

Volixibat for the Treatment of Cholestatic Pruritus in Primary Biliary Cholangitis: An Adaptive, Randomized, Placebo-Controlled Phase 2b Trial (VANTAGE): 28-Week Interim Results

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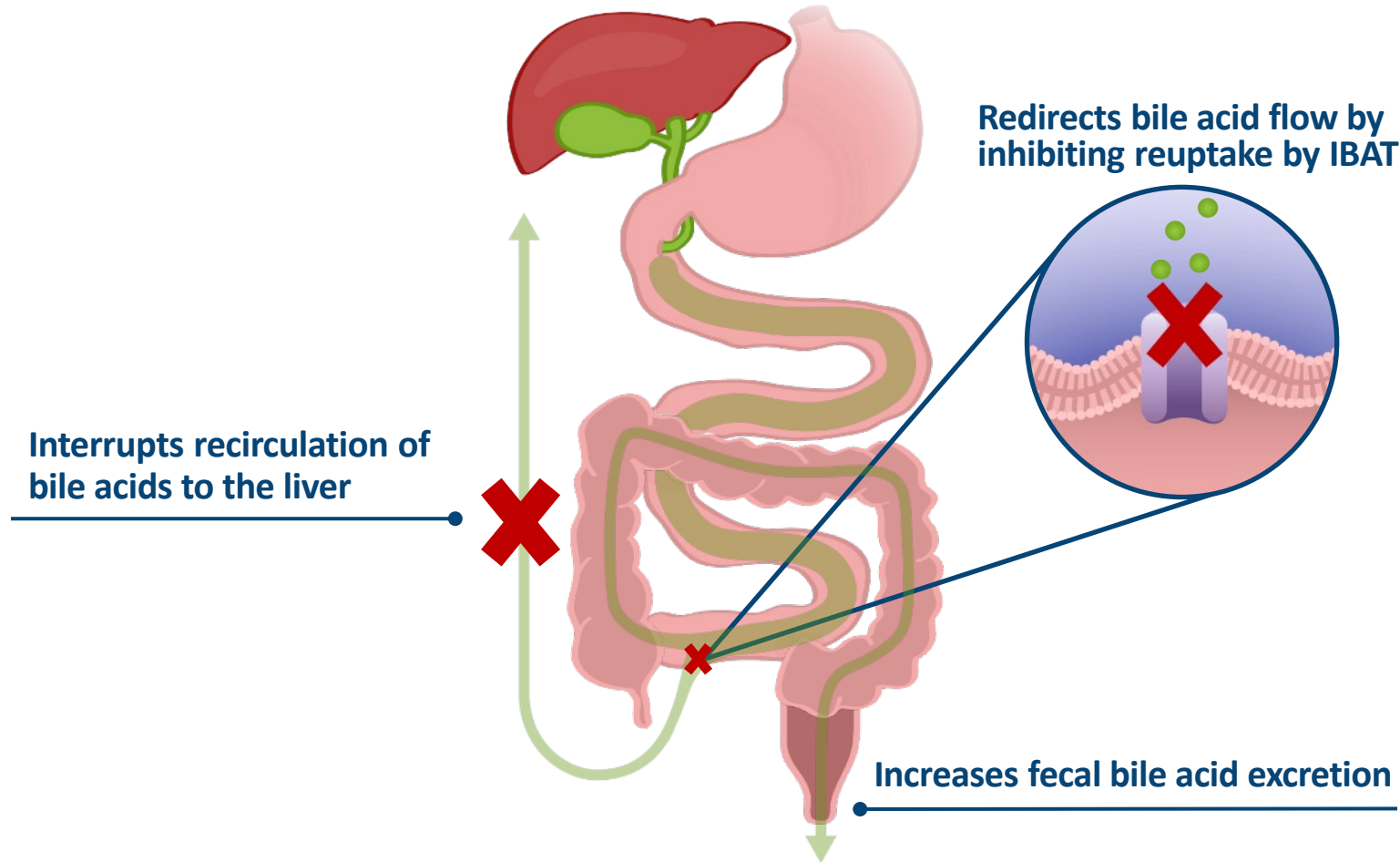


Primary Biliary Cholangitis (PBC)

- Chronic, progressive, immune-mediated condition leading to 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}

Newer therapies for PBC aim to prevent disease progression; however, they are not designed to address all symptoms, including pruritus³

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



Clinical effects of IBAT inhibitors seen in cholestasis¹⁻³

IBATi clinical studies show:

- ✓ Reductions in pruritus
- ✓ Reduction in sBA levels
- ✓ Impact on bile acid pharmacodynamic markers: cholesterol, 7 α C4, 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 PBC¹

7 α C4, 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.

Figure reprinted from *Lancet*, 398, Gonzales E, et al., 'Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study', 1581-1592, Copyright (2021), with permission from Elsevier.

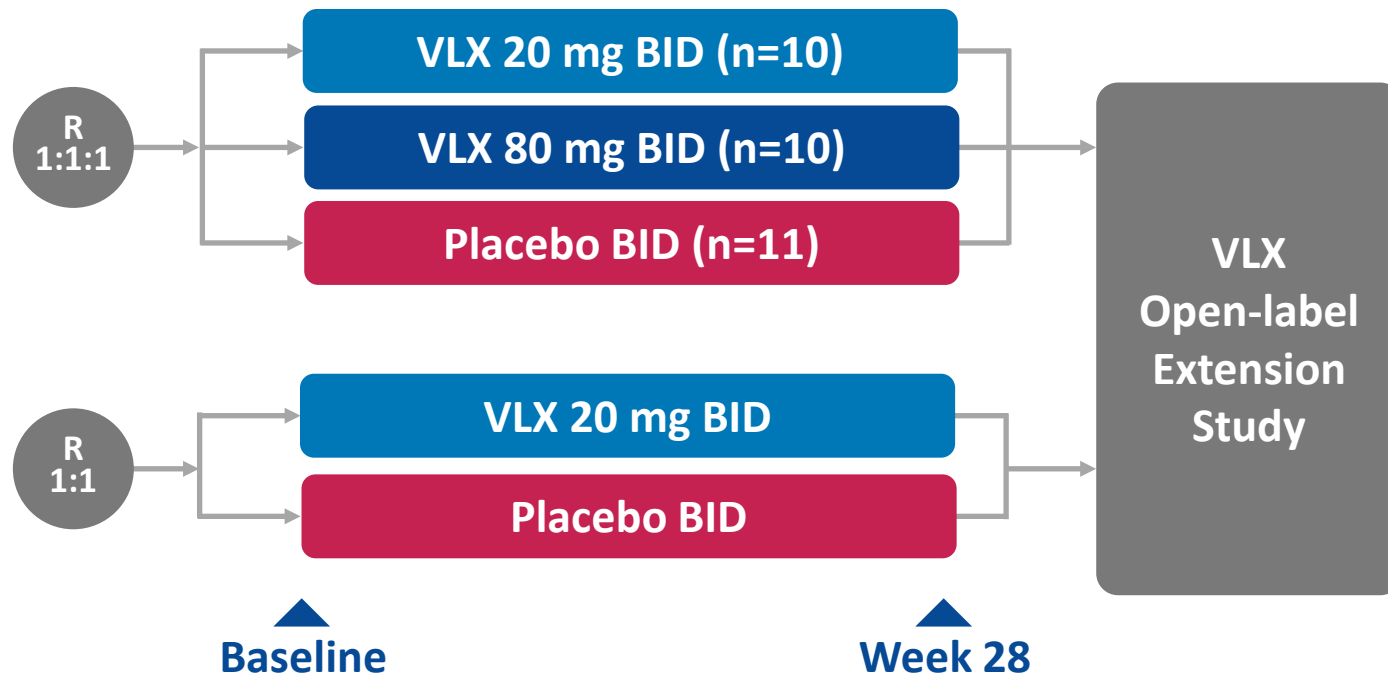
VANTAGE Phase 2 Study Design

Key Entry Criteria

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

Part 1: Dose selection Completed

Part 2: Confirmatory Enrolling



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 and PROMIS

The data being presented are from the interim analysis population now followed through to Week 28

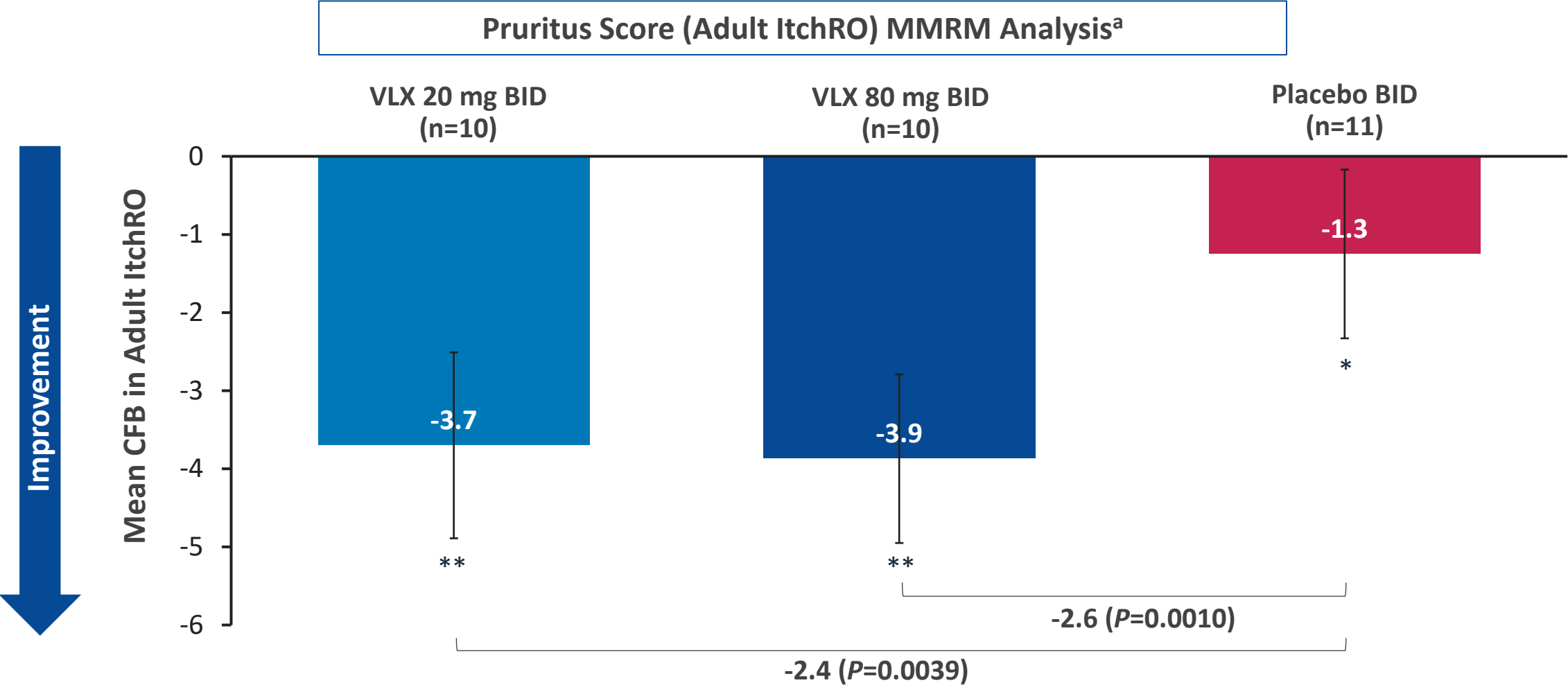
AASLD, American Association for the Study of Liver Diseases; AE, adverse event; BID, twice daily; HRQoL, health-related quality of life; ItchRO, Itch-Reported Outcome; PBC, primary biliary cholangitis; PBC-40, primary biliary cholangitis 40-item questionnaire; PROMIS, Patient-reported Outcomes Measurement Information System; R, randomisation; sBA, serum bile acid; VLX, volixibat.
^aAdult ItchRO is an 11-point (0-10) scale, where 0 = no itch and 10 = worst possible itch. ^bAssessed 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)
<1.67 ULN, n (%)	6 (60.0)	7 (70.0)	9 (81.8)	22 (71.0)
Total bilirubin, μmol/L	20.3 (14.2)	14.9 (12.0)	12.2 (6.3)	15.7 (11.4)

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BID, twice daily; ItchRO, Itch-Reported Outcome; sBA, serum bile acid; ULN, upper limit of normal; VLX, volixibat.
^aContinuous variables present mean (SD). Categorical variables present number (%). ^bAdult ItchRO is an 11-point (0-10) scale, where 0 = no itch and 10 = worst possible itch.

Participants Who Received Volixibat Showed Statistically Significant Reductions in Pruritus

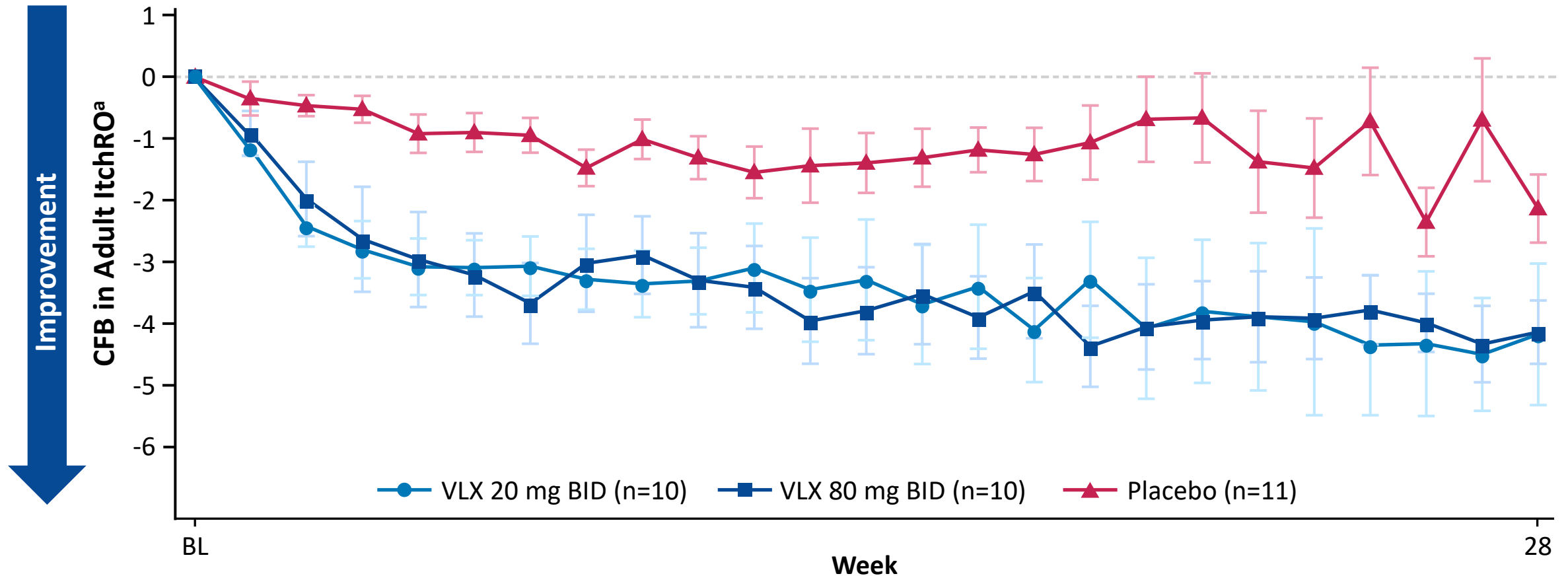


Statistically significant reductions in pruritus were observed with both doses of volixibat compared with placebo

BID, twice daily; CFB, change from Baseline; ItchRO, Itch-Reported Outcome; LS, least squares; MMRM, mixed-effects model for repeated measures; VLX, volixibat.
^aLS 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

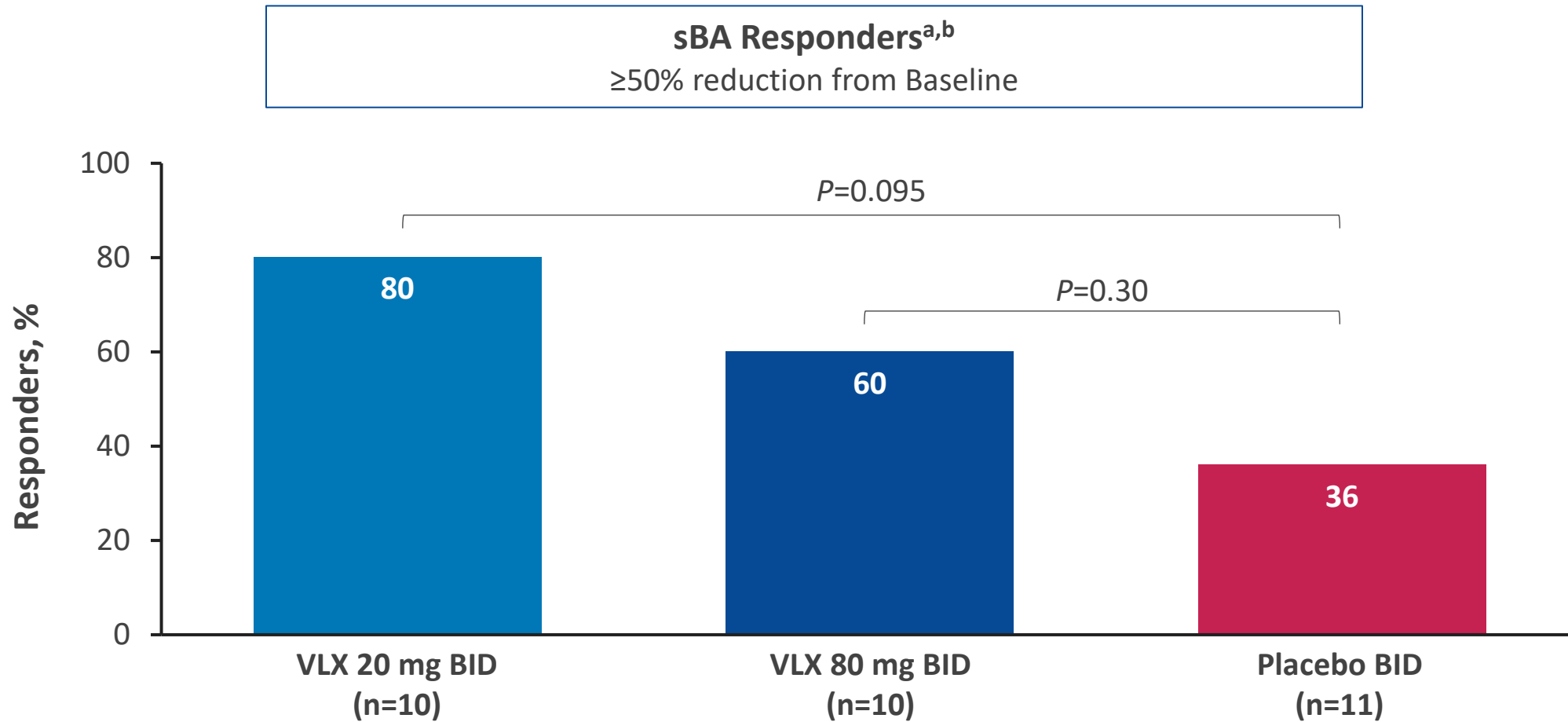
Average Pruritus Score (Adult ItchRO) Over 28 Weeks



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

BID, twice daily; BL, Baseline; CFB, change from Baseline; ItchRO, Itch-Reported Outcome; VLX, volixibat.
^aData are mean (\pm SE).

A Majority of Participants Who Received Volixibat Showed an sBA Response

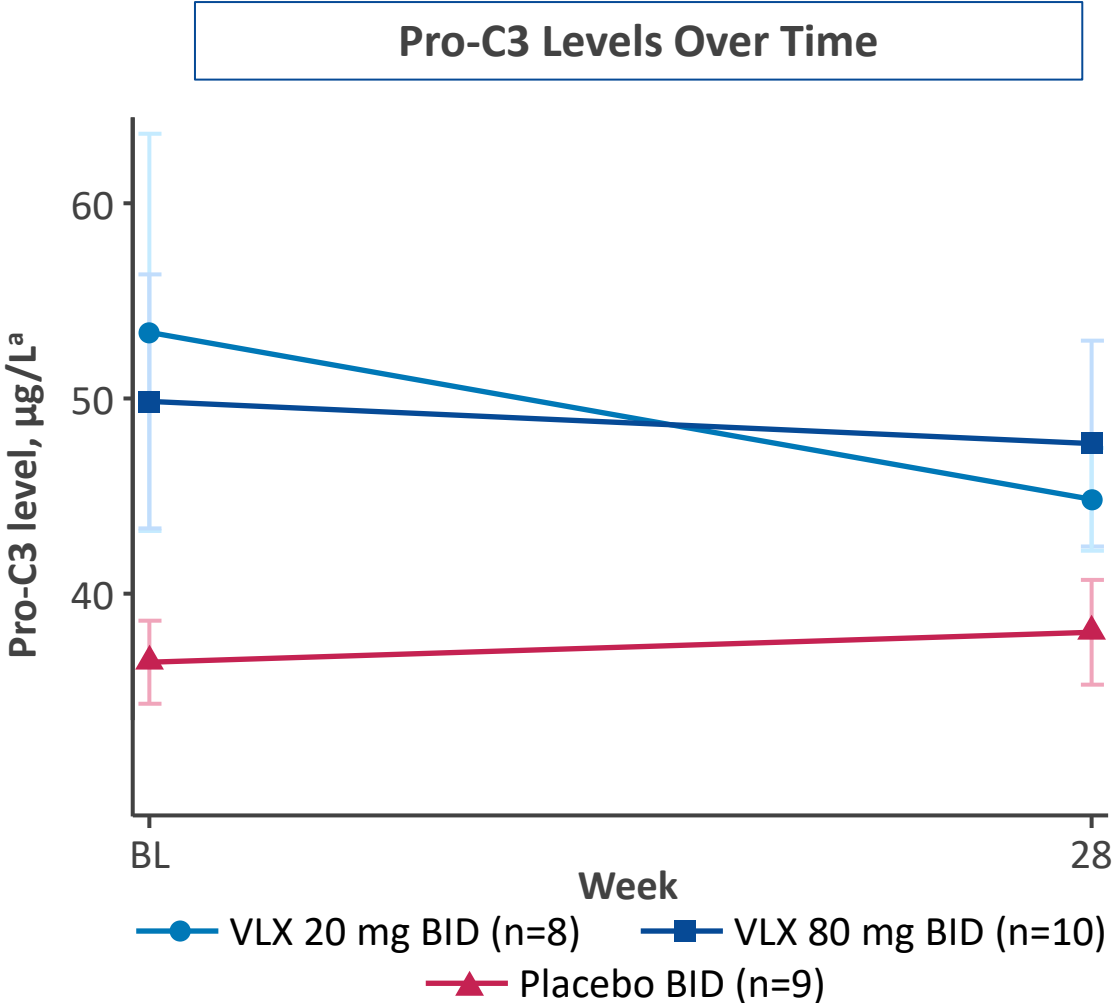
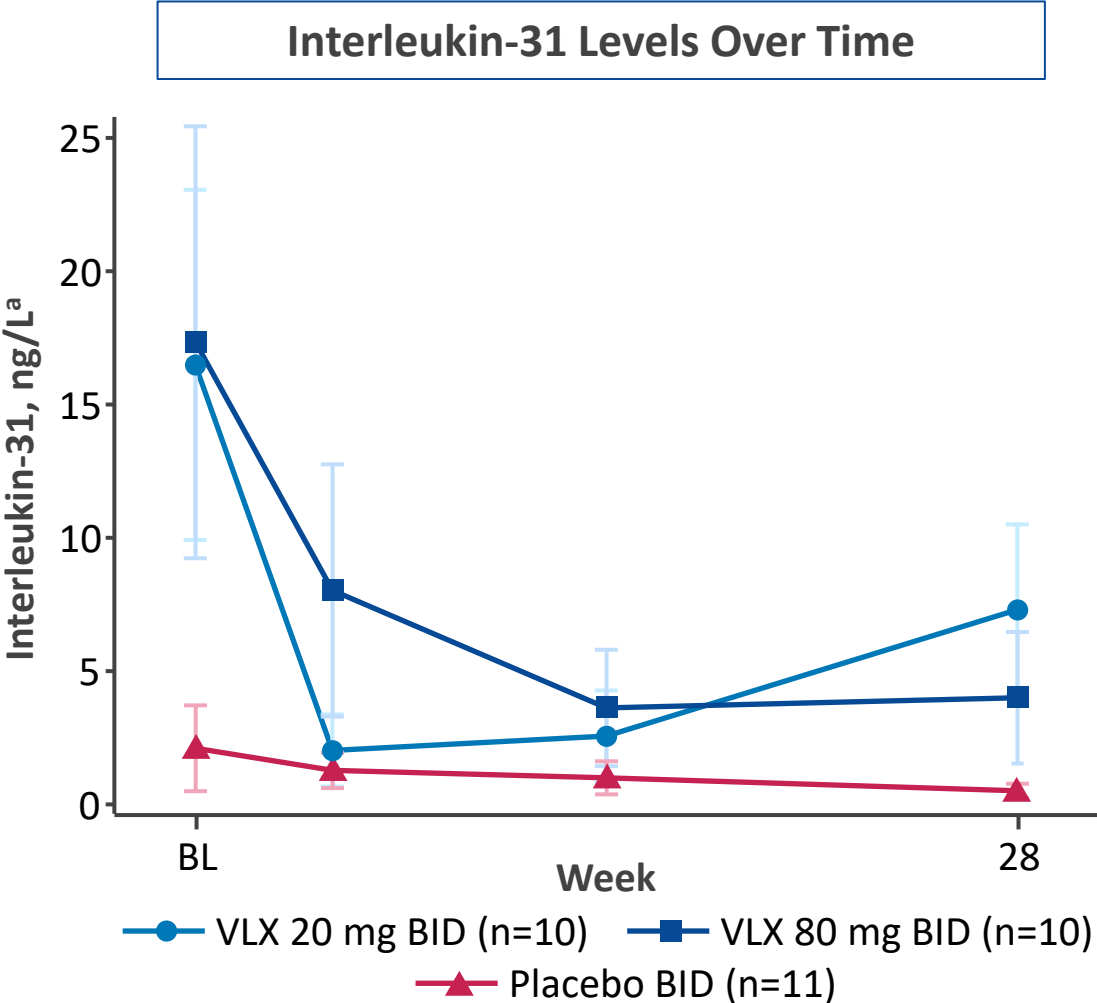


A higher proportion of participants who received volixibat showed an sBA response compared with those who received placebo

BID, twice daily; sBA, serum bile acid; VLX, volixibat.

^aResponder is defined as ≥50% reduction in sBA levels from Baseline. ^bP values were calculated using stratified Cochran-Mantel-Haenszel test (stratified for Adult ItchRO score [<4 , ≥ 4 and <7 , ≥ 7], baseline ALP level [$<1.67 \times \text{ULN}$, $\geq 1.67 \times \text{ULN}$], and use of systemic therapies for cholestatic pruritus [yes, no]).

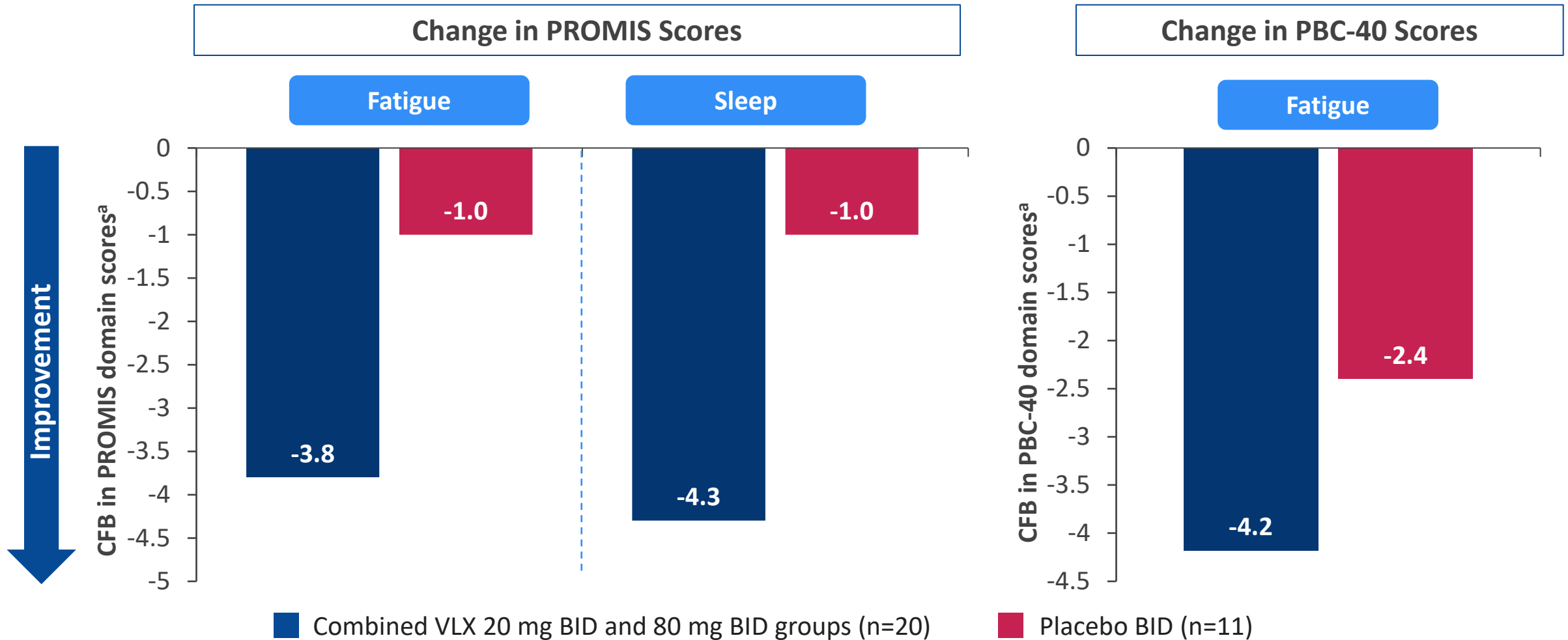
Interleukin-31 and Pro-C3 Levels After Volixibat Treatment



Reductions from Baseline in Interleukin-31 and Pro-C3 levels were observed in participants who received volixibat

BID, twice daily; BL, Baseline; Pro-C3, N-terminal pro-peptide of type III collagen; VLX, volixibat.
Data are mean (±SE).

Participants Who Received Volixibat Showed Improvements in HRQoL



Improvements in fatigue and sleep from Baseline were observed 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; PROMIS, Patient-reported Outcomes Measurement Information System; VLX, volixibat.
^aLS Mean CFB to Week 28.

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.

^aSafety analysis set included primary and secondary cohorts, double-blind period.

Additional Safety Details

- Diarrhoea was the most common TEAE, reported in up to 77% (17 of 22) of all participants receiving volixibat
 - Diarrhoea 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

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
- Numerically greater reductions in sBA levels were observed with volixibat treatment compared with placebo
- Improvements in fatigue, a relevant measure of HRQoL, were observed with volixibat treatment
- 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 enrolment), constituting a new promising therapy to address important symptoms in PBC

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