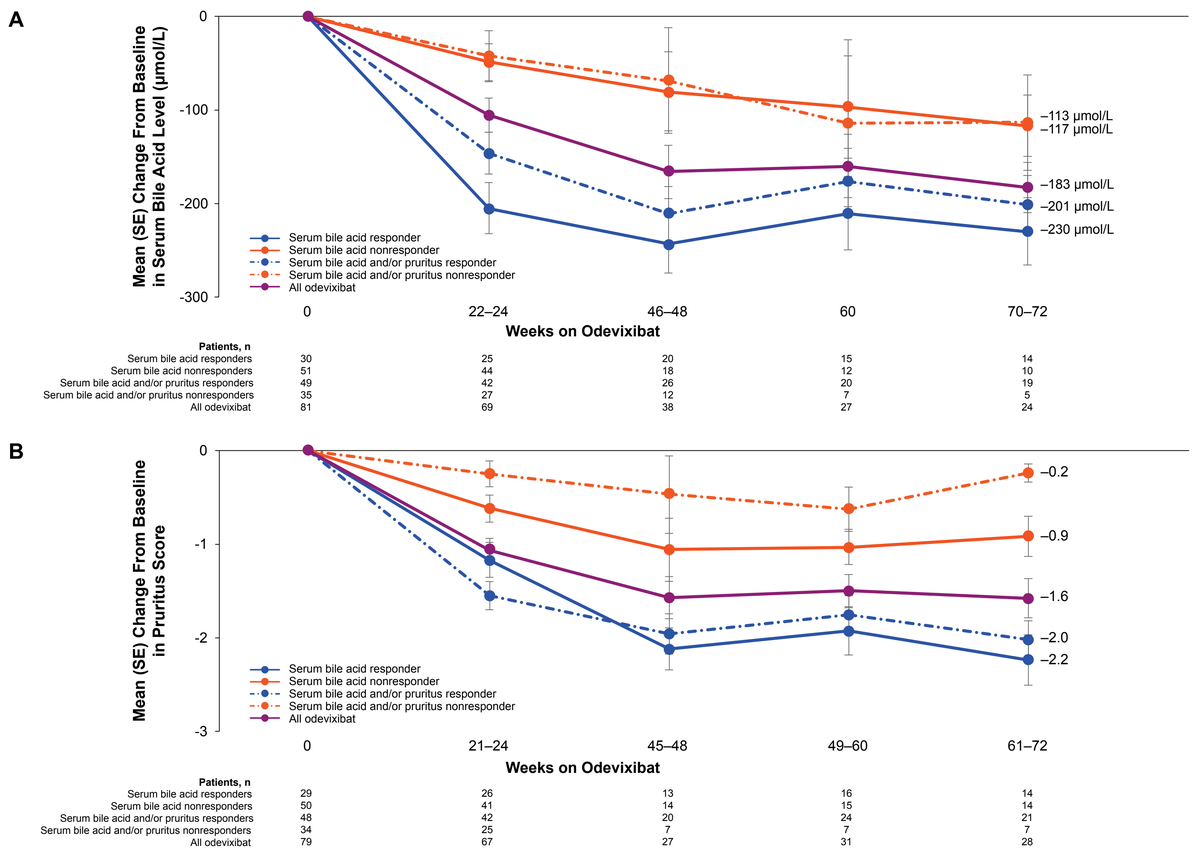
Figure 2. Numbers of Patients Meeting Responder Criteria Over Time During Odevixibat Treatment



Serum Bile Acid Levels and Pruritus Scores

- From the start of odevixibat treatment to the end of the assessment period, responders had greater mean changes from baseline in serum bile acid levels and pruritus scores than nonresponders (**Figure 3A** and **B**)

Figure 3. Change From Baseline in Serum Bile Acid Levels (A) and Pruritus Scores (B) Over Time in Treatment Responders and Nonresponders and Among All Odevixibat-Treated Patients



Values at the right side of the graph represent mean changes during the last assessment interval.
SE, standard error.

Safety

- Among all patients, 85% had any treatment-emergent adverse events (TEAEs); this was similar across responders and nonresponders (83%–87%; **Table 2**)
- The most common TEAEs in odevixibat-treated patients were pyrexia, upper respiratory tract infections, and diarrhea (**Table 2**)

Table 2. Treatment-Emergent Adverse Events

		Serum Bile Acid Response (≥70% reduction in serum bile acids or serum bile acids ≤70 µmol/L)		Serum Bile Acid and/or Pruritus Response (pruritus score reduction of ≥1 point from baseline)	
Patients, n (%)	All Odevixibat N=84	Responder n=30	Nonresponder n=51	Responder n=49	Nonresponder n=35
Any TEAEs	71 (85)	26 (87)	44 (86)	42 (86)	29 (83)
Mild	30 (36)	11 (37)	18 (35)	18 (37)	12 (34)
Moderate	33 (39)	11 (37)	22 (43)	18 (37)	15 (43)
Severe	8 (10)	4 (13)	4 (8)	6 (12)	2 (6)
TEAEs leading to discontinuation	5 (6)	2 (7)	2 (4)	3 (6)	2 (6)
Drug-related TEAEs	35 (42)	14 (47)	20 (39)	24 (49)	11 (31)
Serious TEAEs	9 (11)	3 (10)	6 (12)	4 (8)	5 (14)
TEAEs occurring in ≥10% of the study population					
Pyrexia	23 (27)	8 (27)	15 (29)	13 (27)	10 (29)
Upper respiratory tract infection	20 (24)	10 (33)	10 (20)	15 (31)	5 (14)
Diarrhea	17 (20)	12 (40)	5 (10)	15 (31)	2 (6)
Increased blood bilirubin	15 (18)	3 (10)	12 (24)	8 (16)	7 (20)
Increased ALT	13 (16)	7 (23)	6 (12)	8 (16)	5 (14)
Cough	13 (16)	5 (17)	8 (16)	7 (14)	6 (17)
Vomiting	11 (13)	5 (17)	6 (12)	7 (14)	4 (11)
Nasopharyngitis	9 (11)	6 (20)	3 (6)	8 (16)	1 (3)
Increased INR	9 (11)	3 (10)	6 (12)	4 (8)	5 (14)
Pruritus	9 (11)	2 (7)	7 (14)	3 (6)	6 (17)
Splenomegaly	8 (10)	4 (13)	4 (8)	5 (10)	3 (9)

ALT, alanine aminotransferase; INR, international normalized ratio; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Patients with PFIC who responded to odevixibat had sustained improvements in mean serum bile acids and pruritus scores over time
- Serum bile acid responders had larger improvements in pruritus than serum bile acid nonresponders; pruritus improvements in those who did not meet serum bile acid response criteria may reflect either perceived treatment effects or patients with a partial serum bile acid response (ie, a sub-threshold reduction in serum bile acids)
- Odevixibat treatment was generally well tolerated in both responders and nonresponders

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AUTHOR DISCLOSURES

K.M. Loomes: Albireo, Mirum Pharma, and Travere Therapeutics – Consultant. **H.J. Verkade:** Ausnutria BV, Albireo, Danone/Nutricia Research, Intercept, Mirum Pharma, Orphalan, and Vivet – Consultant. **R. J. Thompson:** Albireo, Alnylam, EVOX Therapeutics, Generation Bio, Mirum Pharma, Rectify Therapeutics, Retrophin, Qing Therapeutics, and Sana Biotechnology – Consultant. **B.M. Kamath:** Albireo, Mirum Pharma, Audentes – Consultant; Albireo and Mirum Pharma – Unrestricted educational grants. **F. Lacaille:** Alexion – Consultant. **T. Grammatikopoulos:** Albireo – Consultant. **J.M. Vittorio:** Mirum Pharma – Consultant. **P. McKiernan:** SOBI AB and Albireo – Consultant. **W. Hardikar, Y. Mozer-Glassberg, E. Shteyer, P.L. Calvo, B. Dalgic, S.R. Rajwal, N. Soufi,** and **M.E. Tessier:** None. **Q. Yu, L. Kjems,** and **P. Horn:** Albireo – Current or former employment

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