Volixibat for the Treatment of Cholestatic Pruritus in Primary Biliary Cholangitis: An Adaptive, Randomized, Placebo-Controlled Phase 2b Trial (VANTAGE): Interim Results

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Faculty Disclosure

Company Name	Honoraria/ expenses	Consulting/ advisory board	Funded research	Royalties/ patent	Stock options	Ownership/ equity position	Employee	Other (please specify)
Akero Therapeutics, Inc			X					
Altimmune, Inc			X					
Camrus AB			X					
Durect Corporation			X					
89bio, Inc			X					
GALExtin			X					
Genentech, Inc		X	X					
Gilead Science, Inc		X	X					
Hamni Pharm. Co., Ltd			X					
HepQuant, LLC		X	X					
HighTide Therapeutics, Inc			X					
Intercept Pharmaceuticals, Inc		X	X					
Intra-Sana Laboratories LLC		X						
Inventiva SA			X					
Ipsen Biopharmaceuticals, Inc		X	X					
Madrigal Pharmaceuticals		X	X					
Mirum Pharmaceuticals, Inc.		X	X					
Novo Nordisk A/S			X					
Oncoustics			X					
Pliant Therapeutics, Inc			X					
Salix Pharmaceuticals			X					
Viking Therapeutics			X					
Zydus Pharmaceuticals, Inc			X					

Primary Biliary Cholangitis (PBC)

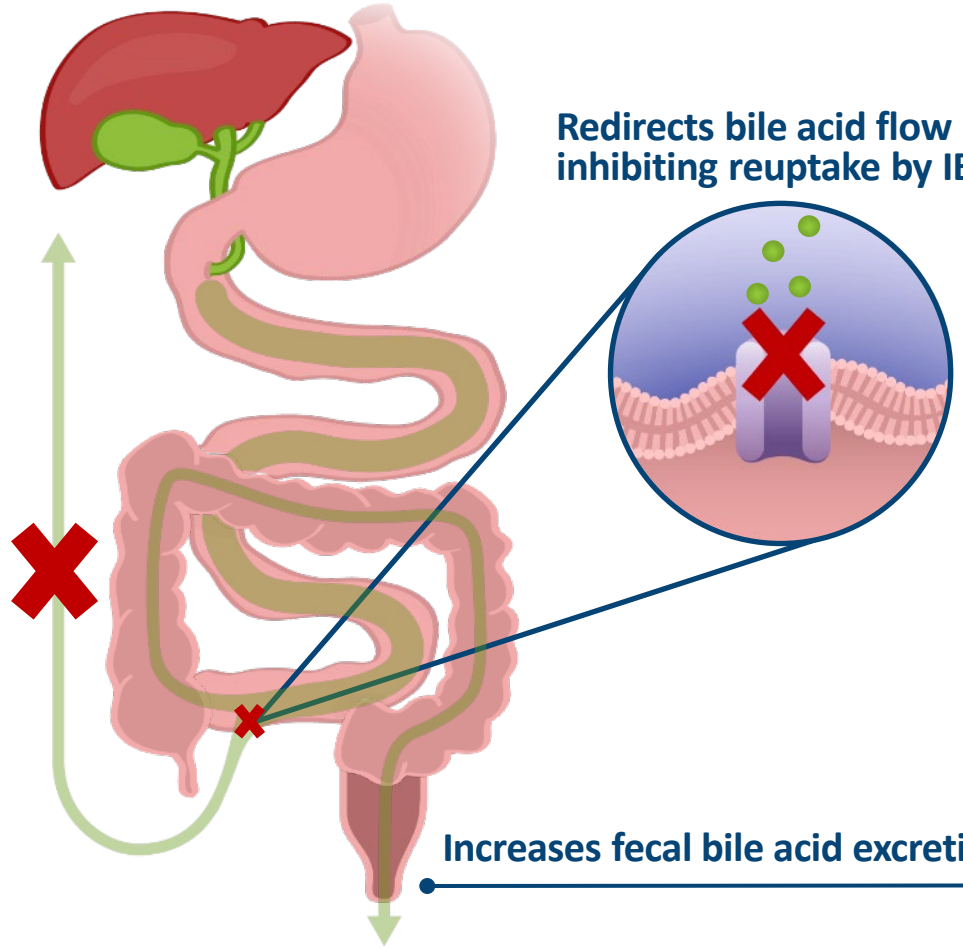
- Chronic, progressive, immune-mediated inflammatory disease which causes the destruction of small intrahepatic bile ducts[1,2]
- Estimated prevalence 1.9 to 40.2 per 100,000 persons. Women are predominantly affected,[1] with a sex ratio of 9:1
- Key clinical features and complications include cholestatic pruritus, fatigue, sicca syndrome, abdominal pain, cirrhosis, and hepatocellular carcinoma[1,2]:
  - Cholestatic pruritus and fatigue are two of the most debilitating symptoms and greatly affect overall health-related quality of life (HRQoL)[2]
  - Cholestatic pruritus affects up to 80% of individuals and is thought to result in part from accumulation of toxic bile acids[1,2]

Although recently approved second-line therapies for PBC also reduce pruritus, these agents are not indicated for the treatment of pruritus in patients who have responded to first-line therapies[3]

HRQoL, health-related quality of life; PBC, primary biliary cholangitis.

1. Gungabissoon U, et al. *BMJ Open Gastroenterol.* 2022;9:e000857. **2.** Hirschfield G, et al. *Gut.* 2018;67:1568-1594. **3.** Tanaka A, et al. *Lancet.* 2024;14;404(10457):1053-1066.

IBAT Inhibitors May Reduce Clinical Effects of Cholestasis in Patients With PBC



Clinical effects of IBAT inhibitors seen in cholestasis[1-3]

IBATi clinical studies show:

- ✓ Reductions in pruritus
- ✓ Reduction in sBA levels
- ✓ Impact on bile acid pharmacodynamic markers: cholesterol, 7αC4, FGF-19

Volixibat is a minimally absorbed IBAT inhibitor that interrupts the enterohepatic recirculation of bile acids, thus reducing sBA levels and potentially improving cholestasis, pruritus, and other clinical outcomes in PBC[1]

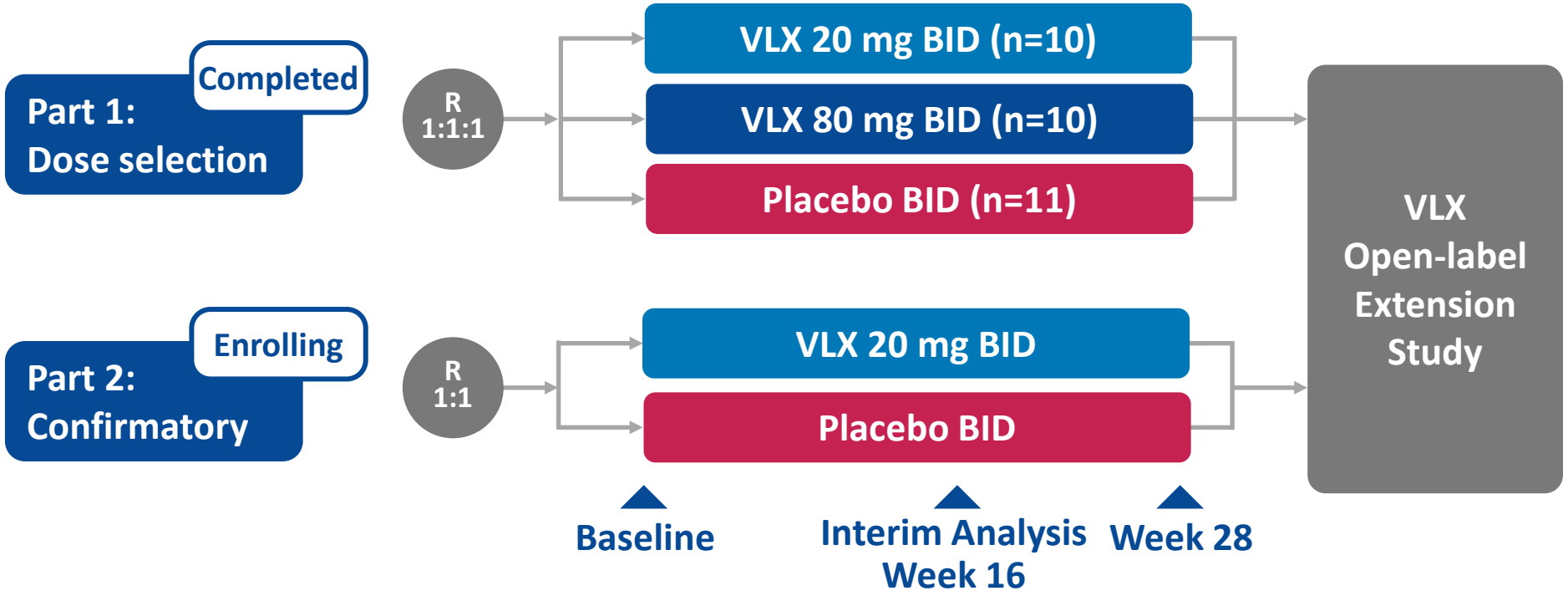
7αC4, 7-alpha-hydroxy-4-cholesten-3-one; FGF-19, fibroblast growth factor 19; IBAT, ileal bile acid transporter; IBATi, ileal bile acid transporter inhibitor; PBC, primary biliary cholangitis; sBA, serum bile acid.

1. Key C, et al. Presented at: AASLD 2020. **2.** Gonzales E, et al. *Lancet.* 2021;398:1581-1592. **3.** Loomes MK, et al. *Hepatol Commun*. 2022;6:2379-2390.

VANTAGE Phase 2 Study Design

Key Entry Criteria

- Confirmed diagnosis of PBC per AASLD guidelines
- Aged ≥18 years at Baseline
- Moderate to severe pruritus



Primary Endpoint

- Mean change in daily itch scores using the ItchRO[a] questionnaire from Baseline to Week 28

Select Secondary Endpoints[b]

- Incidence of AEs
- Change in sBA
- Change in HRQoL using PBC-40

Interim analysis on Part 1 was conducted when approximately 12 participants per treatment arm completed Week 16 or prematurely discontinued study drug

AASLD, American Association for the Study of Liver Diseases; AE, adverse event; ALP, alkaline phosphatase; BID, twice daily; HRQoL, health-related quality of life; ItchRO, Itch-Reported Outcome; PBC, primary biliary cholangitis; PBC-40, primary biliary cholangitis 40-item questionnaire; PROMIS, Patient-Reported Outcomes Measurement Information Systems; R, randomization; sBA, serum bile acid; VLX, volixibat.
[a]Adult ItchRO is an 11-point (0-10) scale, where 0 = no itch and 10 = worst possible itch. [b]Assessed from Baseline to Week 28.
ClinicalTrials.gov identifier: NCT05050136. Updated March 4, 2025. Accessed March 11, 2025. https://clinicaltrials.gov/ct2/show/NCT05050136

Key Demographics and Baseline Characteristics

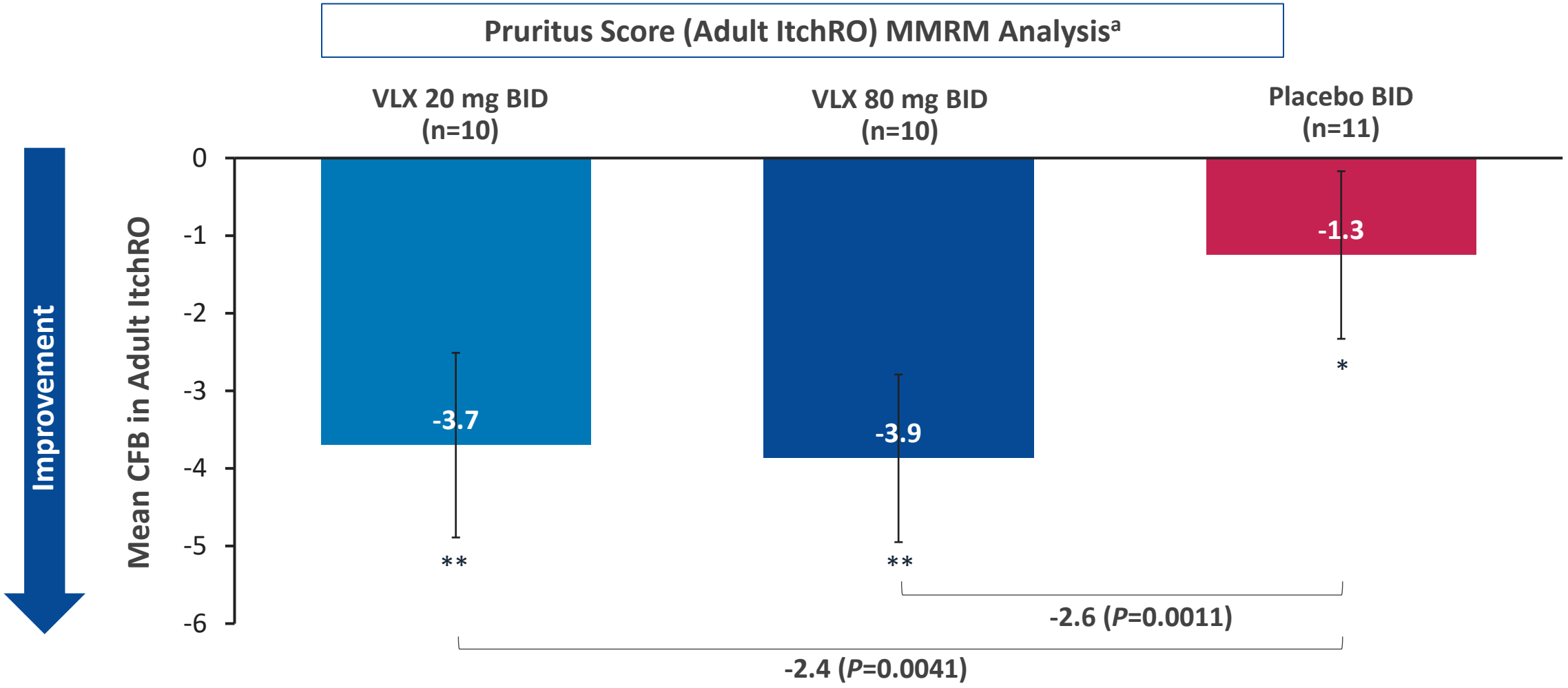
Parameter[a]	VLX 20 mg BID (n=10)	VLX 80 mg BID (n=10)	Placebo BID (n=11)	Total (N=31)
Age, years	53.9 (15.8)	52.3 (5.9)	62.1 (9.7)	56.3 (11.7)
Sex, female	8 (80)	9 (90)	10 (91)	27 (87)
Pruritus, Adult ItchRO score[b]	6.8 (1.6)	6.3 (1.8)	6.2 (1.5)	6.4 (1.6)
sBA, µmol/L	53 (53)	44 (73)	31 (52)	42 (59)
ALT, U/L	48 (41)	51 (34)	45 (37)	48 (36)
AST, U/L	42 (25)	46 (38)	35 (12)	41 (27)
ALP, U/L	238 (134)	232 (107)	167 (114)	211 (119)
Total bilirubin, mg/dL	1.2 (0.8)	0.9 (0.7)	0.7 (0.4)	0.9 (0.7)
Direct bilirubin, mg/dL	0.7 (0.6)	0.5 (0.5)	0.3 (0.3)	0.5 (0.5)
PBC-40 domains[c]				
Symptoms	14.6 (4.6)	18.0 (5.0)	15.9 (2.7)	16.1 (4.3)
Itch	9.2 (2.4)	9.0 (3.1)	7.8 (4.1)	8.7 (3.2)
Fatigue	33.0 (7.8)	34.6 (13.0)	31.0 (9.5)	32.9 (10.0)
Cognitive	16.1 (3.5)	14.1 (6.8)	16.4 (6.4)	15.6 (5.6)
Emotional	9.2 (2.7)	9.7 (3.5)	8.4 (4.1)	9.1 (3.4)
Social	28.1 (6.8)	28.8 (11.2)	27.6 (11.7)	28.1 (9.8)

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BID, twice daily; HRQoL, health-related quality of life; ItchRO, Itch-Reported Outcome; PBC-40, primary biliary cholangitis 40-item questionnaire; sBA, serum bile acid; VLX, volixibat.

[a]Continuous variables present mean (SD). Categorical variables present number (%). [b]Adult ItchRO is an 11-point (0-10) scale, where 0 = no itch and 10 = worst possible itch. [c]The possible score range for each domain is as follows: symptoms (7-35), itch (3-15), fatigue (11-55), cognitive (6-30), emotional (3-15), and social (10-50). Each domain consists of a Likert scale of 1 to 5 points, with 1 corresponding to "never" and 5 corresponding to "always" with higher scores denoting worse HRQoL.[1]

1. Jacoby A, et al. *Gut.* 2005;54(11):1622-1629.

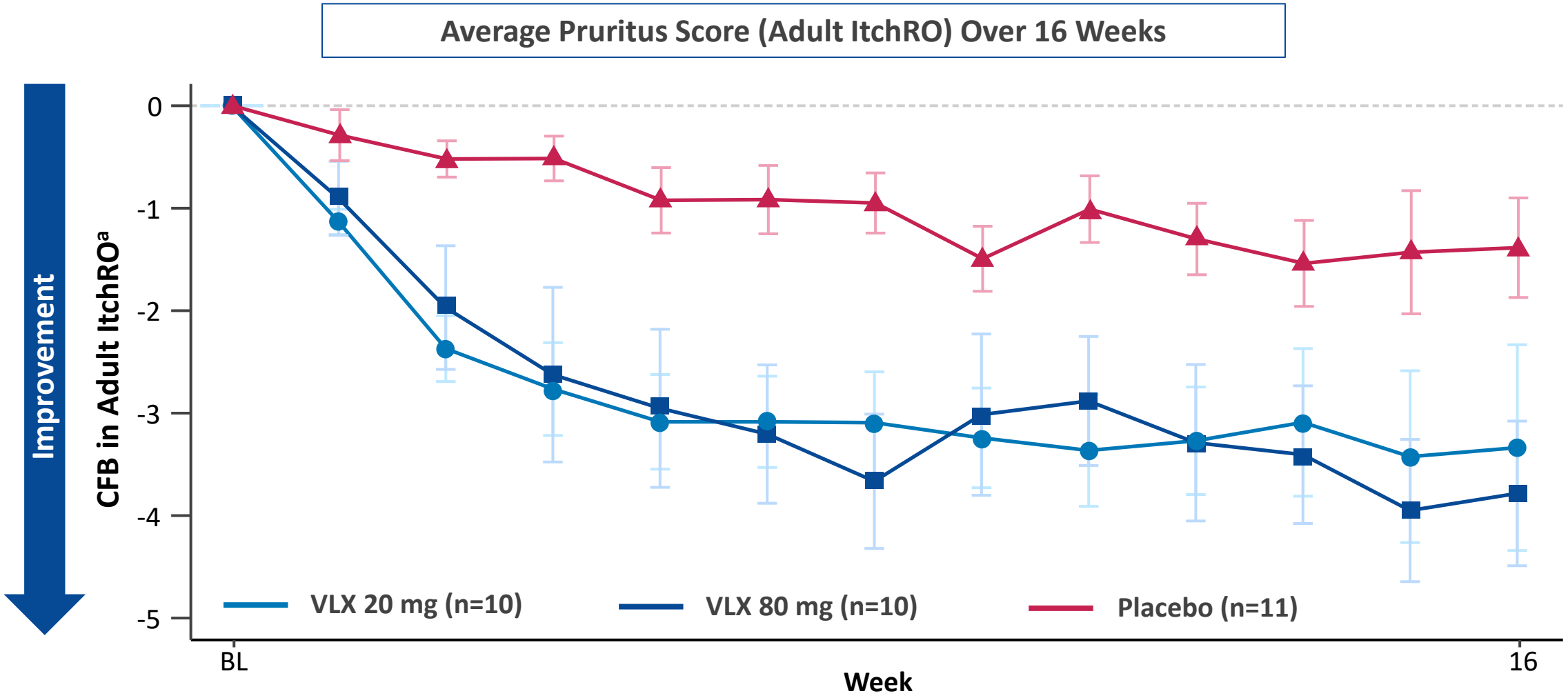
Participants Who Received Volixibat Showed Statistically Significant Reductions in Pruritus



Statistically significant reductions in pruritus were observed with both doses of volixibat compared with placebo

BID, twice daily; CFB, change from Baseline; ItchRO, Itch-Reported Outcome; LS, least squares; MMRM, mixed models for repeated measures; VLX, volixibat.
[a]LS mean (95% CI) change from Baseline to the average of the last 12 weeks of treatment. LS means and *P* values were calculated using an MMRM model. Within-group *P* values are depicted as *≤0.05, **≤0.0001.

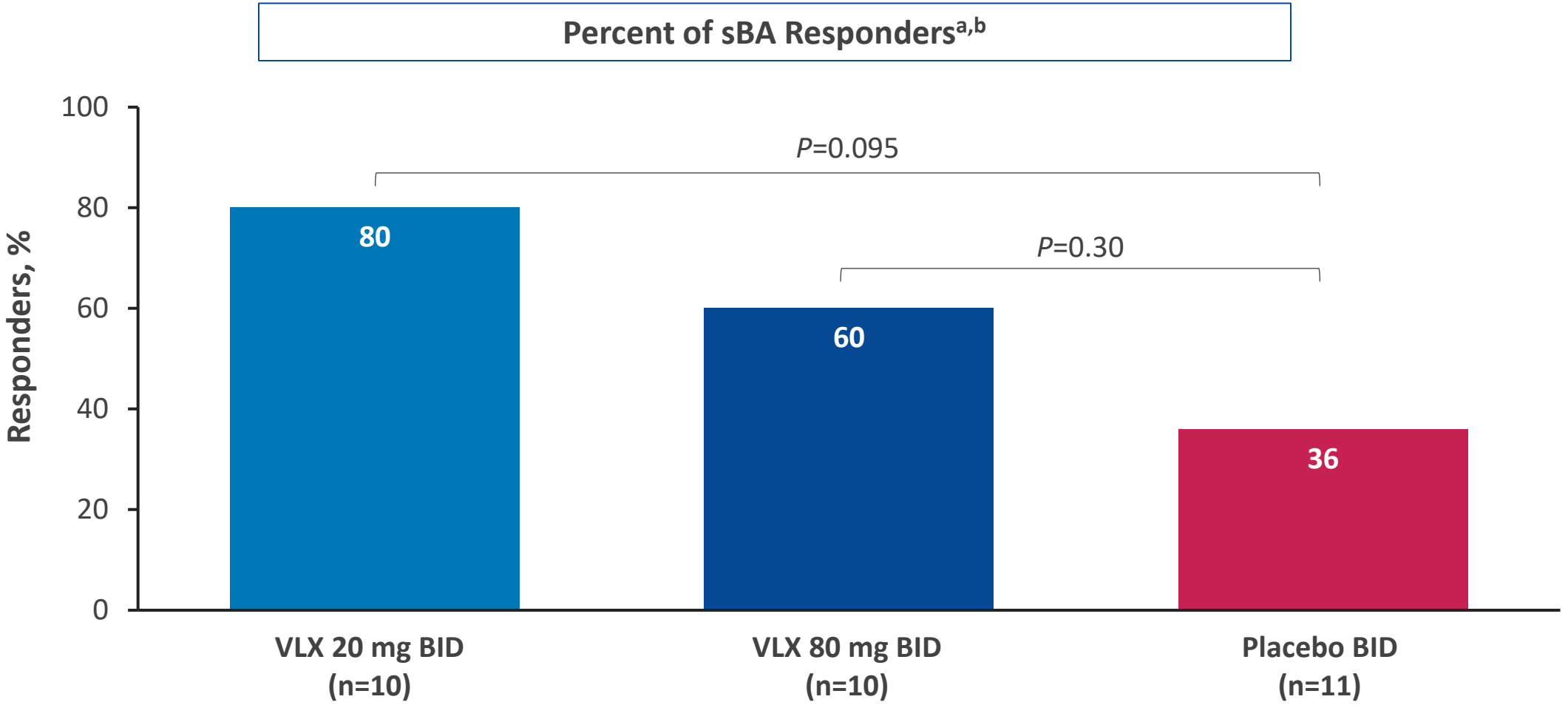
Participants Who Received Volixibat Showed Reductions in Pruritus Over Time



Rapid reductions in pruritus were observed after treatment with volixibat starting at Week 1 and were maintained over time

BL, Baseline; CFB, change from Baseline; ItchRO, Itch-Reported Outcome; VLX, volixibat.
[a]Data are mean (±SE).

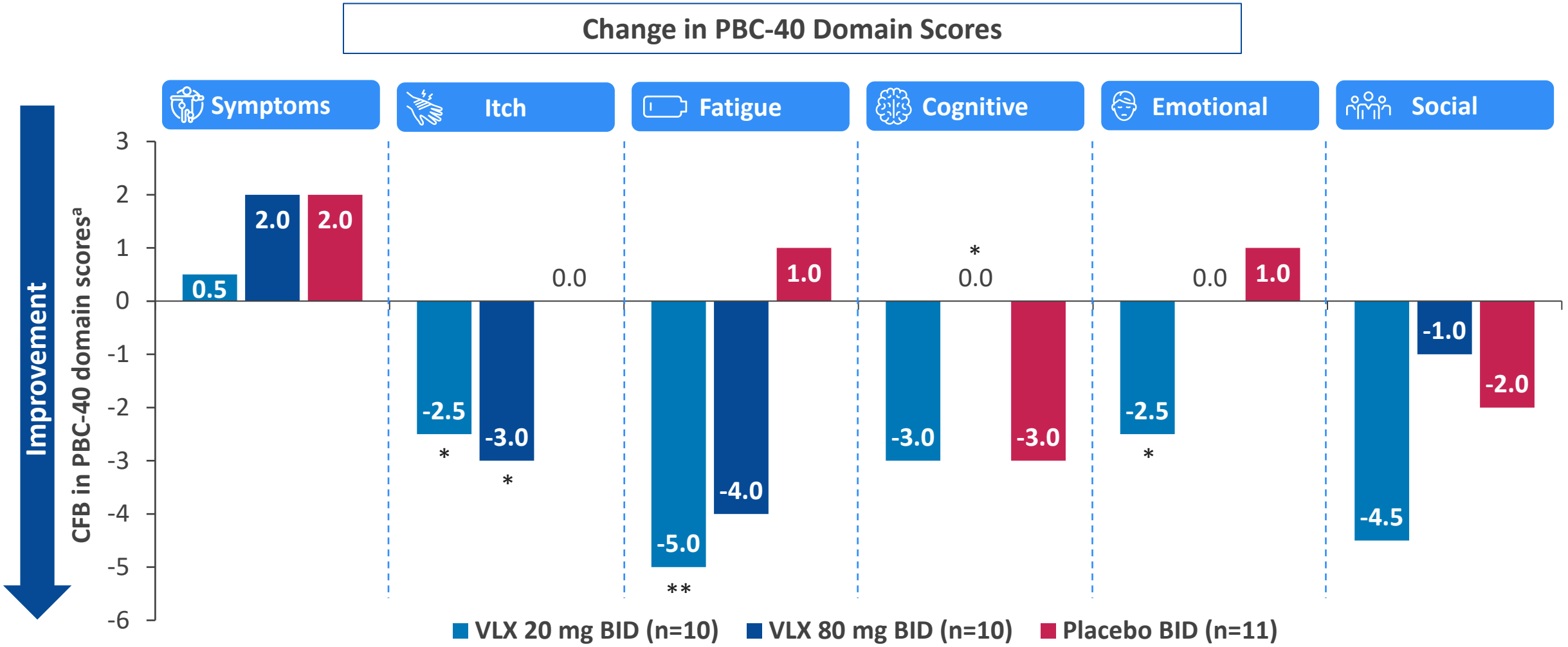
A Majority of Participants Who Received Volixibat Showed an sBA Response



A higher proportion of participants who received volixibat showed an sBA response compared with those who received placebo

BID, twice daily; sBA, serum bile acid; VLX, volixibat.
[a]Responder is defined as ≥50% reduction in sBA levels from Baseline. [b]*P* values were calculated using stratified Cochran-Mantel-Haenszel test (stratified for Adult ItchRO score [<4, ≥4 and <7, ≥7], baseline ALP level [<1.67 x ULN, ≥1.67 x ULN], and use of systemic therapies for cholestatic pruritus [yes, no]).

Participants Who Received Volixibat Showed Improvements in HRQoL



Improvements in HRQoL from Baseline were observed across multiple PBC-40 domains in participants who received volixibat

BID, twice daily; CFB, change from Baseline; HRQoL, health-related quality of life; PBC-40, primary biliary cholangitis 40-item questionnaire; VLX, volixibat.
[a]Median CFB to Week 16. *P* values from 2-sample *t* test comparing active vs placebo; *$P<0.05$ **$P<0.01$.

Summary of TEAEs

TEAE, n (%)[a]	VLX 20 mg (n=11)	VLX 80 mg (n=11)	Placebo (n=16)	Total (N=38)
Any TEAE	11 (100.0)	11 (100.0)	12 (75.0)	34 (89.5)
TEAEs grade ≥3	2 (18.2)	2 (18.2)	1 (6.3)	5 (13.2)
TEAEs related to study drug	9 (81.8)	8 (72.7)	3 (18.8)	20 (52.6)
TEAEs related to study drug grade ≥3	1 (9.1)	0	0	1 (2.6)
Serious TEAEs	1 (9.1)	1 (9.1)	1 (6.3)	3 (7.9)
Serious TEAEs related to study drug	0	0	0	0
TEAEs leading to premature discontinuation of study drug	1 (9.1)	0	1 (6.3)	2 (5.3)
TEAEs leading to drug interruption	4 (36.4)	1 (9.1)	1 (6.3)	6 (15.8)

No new safety signals were observed

TEAE, treatment-emergent adverse event; VLX, volixibat.
[a]Safety analysis set included primary and secondary cohorts, double-blind period.

Additional Safety Details

- Diarrhea was the most common TEAE, reported in up to 77% (17 of 22) of all participants receiving volixibat
  - Diarrhea was mild to moderate in severity and led to 1 discontinuation
- Serious TEAEs were unrelated to study drug, including:
  - Syncope and suicide attempt (VLX 20 mg: 2 events, grades 3 and 4; n=1)
  - DILI due to ibuprofen and alcohol (VLX 80 mg: 1 event, grade 4, n=1)
  - Small intestine obstruction (placebo: 1 event, grade 3, n=1)
- TEAEs grade ≥3 related to study drug included:
  - Hyperbilirubinemia and LFT increased (VLX 20 mg: 2 events, grade 3; n=1)
- No dose-dependent changes in ALP, ALT, AST, or bilirubin noted in participants treated with volixibat
  - Differences in LFT Baseline values between placebo and volixibat arms were observed

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug induced liver injury; LFT, liver function test; TEAE, treatment-emergent adverse event; VLX, volixibat.

Conclusions

- Rapid and statistically significant reductions in cholestatic pruritus were observed after treatment with volixibat
  - Change from Baseline in Adult ItchRO was similar between the volixibat 20 mg and volixibat 80 mg cohorts
- Improvements in some PBC-40 domains, including fatigue, were observed with volixibat
- Numerically greater reductions in sBA levels were observed with volixibat treatment compared with placebo
- No new safety signals were identified with volixibat compared with placebo

Given the similar results between volixibat doses, the 20 mg BID dose was selected for Part 2 of VANTAGE (continuing enrollment), constituting a new promising therapy to address important symptoms in PBC

BID, twice daily; ItchRO, Itch-Reported Outcome; PBC, primary biliary cholangitis; PBC-40, primary biliary cholangitis 40-item questionnaire; sBA, serum bile acid.

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