Efficacy and Safety of Volixibat, an IBAT Inhibitor, in Patients With Primary Sclerosing Cholangitis and Moderate-to-Severe Pruritus: Results of the VISTAS Trial

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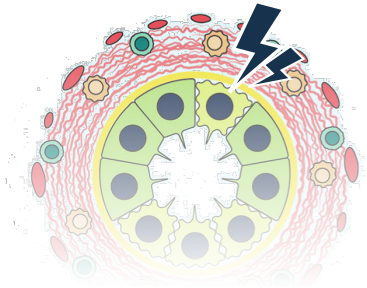
Primary Sclerosing Cholangitis (PSC)[1-7]

Progressive Biliary Injury Drives Cholestasis and Liver Damage



Progressive biliary strictures

↓

Impaired bile flow, bile acid accumulation

↓

Scarring and destruction of bile ducts

↓

Biliary fibrosis and cirrhosis

Serious and Compounding Disease Consequences

Pruritus and Fatigue
Heavy symptom burden

Elevated Laboratory Tests
ALP, Bilirubin, ALT, AST

Cholangitis
Recurrent, unpredictable

Frequent Association with IBD
~70% have concomitant IBD

Increased Cancer Risk
Cholangiocarcinoma, colorectal, gallbladder

Significant Unmet Need

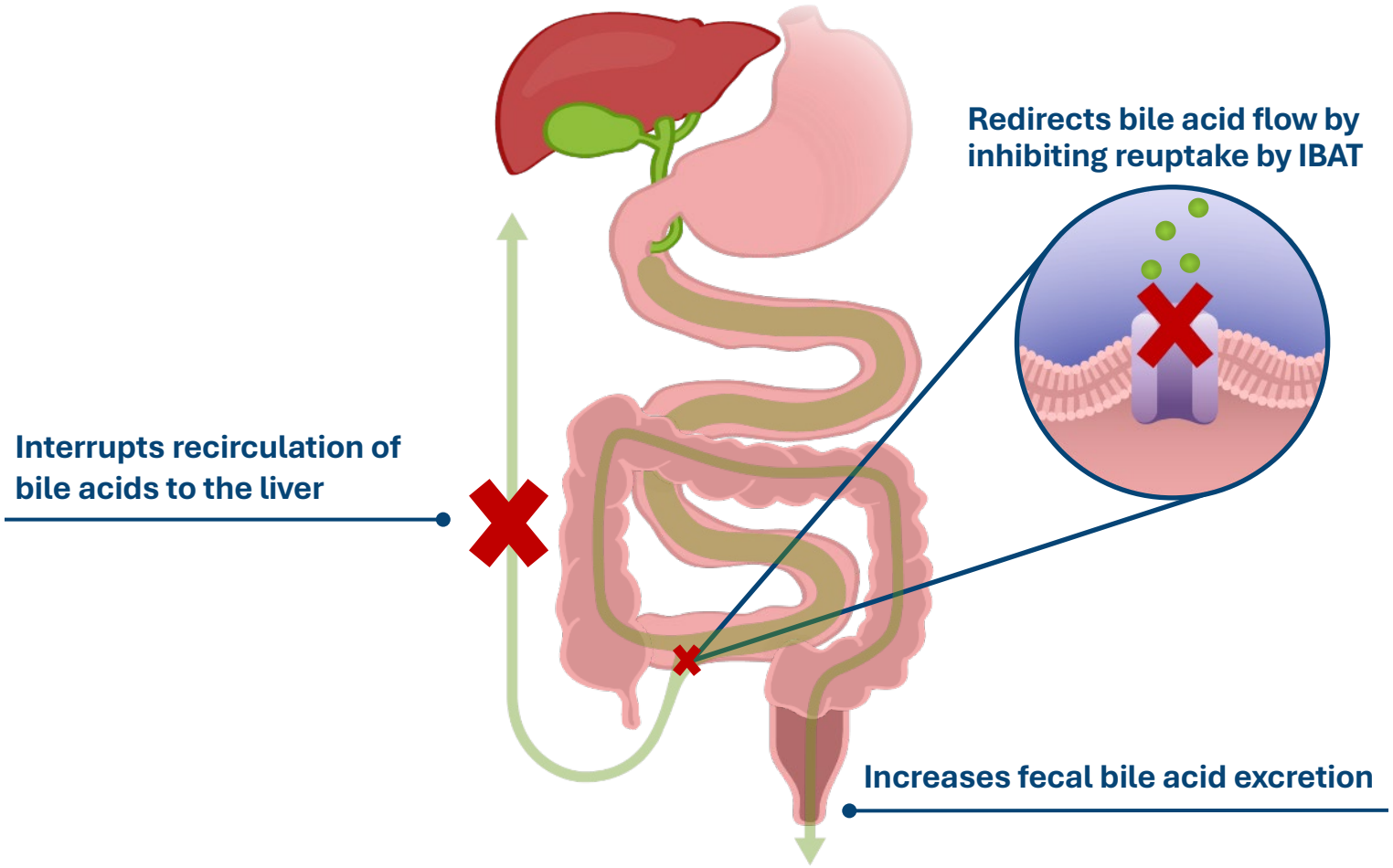
No Approved Therapies for Disease and Symptoms

Emerging evidence supports a potential role for IBAT inhibitors in patients with PSC

PSC, primary sclerosing cholangitis.

1. Eaton JE, et al. *Gastroenterol*. 2013;145:521-536. **2.** Kuo A, et al. *Clin Gastroenterol Hepatol*. 2019;17:1372-1378. **3.** Fung BM, et al. *World J Gastroenterol*. 2019;25:659-671. **4.** PSC Partners Seeking a Cure. Voice of the Patient: Primary Sclerosing Cholangitis (PSC). Available at: pscpartners.org/about/the-disease/diagnosing-psc.html (accessed Jun 2024). **5.** Sirpal S, et al. *Clin Exp Gastroenterol*. 2017;10:265-273. **6.** Kowdley KV, et al. Hepatol Commun. 2026;10:e00904 **7.** Trivedi PJ, et al. *Gastroenterol*. 2024;166:995-1019.

IBAT Inhibitors May Reduce Clinical Effects of Chronic Cholestasis



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

IBATi clinical studies show:

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

Volixibat is a minimally absorbed IBAT inhibitor that interrupts the enterohepatic recirculation of bile acids, reducing sBA levels and potentially improving cholestasis, pruritus and other clinical outcomes in PSC[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; PSC, primary sclerosing 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.

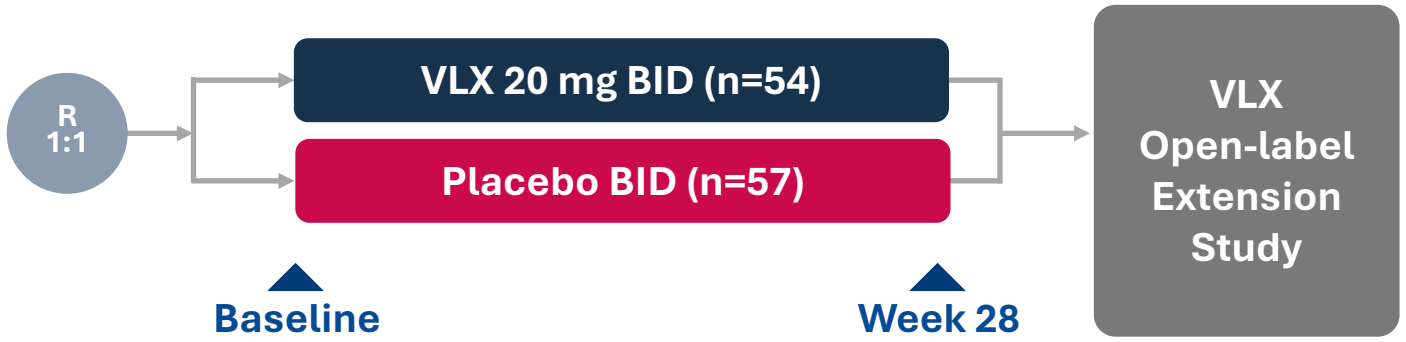
VISTAS: Largest Global Clinical Trial With IBAT Inhibitors in PSC With 103 Study Sites

IBAT, ileal bile acid transporter; PSC, primary sclerosing cholangitis.

VISTAS Study Design: Primary Cohort

Key Entry Criteria

- Confirmed diagnosis of PSC per AASLD guidelines
- Aged ≥12 years at Baseline
- Moderate to severe pruritus
- Concomitant IBD allowed with stable treatment



Primary Endpoint	Select Secondary Endpoints[b]	
• Change in pruritus by Adult ItchRO score from Baseline to the last 12 weeks of the double-blind period	• Other pruritus measures	• Change in sBA
	• Pruritus in secondary cohort*	• Change in ALP and total bilirubin
	• HRQoL measures	• Incidence of AEs

*Participants were randomized to the secondary cohort (n=47) if they had mild pruritus at Baseline

The efficacy data being presented are from the primary cohort[c] and the safety data (N=158) are from all participants (primary and secondary cohorts) enrolled in VISTAS

AASLD, American Association for the Study of Liver Diseases; AE, adverse event; BID, twice daily; ItchRO, Itch-Reported Outcome; PSC, primary sclerosing cholangitis; R, randomisation; 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.[c]Except where otherwise noted.
ClinicalTrials.gov identifier: NCT04663308. Updated February 4, 2026. Accessed May 4, 2026. https://clinicaltrials.gov/ct2/show/NCT04663308.

Adult Itch-Reported Outcome (ItchRO) Scale: Description

- The Adult ItchRO is a single-item daily diary that assesses the severity of itching over the past 24 hours with use of a worst itch numeric rating scale (WI-NRS)
  - Originally developed, tested, and content validity confirmed in patients with PBC[1]
  - Scored by averaging the daily ratings over the 7 days preceding a study visit

Adult ItchRO

ItchRO, Itch-Reported Outcome; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; WI-NRS; worst-itch numeric rating scale.
[a]Adult ItchRO is an 11-point (0-10) scale, where 0 = no itch and 10 = worst possible itch.
[1]Boonstra K, et al. *J Hepatol.* 2012;56:1181–8.

VISTAS Primary Cohort: Key Demographic Characteristics

Parameter[a]	VLX 20 mg BID (n=54)	Placebo BID (n=57)
Age at enrollment, years[b]	45.2 (15.7)	44.3 (14.2)
Time since PSC diagnosis in years	8.4 (7.2)	9.7 (8.3)
Male	29 (53.7)	22 (38.6)
PSC Type		
Large Duct	49 (90.7)	53 (93.0)
IBD	40 (74.1)	42 (73.7)
UC	29 (72.5)	29 (69.0)
CD/Other	11 (27.5)	13 (31.0)
Partial Mayo IBD Score (Overall Score)[c]	n=29	n=29
0-2 Remission	25 (86.2)	29 (100)
3-5 Mild	4 (13.8)	0
UDCA use at Baseline	43 (79.6)	43 (75.4)

CD, Crohn's disease; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; UC, ulcerative colitis; VLX, volixibat.
[a]Continuous variables present mean (SD) and categorical variables present N (%). [b]VLX group included participant who was 17 years old and PBO group included participant who was 16 years old. [c]Partial Mayo IBD score only calculated for those with UC. No participant had moderate (6-7) or severe (8-9) activity based on the partial Mayo IBD score.

VISTAS Primary Cohort: Additional Key Baseline Characteristics

Parameter[a]	VLX 20 mg BID (n=54)	Placebo BID (n=57)
ItchRO Score[b]	**6.3 (1.6)**	**6.1 (1.5)**
sBA, μmol/L	109.6 (137.5)	61.4 (83.2)
ALT, U/L	73 (46.8)	87 (58.5)
AST, U/L	61 (30.2)	72 (46.7)
Total Bilirubin, μmol/L	20.1 (13.9)	18.5 (14.2)
Direct Bilirubin, μmol/L	11.5 (10.7)	9.6 (10.0)
ALP, U/L	334 (189.6)	365 (232.2)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; sBA, serum bile acid.
[a]Continuous variables present mean (SD) and categorical variables present N (%). [b]Adult ItchRO is an 11-point (0-10) scale, where 0 = no itch and 10 = worst possible itch

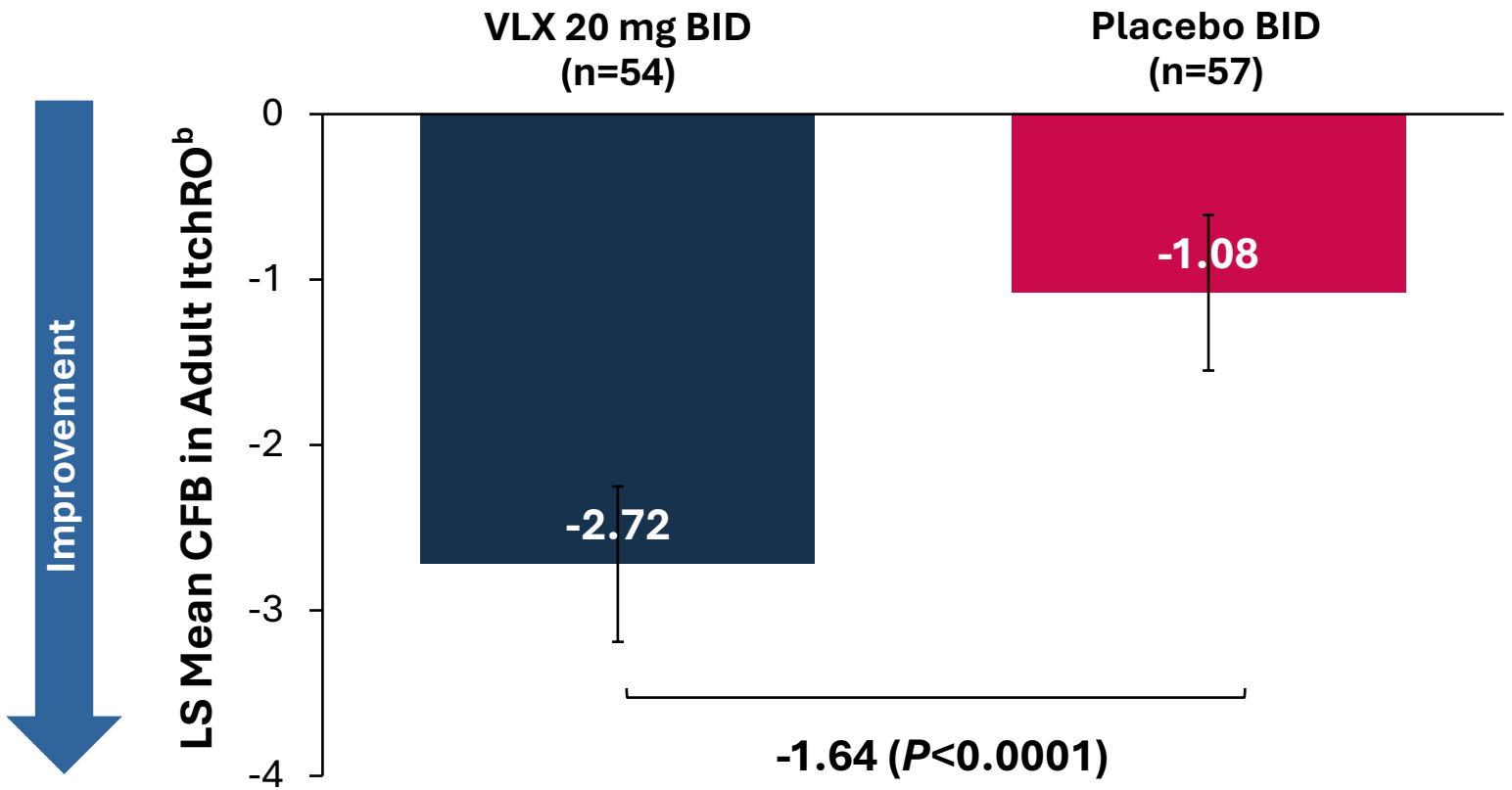
VISTAS Primary Cohort Results: Participants Who Received Volixibat Showed Statistically Significant Reductions in Cholestatic Pruritus

Mean (SD) Adult ItchRO Scores at Baseline:

VLX 20 mg BID: 6.3 (1.6)

Placebo BID: 6.1 (1.5)

Pruritus Score (Adult ItchRO) MMRM Analysis[a]

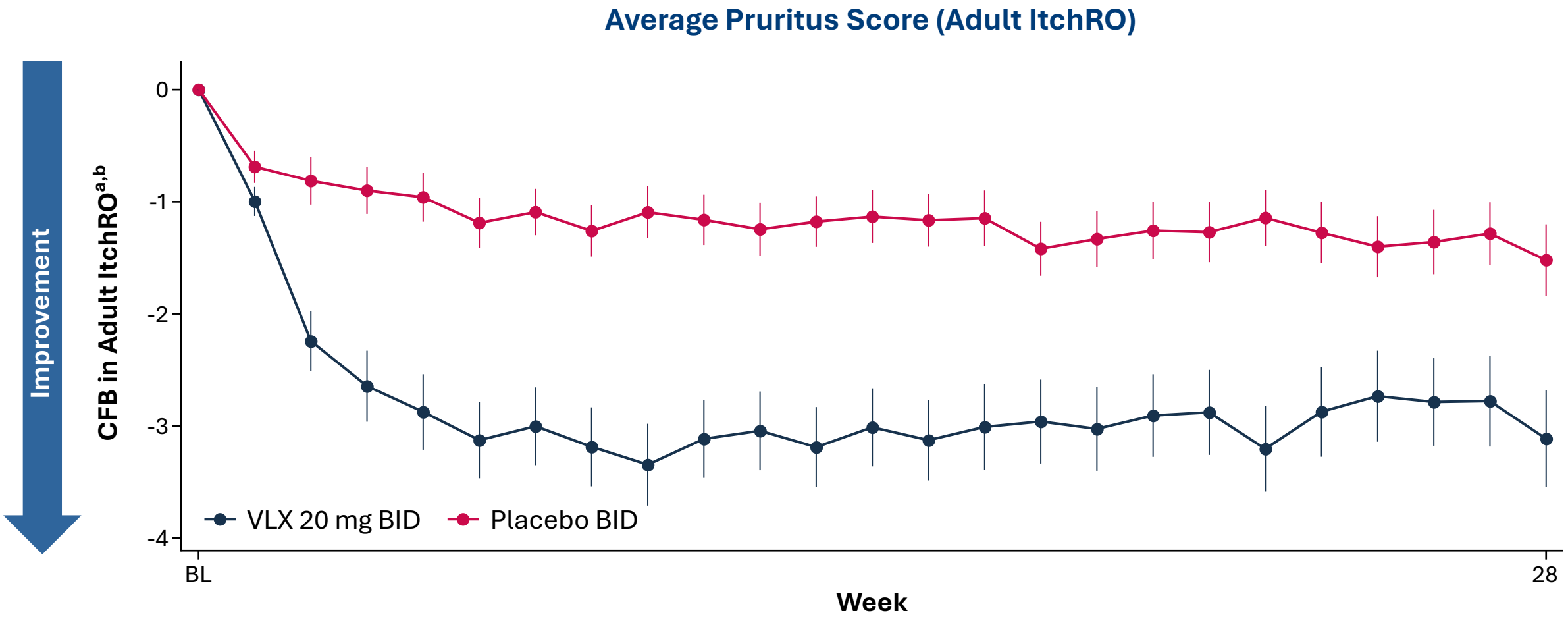


Clinically meaningful and statistically significant reductions in pruritus were observed with volixibat compared with placebo

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

[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; **<0.01; ***<0.0001. [b]Adult ItchRO is an 11-point (0-10) scale, where 0 = no itch and 10 = worst possible itch.

VISTAS Primary Cohort Results: Participants Who Received Volixibat Showed Reductions in Cholestatic Pruritus Over Time

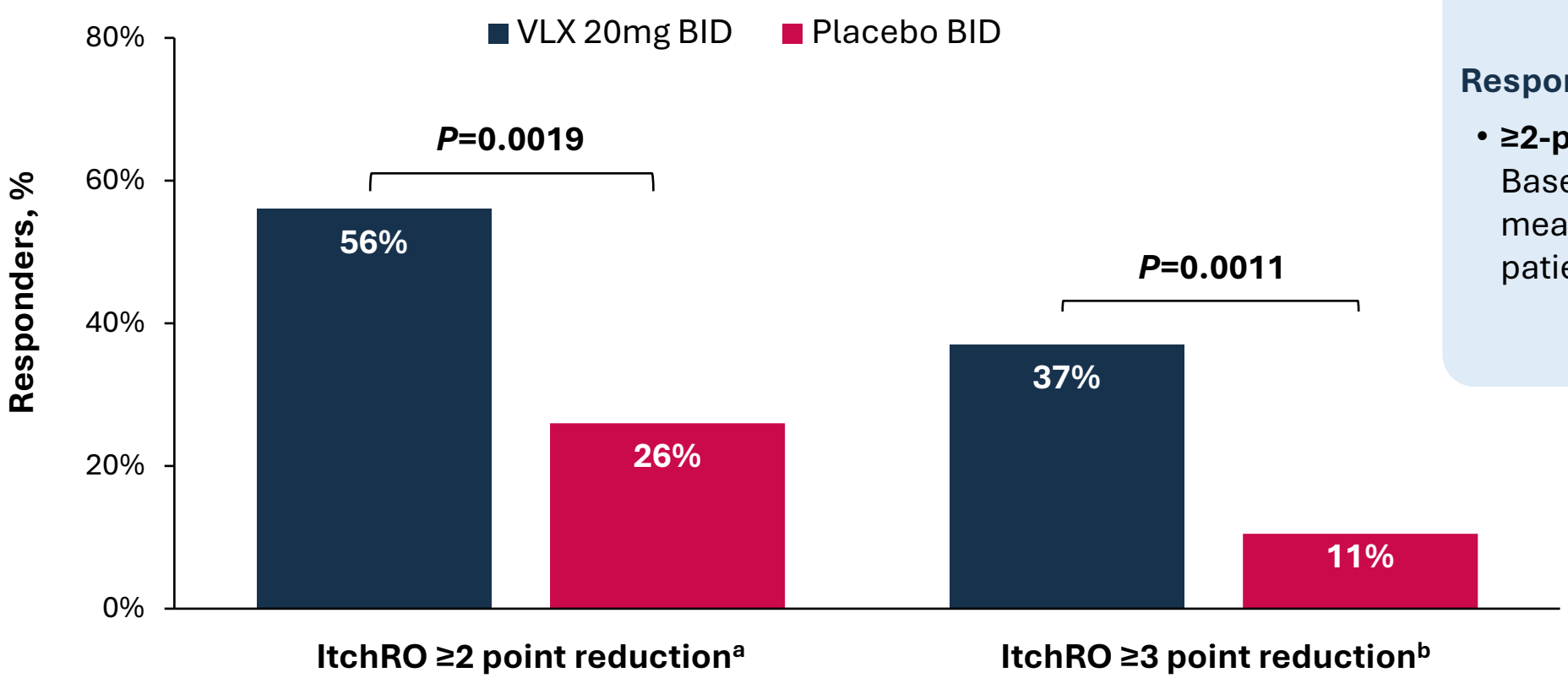


Rapid and sustained reductions in pruritus were observed after treatment with volixibat as early as Week 2 and maintained over time

BID, twice daily; CFB, change from Baseline; ItchRO, Itch-Reported Outcome; VLX, volixibat.
[a]Data are mean (SE). . [b]Adult ItchRO is an 11-point (0-10) scale, where 0 = no itch and 10 = worst possible itch.

VISTAS Primary Cohort Results: Pruritus Responder Analysis Across Participants

Proportion of Pruritus Responders



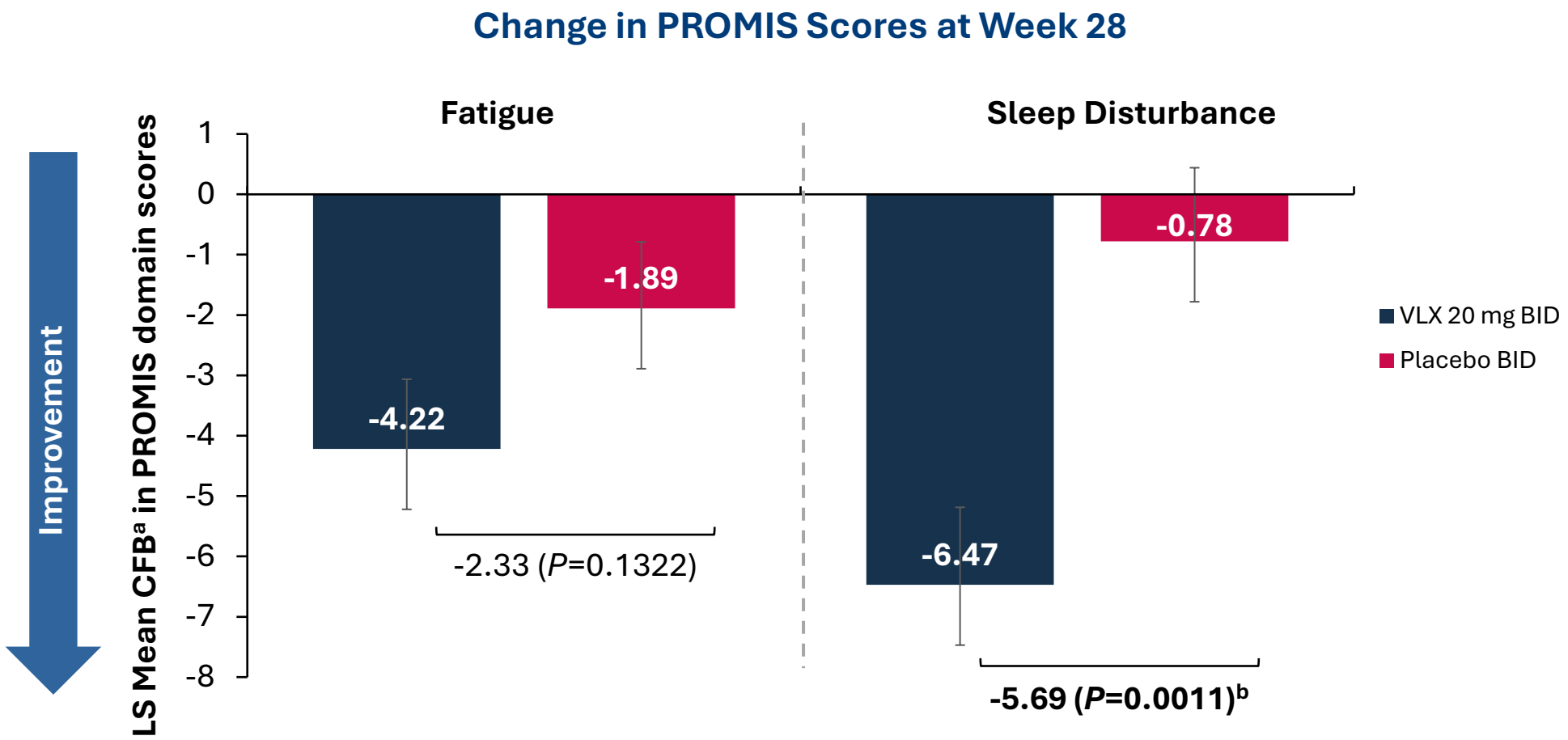
Responder Thresholds:

- **≥2-point reduction** from Baseline defined as meaningful improvement for patients

Statistically significant reductions with volixibat versus placebo for all pruritus responder analyses

BID, twice daily; ItchRO, Itch-Reported Outcome; VLX, volixibat·
[a]ItchRO responder is defined as ≥2-point reduction in the adult ItchRO score from Baseline. [a]ItchRO responder is defined as ≥3-point reduction in the adult ItchRO score from Baseline.
Foster B, et al. Presented at: The Digital International Liver Congress 2020.

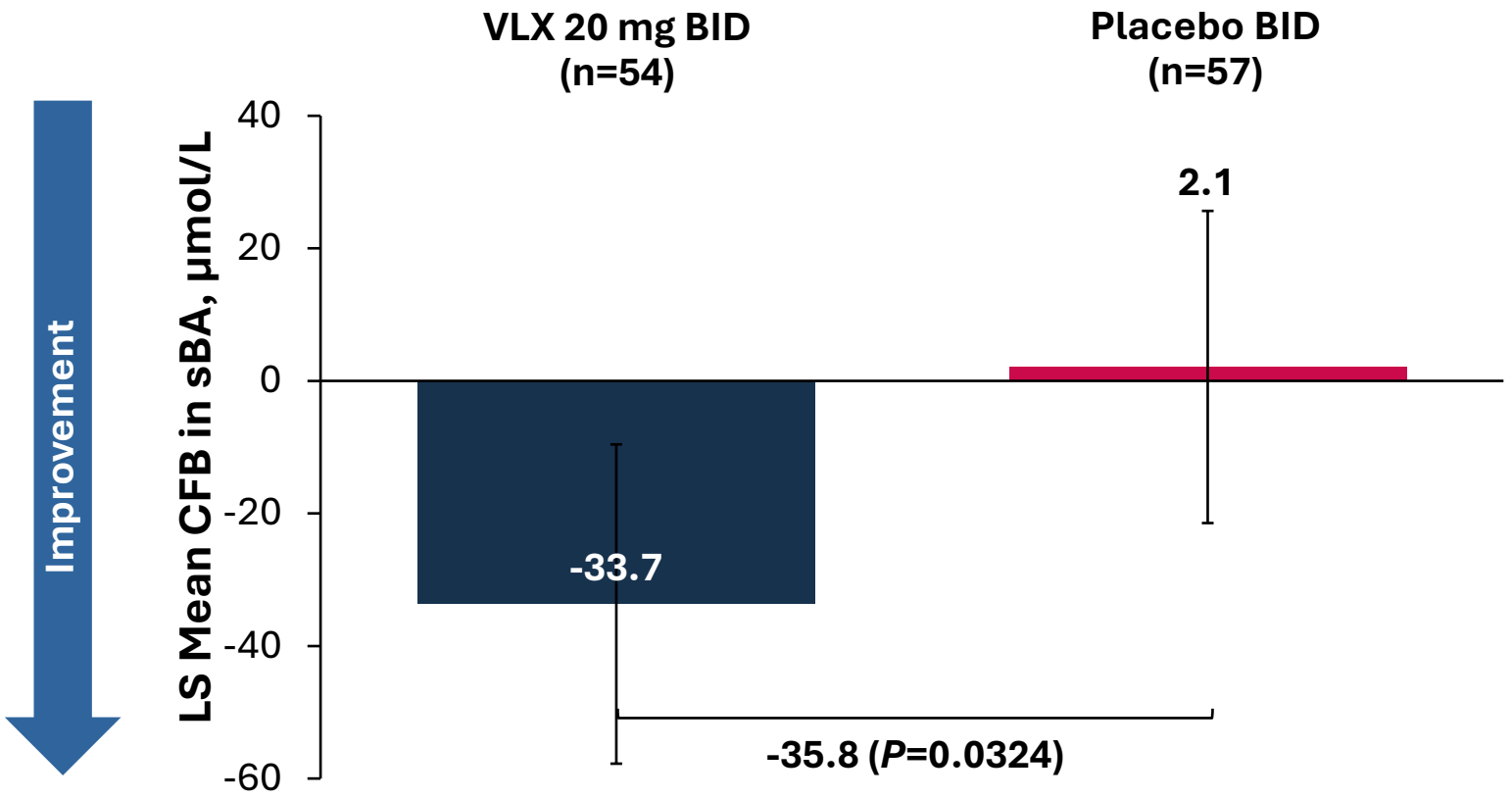
VISTAS Primary Cohort Results: Participants Who Received Volixibat Showed Improvements in Fatigue and Sleep



BID, twice daily; CFB, change from Baseline; HRQoL, health-related quality of life; MMRM, mixed-effects model for repeated measures; PROMIS, Patient-reported Outcomes Measurement Information System; VLX, volixibat.
[a]Data are LS mean with ±SE. Effect size compared the difference between volixibat and placebo, averaged over the last 12 weeks using MMRM. [b]Nominal p-value due to hierarchy of regression analysis.

VISTAS Primary Cohort Results: Participants Who Received Volixibat Showed Statistically Significant Reductions in sBA Levels

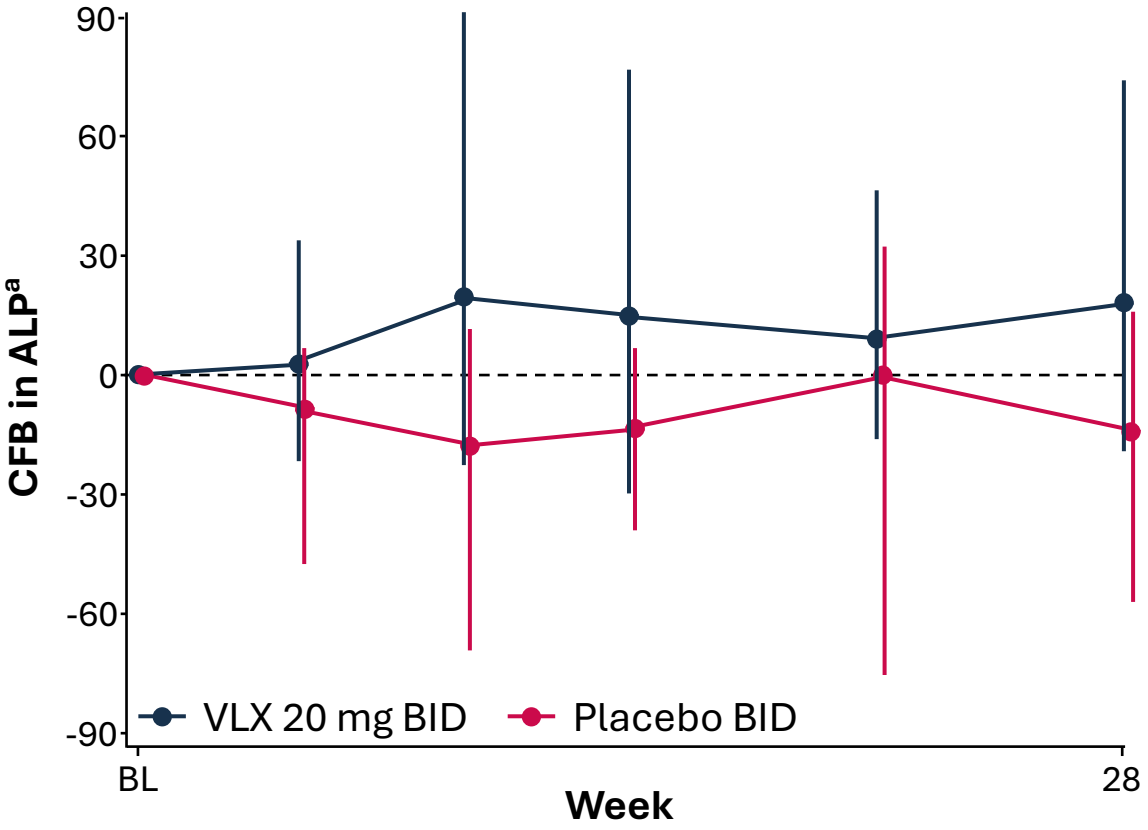
sBA Levels MMRM Analysis[a]

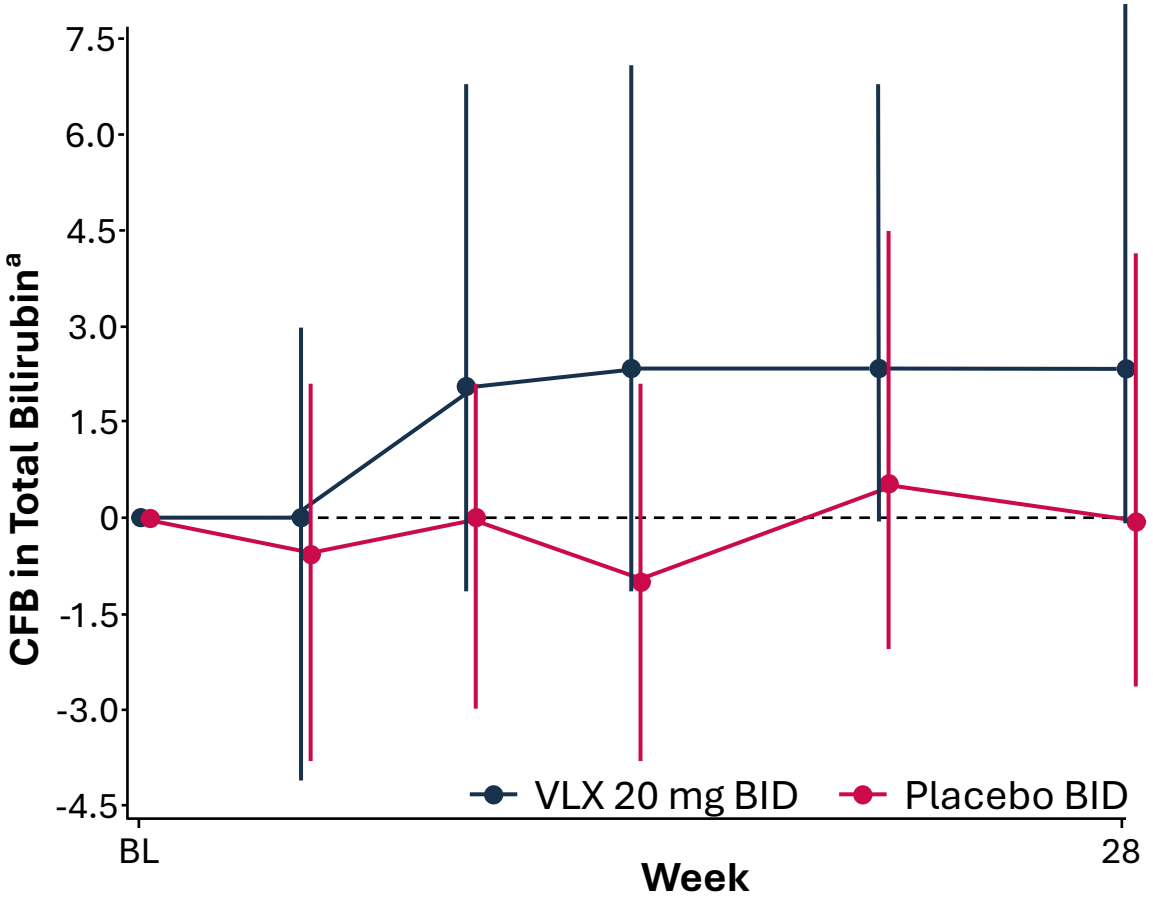


Statistically significant reductions in sBA were observed with volixibat compared with placebo

BID, twice daily; CFB, change from Baseline; MMRM, mixed-effects model for repeated measures; sBA, serum bile acid; VLX, volixibat.
[a]Data are LS mean with standard error bars. Effect size compared the difference between volixibat and placebo, averaged over the last 12 weeks using MMRM.

Median Change from Baseline in Alkaline Phosphatase and Total Bilirubin: Primary Cohort





[a]Data are median (Q1, Q3) changes from baseline.

VISTAS Safety Analysis in Primary and Secondary Cohorts: Summary of TEAEs

Parameter	VLX 20 mg BID (N=77)	Placebo BID (N=81)
No. (%) of Participants with Any TEAE	72 (93.5)	68 (84.0)
Related TEAEs	34 (44.2)	16 (19.8)
Grade 3 or higher TEAEs	10 (13.0)	9 (11.1)
Related Grade 3 or higher TEAEs	2 (2.6)	3 (3.7)
Serious TEAEs	8 (10.4)	5 (6.2)
Related Serious TEAEs	0	0
TEAE that led to premature DC of study drug	7 (9.1)	2 (2.5)
Study drug DC due to diarrhea	3 (3.9)	1 (1.2)
TEAE that led to death	0	1 (1.2)[a]

- SAE in VLX group: acute cholangitis, infection (sepsis, liver abscess, viral infection), abdominal pain, cholangiocarcinoma, sclerosing cholangitis (progression), biliary colic, pyrexia, back pain, procedure-related pancreatitis; none related to treatment
- SAEs in Placebo group: acute cholangitis, constipation, spontaneous bacterial peritonitis[a], liver function tests increased, radius fracture; none related to treatment
- TEAEs that led to premature DC of study drug: VLX: diarrhea (n=3), IBD (n=1), cholangitis sclerosing (progression; n=1), alanine aminotransferase increased (n=1), cholangiocarcinoma (n=1); PBO: diarrhea (n=1), ascites (n=1).

BID, twice daily; DC, discontinuation; IIBD, irritable bowel disease; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event; VLX, volixibat
[a]Death in placebo group due to spontaneous bacterial peritonitis.

VISTAS Safety Analysis in Primary and Secondary Cohorts: Participants With Any TEAE ≥5%

Preferred Term	VLX 20 mg BID (N=77)	Placebo BID (N=81)
No. (%) of Participants with Any TEAE	72 (93.5)	68 (84.0)
Diarrhoea	31 (40.3)	7 (8.6)
Abdominal Pain	14 (18.2)	8 (9.9)
Nausea	10 (13.0)	3 (3.7)
Vitamin D deficiency	8 (10.4)	4 (4.9)
Abdominal pain upper	7 (9.1)	6 (7.4)
Alanine aminotransferase increased	7 (9.1)	3 (3.7)
Upper respiratory tract infection	6 (7.8)	6 (7.4)
Back pain	5 (6.5)	2 (2.5)
Fatigue	5 (6.5)	4 (4.9)
Blood bilirubin increased	4 (5.2)	3 (3.7)
Jaundice	4 (5.2)	1 (1.2)
Pyrexia	4 (5.2)	1 (1.2)
Influenza	3 (3.9)	5 (6.2)

- Elevations in ALT, AST, ALP, and bilirubin were observed more frequently in volixibat-treated than placebo-treated participants

The safety of volixibat is generally consistent with the known effects of IBAT inhibition

BID, twice daily; TEAE, treatment-emergent adverse event; VLX, volixibat.

Conclusions

VISTAS is the largest interventional study investigating the efficacy and safety of an IBAT inhibitor in PSC and is the first controlled evidence of a potential therapy addressing the cholestatic symptom burden in patients with PSC.

Volixibat led to rapid, significant, and sustained improvement in cholestatic pruritus while showing a safety profile that is consistent with IBAT inhibition.

Improvements in quality of life, specifically sleep, were observed with volixibat.

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