Substantial Clinical Benefits With Odevixibat Treatment Across Progressive Familial Intrahepatic Cholestasis Genetic Deficiencies: Subgroup Analysis of Serum Bile Acids, Pruritus, and Safety Using Pooled Data From the PEDFIC 1 and 2 Studies

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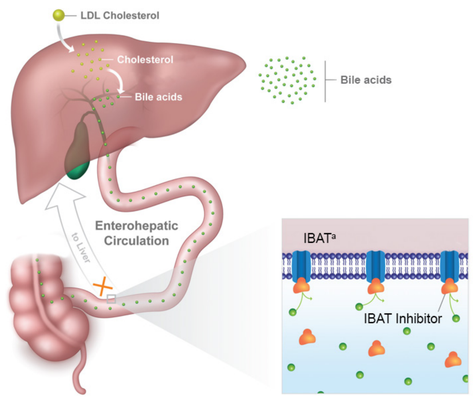
INTRODUCTION

- Progressive familial intrahepatic cholestasis (PFIC): a group of rare genetic diseases of hepatocellular origin characterized by cholestasis, fat-soluble vitamin deficiency, and progressive liver disease[1]
  - Mutations in proteins with diverse functions underlie PFIC, including familial intrahepatic cholestasis protein 1 (FIC1; encoded by *ATP8B1*) and bile salt export pump (BSEP; encoded by *ABCB11*), corresponding with PFIC type 1 (PFIC1) and PFIC type 2 (PFIC2), respectively[2]
  - PFIC2 can be further categorized by BSEP subtype[3]
    - BSEP subtype 1: patients with p.E297G and/or p.D482G missense mutations that result in residual BSEP activity
    - BSEP subtype 2: patients with ≥1 missense mutation but not p.D482G and/or p.E297G; this group likely has a range of BSEP function, depending on the type of amino acid substituted
    - BSEP subtype 3: patients with protein-truncating mutations and no residual BSEP function
- Ileal bile acid transporter (IBAT): resorbs intestinal bile acids for recirculation to the liver; potential therapeutic target for pharmacologic inhibition of the enterohepatic circulation[4] (**Figure 1**)

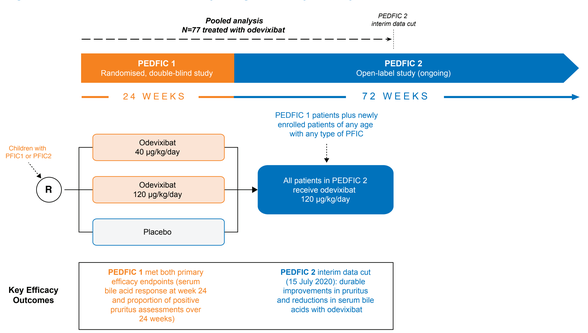
Figure 1. Role of IBAT in the Enterohepatic Circulation of Bile Acids and Effects of IBAT Inhibition



[a]Also known as the apical sodium-dependent bile acid transporter.
IBAT, ileal bile acid transporter; LDL, low-density lipoprotein.

- Odevixibat: orally administered, reversible, potent, and selective IBAT inhibitor that decreases bile acid reuptake and increases bile acid clearance through the colon[5]
- Odevixibat investigated as treatment for PFIC in two phase 3 studies: PEDFIC 1 and PEDFIC 2 (**Figure 2**)[6,7]
  - PEDFIC 1 enrolled patients with PFIC1 and PFIC2
  - PEDFIC 2 enrolled patients with any PFIC subtype

Figure 2. PEDFIC 1 and PEDFIC 2 Study Designs and Key Efficacy Outcomes[6,7]



R, randomised; PFIC, progressive familial intrahepatic cholestasis.

- Objective: describe outcomes by genotype subgroup using pooled data from these studies

METHODS

Patients and Pooling of Data

- Patients eligible for PEDFIC 1 and PEDFIC 2 had PFIC, elevated serum bile acids, and significant pruritus
- Pooled analysis period: from first-ever odevixibat dose in PEDFIC 1 or PEDFIC 2 through interim data cut of PEDFIC 2 (15 July 2020)
  - Main focus: efficacy data through week 24 of PEDFIC 2
    - Includes up to 48 weeks of cumulative odevixibat exposure for patients who initiated odevixibat in PEDFIC 1
    - Includes less than 48 weeks of exposure for most patients who initiated odevixibat in PEDFIC 2
  - Analysis population: patients with PFIC1 or PFIC2 (BSEP subtypes 1 and 2[3]); patients with PFIC2 with BSEP subtype 3 not included in the analysis

Assessments

- Assessments presented by patient genotype group: serum bile acid response, change in pruritus, and safety
  - Serum bile acid response defined as a ≥70% reduction from baseline or a serum bile acid concentration ≤70 µmol/L
    - Blinded serum bile acid measurements taken at all study visits
  - Change in pruritus based on proportion of positive pruritus assessments (PPAs; ie, scratching score ≤1 or a ≥1-point drop from baseline on the PRUCISION instrument) at the patient level
    - Pruritus scored from 0 to 4 by caregivers using a scale validated by blinded, psychometric analysis conducted by an independent group; higher scores indicate worse symptoms, and a decrease of ≥1 point from baseline is clinically meaningful
  - Safety monitoring included assessment of treatment-emergent adverse events (TEAEs)

RESULTS

Patients

- Of 77 patients who received odevixibat during the pooled analysis period, 20 had PFIC1 (26%), 51 (66%) had PFIC2, and 6 (8%) had other PFIC subtypes (**Table 1**)
  - Of those with PFIC2, BSEP subtype 1 or 2 present in 13 (25%) and 36 (71%) patients, respectively
  - Data for 69 patients with PFIC1 and PFIC2 (BSEP subtype 1 and 2) included in these subgroup analyses
- Patient demographics and baseline characteristics, including mean age and proportions of patients using ursodeoxycholic acid or rifampicin at baseline, were similar among patients with different genotypes (**Table 1**)

Table 1. Patient Demographics and Baseline Characteristics

	Overall, N=77	Patients with PFIC1, n=20	Patients with PFIC2, n=51	Patients with PFIC2, BSEP subtype 1, n=13	Patients with PFIC2, BSEP subtype 2, n=36
Age, mean (SD), years	5.2 (4.3)	4.8 (3.4)	4.9 (4.5)	5.1 (5.1)	4.9 (4.5)
Female, n (%)	39 (51)	7 (35)	26 (51)	6 (46)	20 (56)
PFIC type, n (%)					
PFIC1 (FIC1 deficiency)	20 (26)	20 (100)	–	–	–
PFIC2 (BSEP deficiency)	51 (66)	–	51 (100)	13 (100)	36 (100)
Other PFIC types	6 (8)	–	–	–	–
UDCA at baseline, n (%)	62 (81)	15 (75)	42 (82)	11 (85)	29 (81)
Rifampicin at baseline, n (%)	48 (62)	12 (60)	35 (69)	11 (85)	22 (61)
Significant pruritus present per investigator report, n (%)	74 (96)	19 (95)	49 (96)	12 (92)	35 (97)
Serum bile acid level >100 µmol/L within 6 months prior to screening, n (%)	52 (68)	15 (75)	35 (69)	8 (62)	25 (69)

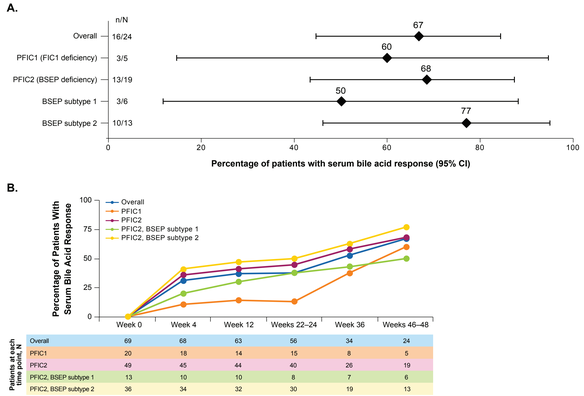
BSEP, bile salt export pump; FIC, familial intrahepatic cholestasis; PFIC, progressive familial intrahepatic cholestasis; SD, standard deviation; UDCA, ursodeoxycholic acid.

Efficacy

Serum Bile Acid Response

- At weeks 46–48 of odevixibat treatment, ≥50% of patients met serum bile acid response criteria, regardless of genotype (**Figure 3A**)
- Percentages of patients who met serum bile acid response increased over time (**Figure 3B**)

Figure 3. Percentage of Patients Who Met Serum Bile Acid Response Criteria After 48 Weeks of Treatment (A) and Over Time (B) With Odevixibat: Subgroup Analysis by Genotype

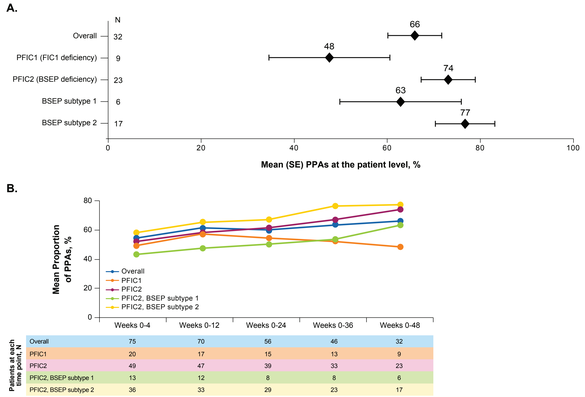


BSEP, bile salt export pump; CI, confidence interval; FIC, familial intrahepatic cholestasis; n/N, patients meeting criteria out of all patients with available data at week 48; N, patients with available data at indicated time point; PFIC, progressive familial intrahepatic cholestasis.

Pruritus

- Proportion of PPAs at the patient level was comparable between PFIC2 and PFIC1 patients, although the PFIC1 group was smaller than the PFIC2 group (**Figure 4A**)
  - Over the interval of 0–48 weeks, mean proportions of PPAs were above 60% for patients with PFIC2 (including BSEP subtypes 1 and 2) and mean proportion of PPAs for patients with PFIC1 were 48%
  - Results for patients with PFIC2 by BSEP subgroup (BSEP1, milder disease presentation vs BSEP2, moderate to severe disease presentation[3]) did not demonstrate a clear difference on treatment effect given differences in sample size
- Patients had rapid improvements in pruritus with odevixibat that were sustained with treatment (**Figure 4B**)

Figure 4. Mean Proportion of PPAs Over 48 Weeks of Treatment (A) and Over Time (B) With Odevixibat: Subgroup Analysis by Genotype



BSEP, bile salt export pump; FIC, familial intrahepatic cholestasis; N, patients with available data at indicated time point; PFIC, progressive familial intrahepatic cholestasis; PPA, positive pruritus assessment; SE, standard error.

Safety

- Incidence of TEAEs in odevixibat-treated patients with PFIC1 or PFIC2 (80% each) and BSEP subtype 1 and 2 (77% and 86%, respectively; **Table 4**) was comparable to that of placebo-treated patients in PEDFIC 1 (85%)[7]
  - Most TEAEs mild or moderate, self-limiting, and considered by the investigator as not related to study drug
  - None of the reported serious TEAEs were considered related to odevixibat treatment

Table 4. Summary of TEAEs and Serious TEAEs by Patient Genotype Group

	Overall, N=77	Patients with PFIC1, n=20	Patients with PFIC2, n=51	Patients with PFIC2, BSEP subtype 1, n=13	Patients with PFIC2, BSEP subtype 2, n=36
Any TEAE, n (%)	61 (79)	16 (80)	41 (80)	10 (77)	31 (86)
TEAEs by preferred term occurring in ≥10% of patients overall, n (%)					
ALT increased	10 (13)	2 (10)	6 (12)	1 (8)	5 (14)
Blood bilirubin increased	12 (16)	4 (20)	6 (12)	2 (15)	4 (11)
Cough	12 (16)	4 (20)	8 (16)	2 (15)	6 (17)
Diarrhoea	15 (19)	5 (25)	10 (20)	1 (8)	10 (28)
Pruritus	9 (12)	3 (15)	6 (12)	3 (23)	3 (8)
Pyrexia	20 (26)	8 (40)	12 (24)	4 (31)	8 (22)
Upper respiratory tract infection	19 (25)	8 (40)	11 (22)	3 (23)	8 (22)
Vomiting	11 (14)	6 (30)	5 (10)	2 (15)	3 (8)
Any serious TEAEs, n (%)	7 (9)	1 (5)	6 (12)	1 (8)	5 (14)
Serious TEAEs by preferred term, n (%)					
Cholestasis	1 (1)	0	1 (2)	1 (8)	0
Dehydration[a]	1 (1)	1 (5)	0	0	0
Hyperbilirubinaemia	1 (1)	0	1 (2)	0	1 (3)
Liver function test increased[a]	1 (1)	1 (5)	0	0	0
Pancreatitis acute	1 (1)	0	1 (2)	0	1 (3)
Stoma complication	1 (1)	0	1 (2)	0	1 (3)
Supraventricular tachycardia	1 (1)	0	1 (2)	0	1 (3)
Urinary tract infection	1 (1)	0	1 (2)	0	1 (3)

[a]Occurred in the same patient.
ALT, alanine aminotransferase; BSEP, bile salt export pump; PFIC, progressive familial intrahepatic cholestasis; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Patients with PFIC1 or PFIC2 had substantial benefits with odevixibat when treated for up to 48 weeks
- Overall, at least 50% of patients treated with odevixibat in each subgroup achieved ≥70% reduction in serum bile acids from baseline or reached a serum bile acid level ≤70 µmol/L at week 48
- Mean proportions of PPAs, which were based on observer-reported outcome (ObsRO) instrument pruritus scores, were high across subgroups, ranging from 48% to 77% at week 48
- Long-term treatment with odevixibat was well tolerated, regardless of PFIC classification or BSEP subtype

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AUTHOR DISCLOSURES

R.J. Thompson: Albireo, Alnylam, Evox Therapeutics, Generation Bio, Mirum Pharma, Rectify Therapeutics, Retrophin, Qing Therapeutics, and Sana Biotechnology – Consultant
P. Horn, Q. Ni, P. Stein, C. Thompson, and **L. Kjems:** – Employed by Albireo Pharma, Inc.
R.H.J Houwen: GMP-Orphan and Univar – Consultant
F. Lacaille: Alexion – Consultant
M.E. Tessier: None
J. M. Vittorio: Mirum Pharma – Consultant

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