



Volixibat Leads to Improvements in Fatigue and Sleep for Adults With Primary Biliary Cholangitis: Data From VANTAGE

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Symptom Burden in Primary Biliary Cholangitis (PBC)

- Primary biliary cholangitis is associated with a significant and complex symptom burden, which is often independent of disease stage and biochemical response¹⁻³
- Pruritus and fatigue are the most debilitating symptoms in PBC, both affecting up to 70% to 80% of patients. Sleep disturbances may affect approximately 60% of patients⁴⁻⁷

Pruritus	Sleep disturbances	Fatigue
Pruritus is often severe, can be localized or generalized, and typically worsens in the evening ¹⁻³	Sleep disturbance can be moderate to severe and is associated with fatigue, anxiety, depression, and pruritus ⁴⁻⁷	Fatigue encompasses lethargy, malaise, lassitude, and exhaustion and is disabling in approximately 25% ^{4,5}

These symptoms are major determinants of impaired health-related quality of life in patients with PBC and have a multifaceted and incompletely understood physiopathology linked to cholestasis^{8,9}

New, effective, and safe treatments to manage symptom burden in patients with PBC are needed^{2,3}

PBC, primary biliary cholangitis.

1. Gungabissoon U, et al. *BMJ Open Gastroenterol.* 2022;9:e000857. 2. Hirschfield G, et al. *Gut.* 2028;67:1568-1594. 3. Lindor KD. *Hepatology.* 2019;69:394-419. 4. Lynch EN. *World J Hepatol.* 2022;14:1111-1119. 5. Huet PM. *Am J Gastroenterol.* 2000;95:760-767. 6. Zhao C, et al. *Frontiers in Medicine.* 2024;11:1444473. 7. Montagnese S. *Liver Int.* 2013;33:203-209. 8. Mells GF. *Hepatology.* 2013;58:273-283. 9. Kaps L. *Digestive Diseases and Sciences.* 2020;65:3006-3013.

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

PBC is characterized by impaired bile flow (cholestasis)^{1,2}

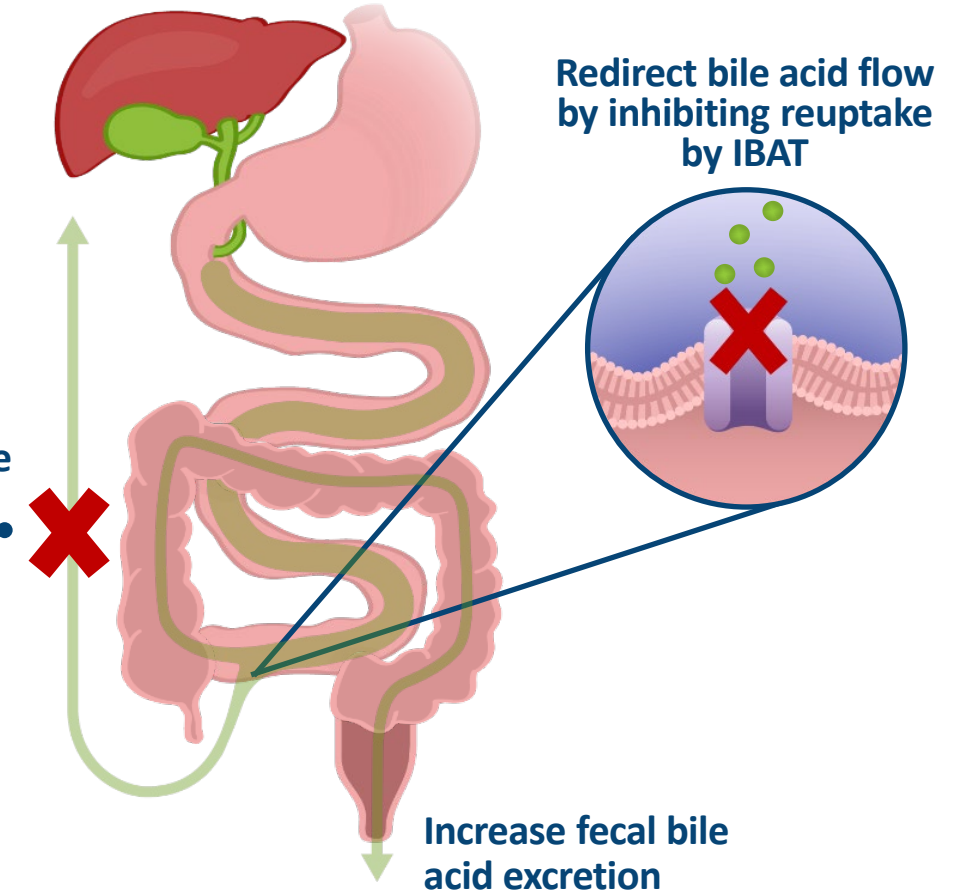
Cholestasis leads to **inflammation** and release of **signaling mediators** within the liver^{3,4}

These mediators may be associated with the **clinical manifestations** of cholestasis⁵

Senescent secretome
Opioids ? Autotaxin ? IL-1β LPA
? TNF-α Oxidative stress markers IL-31
IL-6 ? Anti-mitochondrial antibodies
Reactive oxygen species

IBAT inhibitors⁶⁻¹²:

Interrupt recirculation of bile acids to the liver



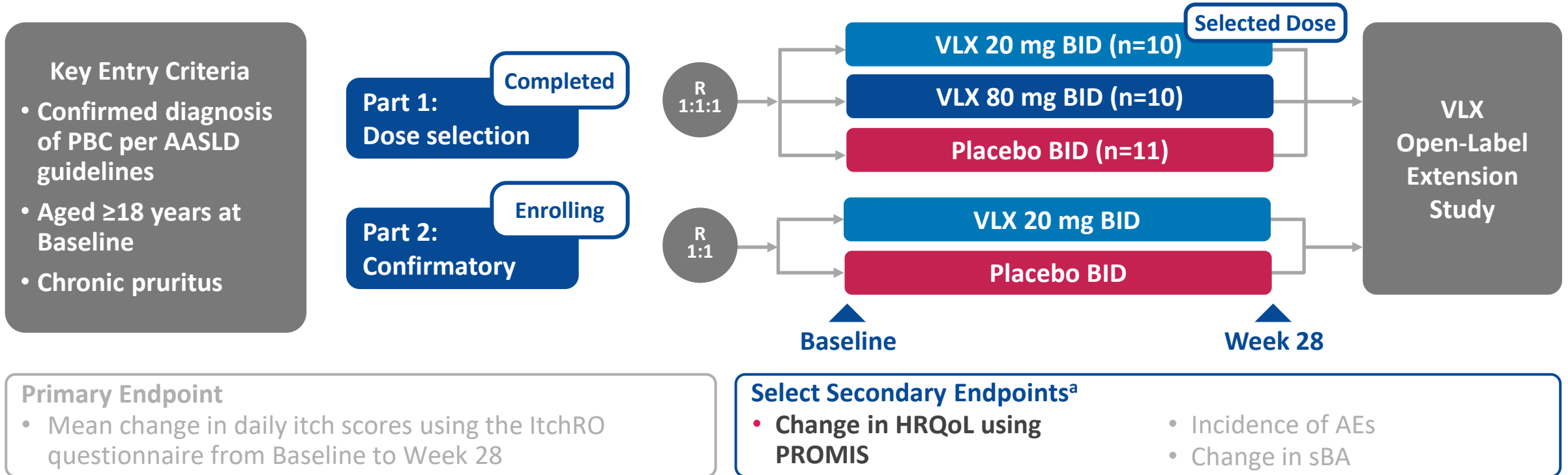
Volixibat is a minimally absorbed IBAT inhibitor that interrupts the enterohepatic recirculation of bile acids, reducing their accumulation and potentially improving cholestatic pruritus and other symptoms in PBC¹³

IBAT, ileal bile acid transporter; IL, interleukin; LPA, lysophosphatidic acid; PBC, primary biliary cholangitis; TNF-α, tumor necrosis factor alpha.

1. Di Ciaula A, et al. *Ann Hepatol.* 2017;16(suppl 1):s4-s14. 2. Hegade VS, et al. *BMC Gastroenterol.* 2016;16:71. 3. Cai S-Y, et al. *Ann Transl Med.* 2021;9:737. 4. Hirschfield GM, et al. *Gastroenterology.* 2010;139:1481-1496. 5. Hegade VS, et al. *Therap Adv Gastroenterol.* 2016;9:376-391. 6. Hegade VS, et al. *Therap Adv Gastroenterol.* 2016;9:376-391. 7. Kamath BM, et al. *Liver Int.* 2020;40:1812-1822. 8. Baker A, et al. *Clin Res Hepatol Gastroenterol.* 2019;43:20-36. 9. Dawson PA. *Handb Exp Pharmacol.* 2011;201:169-203. 10. Miethke AG, et al. *Hepatology.* 2016;63:512-523. 11. Tiessen RG, et al. *BMC Gastroenterol.* 2018;18:3. 12. Gonzales E, et al. *Lancet.* 2021;398:1581-1592. 13. Key C, et al. Presented at: AASLD 2020. 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

VANTAGE is a 2-part, 28-week, randomized, multicenter, double-blind, placebo-controlled phase 2b study evaluating the efficacy and safety of volixibat for the treatment of cholestatic pruritus in adults with PBC



- **PROMIS Fatigue** assesses the impact/experience of fatigue and consists of a 7-item questionnaire
- **PROMIS Sleep** assesses sleep quality, depth, and restoration; it consists of an 8-item questionnaire

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; PROMIS, Patient-Reported Outcomes Measurement Information System; R, randomization; sBA, serum bile acid; VLX, volixibat.

^aAssessed from Baseline to Week 28 for interim analysis.

ClinicalTrials.gov identifier: NCT05050136. Updated September 3, 2025. Accessed October 6, 2025. <https://clinicaltrials.gov/ct2/show/NCT05050136>

Objective

- VANTAGE primary efficacy endpoint (change in pruritus from Baseline to Week 28) has been previously reported
- Rapid and statistically significant reductions in cholestatic pruritus were observed after treatment with volixibat
 - A change from Baseline of -3.7 points in the 10-point Adult ItchRO scale ($P < 0.0001$) and a placebo-adjusted response of -2.4 ($P = 0.0039$)^a in the volixibat 20mg cohort
 - Change from Baseline in Adult ItchRO was similar between the volixibat 20 mg and volixibat 80 mg cohorts^b
- No new safety signals were identified with volixibat compared with placebo

Objective: To evaluate the efficacy of volixibat to treat additional cholestatic symptoms beyond pruritus (fatigue and sleep disturbances)

CFB, Change from Baseline; ItchRO, Itch-Reported Outcome.

^aAdult ItchRO is an 11-point (0-10) scale, where 0 = no itch and 10 = worst possible itch. ^bFor 80mg volixibat cohort: (CFB: -3.9 [$P < 0.0001$]; PBO-adjusted response: -2.6 [$P = 0.0010$])

Heneghan M, et al. Presented at: EASL 2025.

Key Demographics and Baseline Characteristics

Well-balanced Baseline PROMIS Fatigue and Sleep disturbance scores

Parameter ^a	Combined VLX 20 mg and 80 mg groups (n=20)	Placebo (n=11)	Entire population (N=31)
Age at enrollment, years	53.1 (11.7)	62.1 (9.7)	56.3 (11.7)
Sex, female, n (%)	17 (85.0)	10 (90.9)	27 (87.1)
Pruritus, Adult ItchRO score ^b	6.6 (1.6)	6.2 (1.5)	6.4 (1.6)
PROMIS Fatigue score^{c,d}	57.9 (7.6)	56.9 (12.0)	57.6 (9.1)
PROMIS Sleep score^{c,d}	58.7 (6.1)	56.1 (9.1)	57.8 (7.2)
sBA, µmol/L	49 (62)	31 (52)	42 (59)
ALT, U/L	50 (37)	45 (37)	48 (36)
AST, U/L	44 (32)	35 (12)	41 (27)
ALP, U/L	235 (118)	167 (114)	211 (119)
<1.67 × ULN, n (%)	13 (65.0)	9 (81.8)	22 (71.0)
Total bilirubin, mg/dL	1.03 (0.77)	0.71 (0.37)	0.92 (0.67)

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ItchRO, Itch-Reported Outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; sBA, serum bile acid; ULN, upper limit of normal; VLX, volixibat.

^aData are mean (SD) unless otherwise indicated. ^bAdult ItchRO is an 11-point (0-10) scale, where 0 = no itch and 10 = worst possible itch. ^cData were available for 18 in the combined VLX group, 9 in the PBO group, and 27 in the entire population. ^dT-scores were provided by the developer and were used in the analysis.

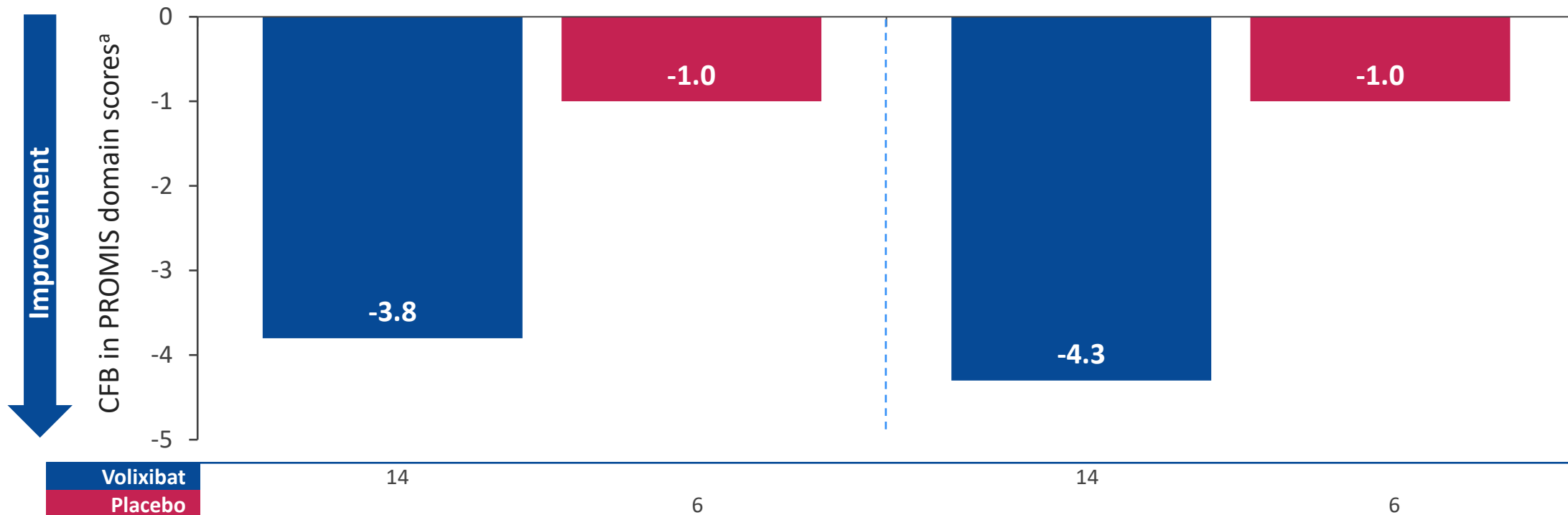
Volixibat-Treated Participants Showed Improvements in HRQoL

Change in PROMIS Scores at Week 28

■ Combined VLX 20 mg and 80 mg groups ■ Placebo

Fatigue

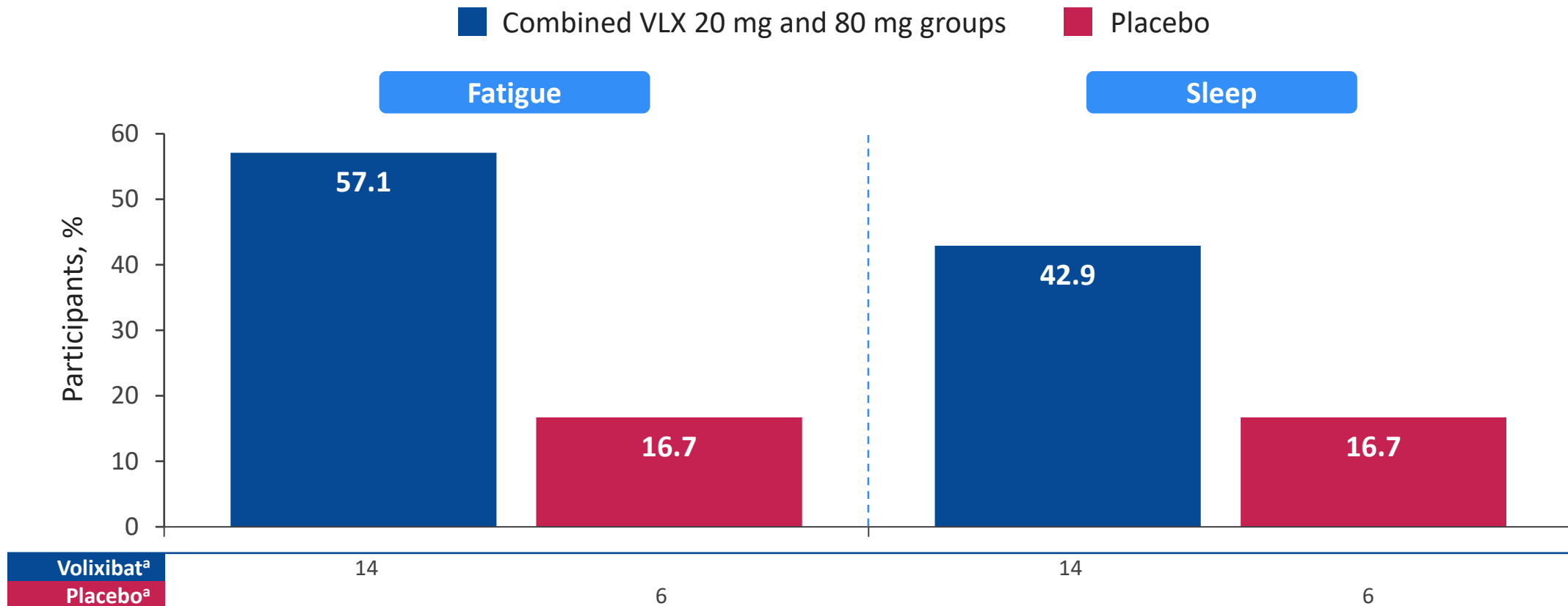
Sleep



Improvements in fatigue and sleep from Baseline were observed in participants treated with volixibat

Volixibat-Treated Participants Had Clinically Meaningful Improvements in PROMIS Fatigue and Sleep Scores

Participants With Improvement \geq MCID in PROMIS Fatigue or Sleep Scores at Week 28
MCID is ≥ 3 -point decrease from Baseline¹



More participants in the volixibat group showed improvements \geq MCID in PROMIS Fatigue and PROMIS Sleep scores

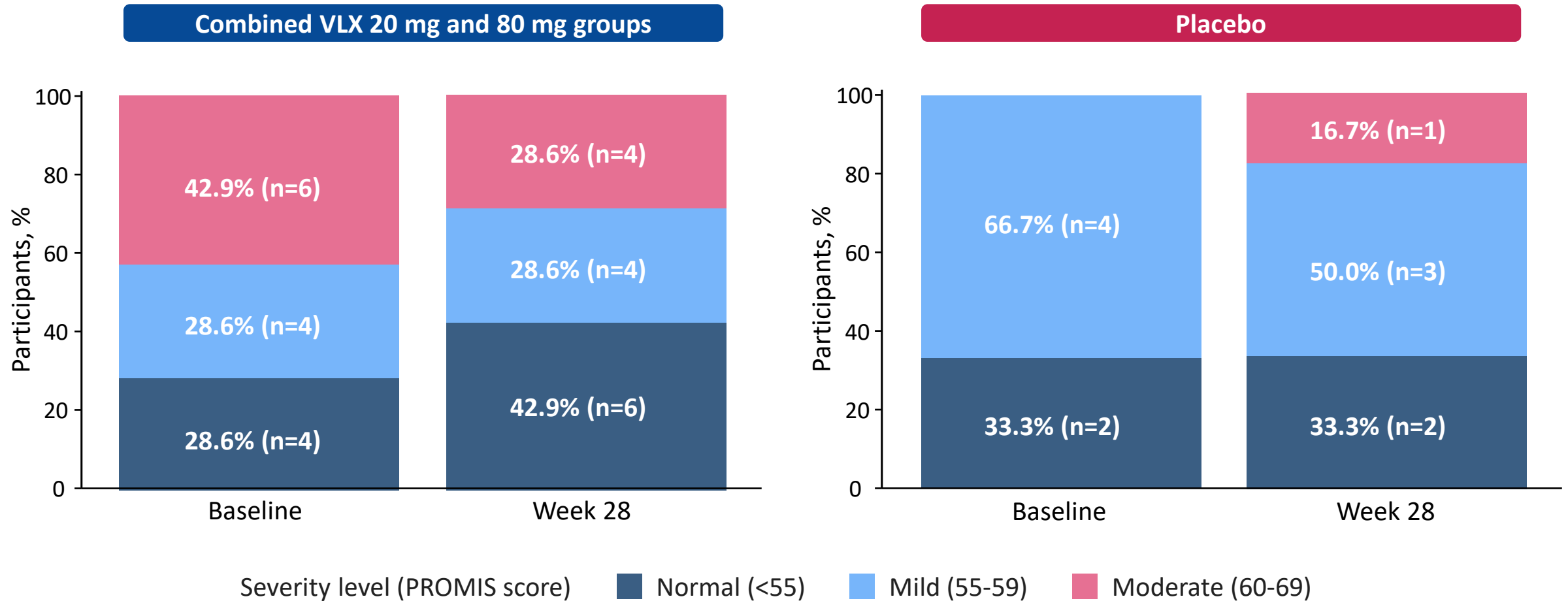
MCID, minimum clinically important difference; PROMIS, Patient-Reported Outcomes Measurement Information System; VLX, volixibat.

^aIncludes participants with nonmissing assessments at Baseline and Week 28.

1. Yost KJ, et al. *J Clin Epidemiol.* 2011;64(5):507-516.

Volixibat Group Had an Increase in the Proportion of Participants Reporting Normal PROMIS Fatigue Scores by Week 28

PROMIS Fatigue Severity at Baseline and Week 28^a

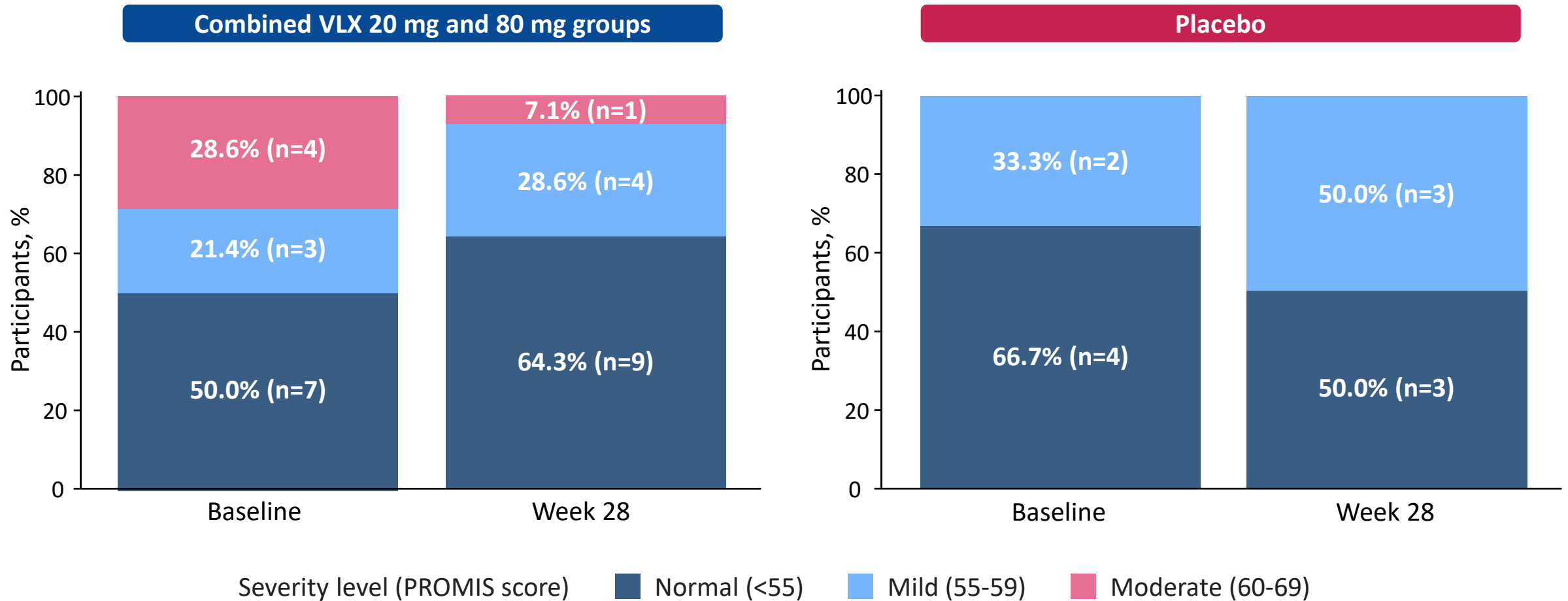


PROMIS, Patient-Reported Outcomes Measurement Information System; VLX, volixibat.

^aAnalysis included participants with nonmissing data at Baseline and Week 28 data.

Volixibat Group Had an Increase in the Proportion of Participants Reporting Normal PROMIS Sleep Scores by Week 28

PROMIS Sleep Severity at Baseline and Week 28^a



PROMIS, Patient-Reported Outcomes Measurement Information System; VLX, volixibat.

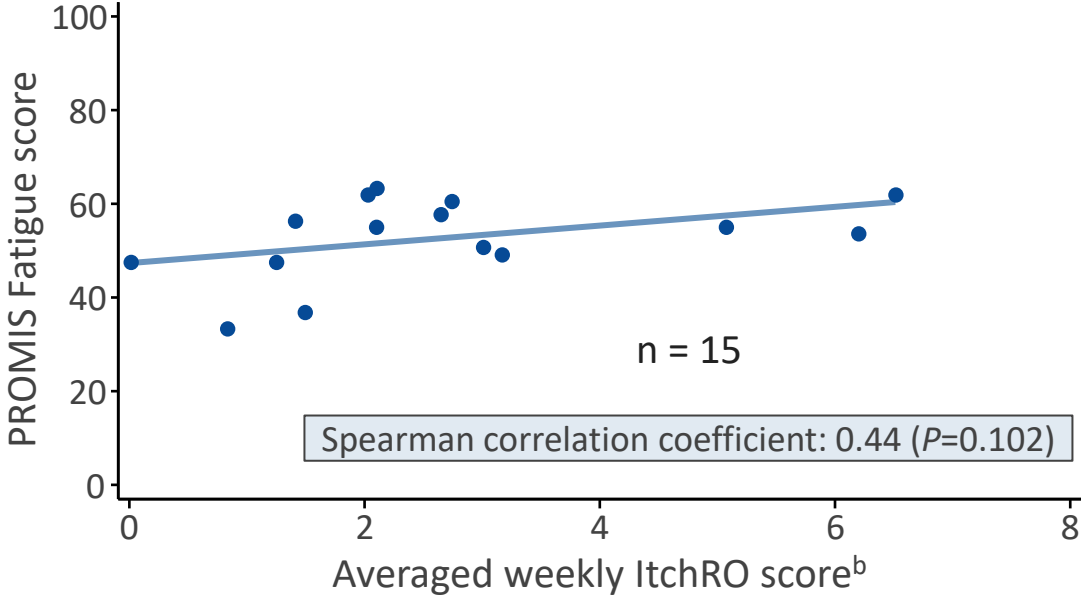
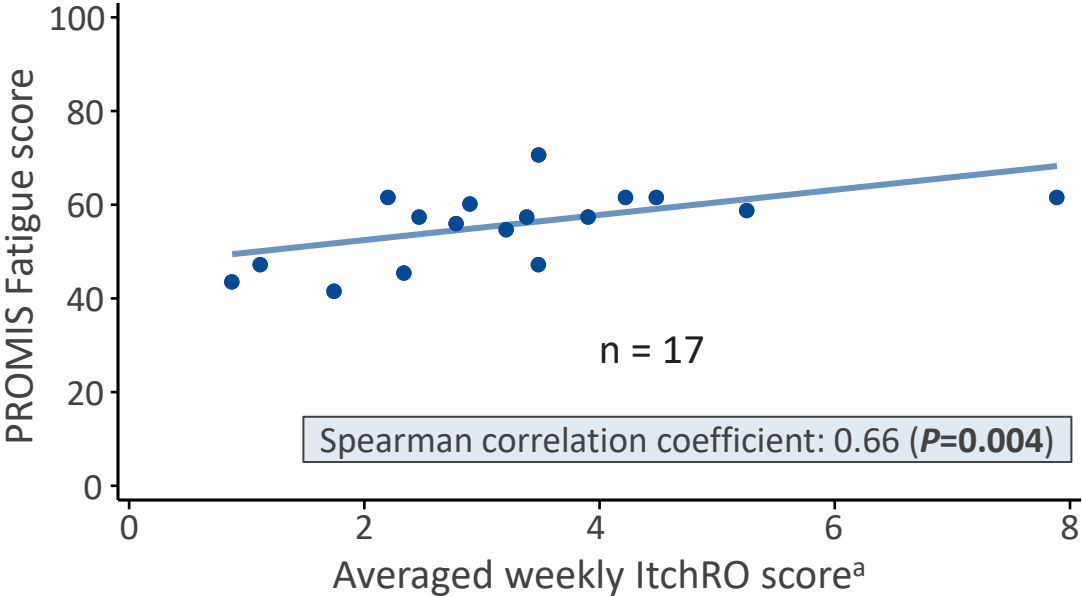
^aAnalysis included participants with nonmissing data at Baseline and Week 28 data.

Correlations Between PROMIS Fatigue Scores and Pruritus

PROMIS Fatigue and Average Weekly ItchRO Scores at Week 16

PROMIS Fatigue and Average Weekly ItchRO Scores at Week 28

● Combined VLX 20 mg and 80 mg groups — Line of regression



PROMIS Fatigue scores were correlated with pruritus, with statistical significance met at Week 16

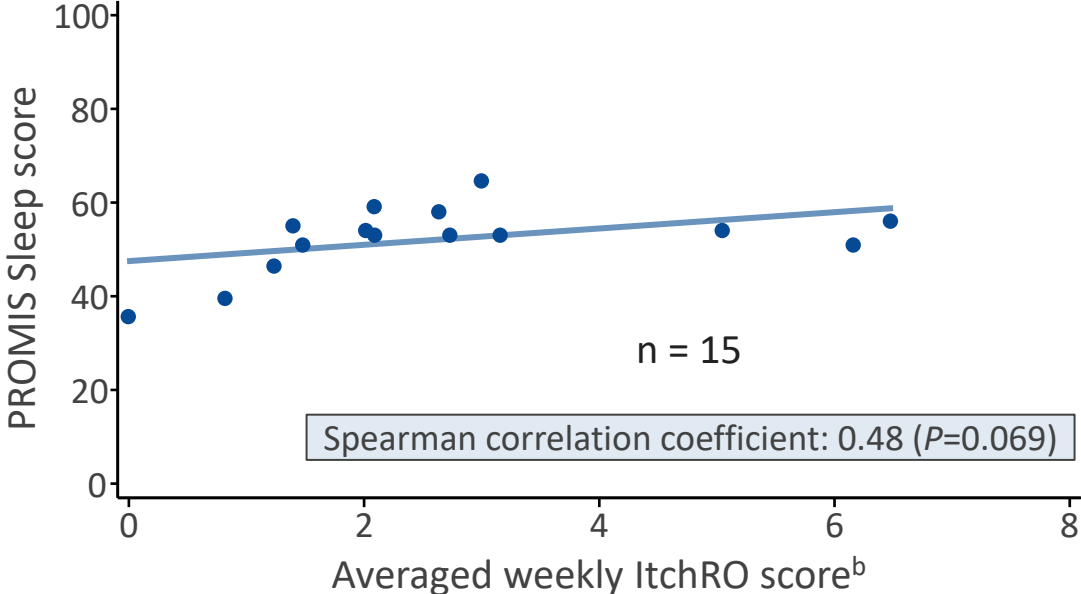
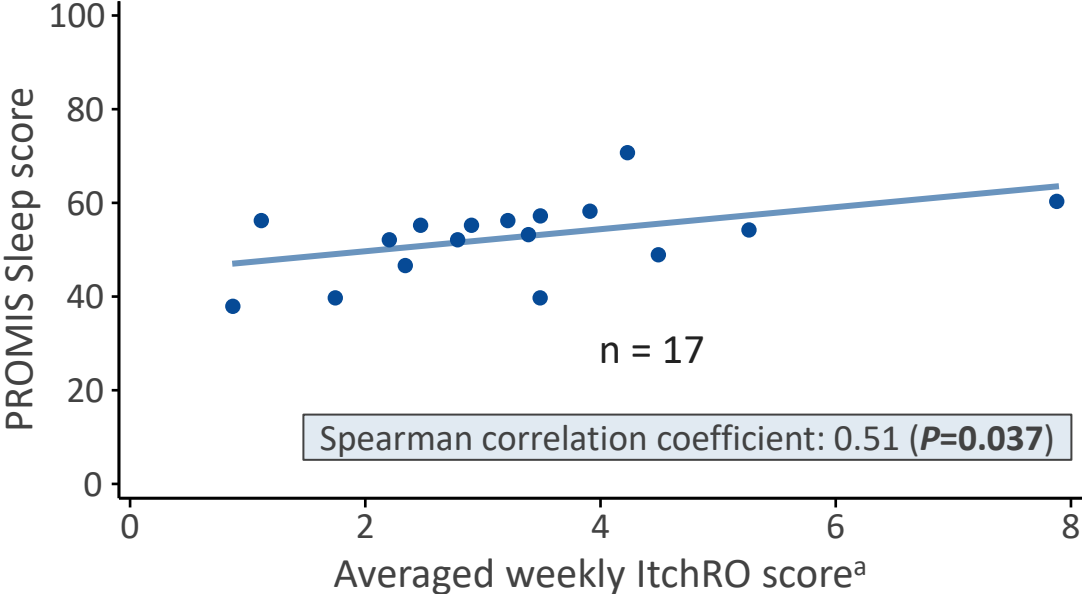
ItchRO, Itch-Reported Outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; VLX, volixibat.
^aAveraged weekly ItchRO score of Weeks 5 to 16. ^bAveraged weekly ItchRO score of Weeks 17 to 28.

Correlations Between PROMIS Sleep Scores and Pruritus

PROMIS Sleep and Average Weekly ItchRO Scores at Week 16

PROMIS Sleep and Average Weekly ItchRO Scores at Week 28

● Combined VLX 20 mg and 80 mg groups — Line of regression



PROMIS Sleep scores were correlated with pruritus, with statistical significance met at Week 16

ItchRO, Itch-Reported Outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; VLX, volixibat.
^aAveraged weekly ItchRO score of Weeks 5 to 16. ^bAveraged weekly ItchRO score of Weeks 17 to 28.

Conclusions

- In VANTAGE Part 1, improvements in fatigue and sleep, relevant measures of HRQoL in PBC, were observed in volixibat-treated participants
- Only the volixibat group had an increase in the proportion of participants reporting normal PROMIS Fatigue and Sleep scores by Week 28
- Moderate correlations between pruritus (Adult ItchRO) and PROMIS Fatigue and Sleep were observed in the volixibat group
- The results of this analysis suggest that improvements in pruritus with volixibat treatment may result in improvements in fatigue and sleep in patients with PBC



The impact of volixibat on fatigue and sleep will be further evaluated in the ongoing Part 2 period of the VANTAGE study

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