Pilot Study of Volixibat Co-Administered With OCA for Primary Biliary Cholangitis (PBC) Treatment: The VLX-602 Trial

Poster 4347

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Introduction

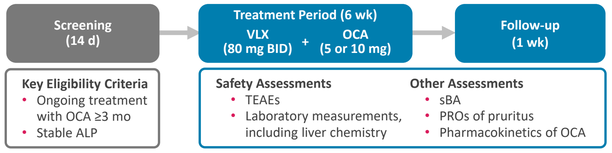
- Primary biliary cholangitis (PBC) is a progressive, autoimmune cholestatic liver disorder associated with dyslipidemia, osteodystrophy, and fat-soluble vitamin deficiency along with markedly reduced health-related quality of life.[1-3]
  - If left untreated, PBC can cause fibrosis, cirrhosis, and ultimately end-stage liver disease.[3]
- Pruritus affects up to 80% of individuals with PBC, can be debilitating and intractable, and is thought to result in part from accumulation of toxic bile acids (BAs).[1,2,4]
- The first-line treatment for PBC is ursodeoxycholic acid (UDCA); however, not all patients show sufficient biochemical response, and UDCA may not impact pruritus.[2-5]
- Obeticholic acid (OCA) is a second-line therapy for patients who have inadequate response to UDCA.[3]
  - Pruritus was the most common adverse event reported in clinical trials of OCA in participants with PBC.[5-8]
- Symptomatic treatments for pruritus in patients with PBC include cholestyramine, rifampin, naltrexone, antihistamines, or selective serotonin reuptake inhibitors.[1,3]
- Volixibat (VLX) is a minimally absorbed ileal BA transporter (IBAT) inhibitor that interrupts enterohepatic recirculation.[9]
  - By inhibiting BA uptake in the small intestine, volixibat leads to increased BA elimination in feces and reductions in the systemic BA pool.[10-12]
- IBAT inhibitors have proven efficacious for the treatment of pruritus in cholestatic diseases, including PBC; however, concurrent use of IBAT inhibitors and OCA is not well described.[4]

Objectives

- To report safety and efficacy of adding treatment with volixibat (80 mg twice daily [BID]) in 6 participants with PBC who were actively receiving OCA treatment (5 or 10 mg).

Methods

Figure 1. Study Design



- VLX-602 was a multicenter, open-label study.
- Itch was assessed using PROs (Worst Itch Numeric Rating Scale [WI-NRS], Patient Impression of Severity of Itch [PIS-Itch]).
  - WI-NRS is a 10-point scale, where 0 = no itch and 10 = worst possible itch.
  - PIS-Itch is a 4-point scale, where 1 = no itch and 4 = severe itch.

Results

Table 1. Key Baseline Demographics, Characteristics, Laboratory Parameters, and PROs

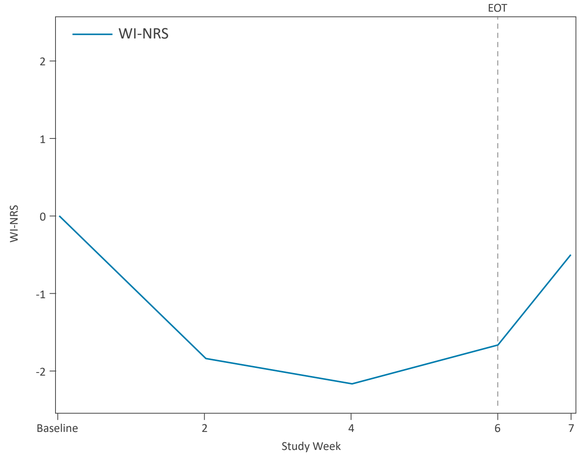
Parameter[a]	1	2	3	4	5	6
Age, y	58	51	62	46	59	63
OCA dose, mg QD	5	5	10	5	10	10
sBA, µmol/L	11	0	19	6	42	20
WI-NRS	4	3	0	5	7	0
PIS-Itch	3	2	1	3	3	1
ALT, U/L	75	14	25	15	8	22
ALP, U/L	279	85	132	232	205	230
AST, U/L	48	22	29	23	13	34
Total bilirubin, mg/dL	0.5	0.4	0.6	1.0	0.4	0.6
Direct bilirubin, mg/dL	0.2	0.1	0.2	0.3	0.2	0.2
GGT, U/L	238	13	138	97	9	29

[a]Baseline is Day 1 value prior to first dose of the study medication. If Day 1 values are not available, the last values obtained during screening are used as the Baseline value.

- Six participants were enrolled in the study, and all were female with a mean age of 56.5 years.

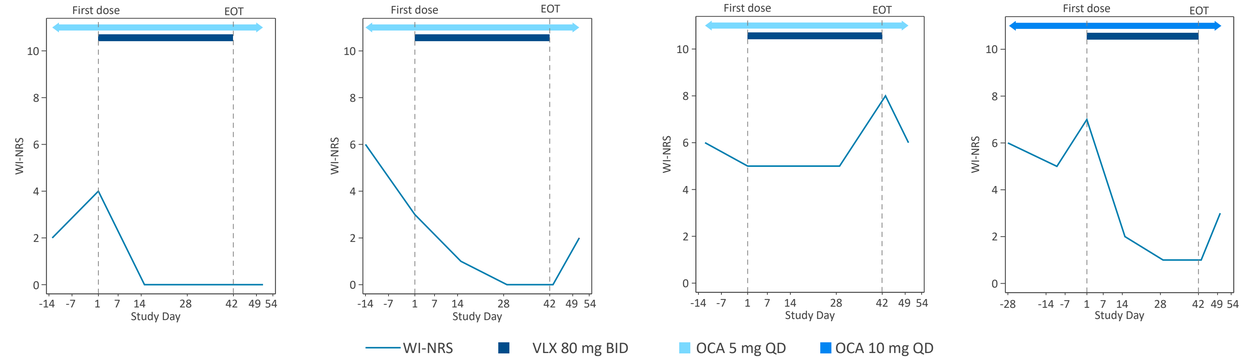
Improvements in Itch Scores Were Observed After Volixibat Treatment

Figure 2. Overall Mean Change From Baseline in WI-NRS Scores Over Time



Clinically Meaningful Improvements in Itch Scores Were Observed in 3 of 4 Participants With Pruritus at Baseline Following Volixibat Treatment Throughout the Trial

Figure 3. Changes in WI-NRS Scores in 4 Participants With Pruritus at Baseline (A-D)



- No clinically meaningful changes in ALT, AST, ALP, GGT, total bilirubin, and direct bilirubin from Baseline to the end of trial were observed.
- sBA levels remained stable throughout the trial.
- Effects of volixibat on the pharmacokinetics of OCA were difficult to determine in this small number of participants with only OCA trough levels recorded.
  - Five of the 6 participants showed a decrease in total OCA plasma drug constituents (OCA parent + the glyco- and tauro-conjugated forms) during volixibat treatment.

Safety Outcomes

Table 3. Summary of TEAEs

TEAE, n (%)	All Participants (N=6)
Any TEAE	5 (83.3)
TEAEs Grade ≥3	0
TEAEs related to study drug	5 (83.3)
TEAEs related to study drug Grade ≥3	0
Serious TEAEs	0
Serious TEAEs related to study drug	0
TEAEs that led to discontinuation of study drug	0
TEAEs that led to death	0

- The most common TEAE was diarrhea (83.3%), which was mild to moderate in severity.
- Other TEAEs were nausea, fatigue, and vomiting that affected 1 participant each (16.7% each).
- TEAEs considered not related to study drug were toothache, nasopharyngitis, and upper respiratory tract infection and affected 1 participant each (16.7% each).

Conclusions

- The results of this pilot safety study were consistent with the known safety profile of IBAT inhibitors.
- Improvements in pruritus were observed in some participants upon addition of volixibat treatment to ongoing OCA treatment, with return of pruritus observed after volixibat cessation.
- These results support further investigation into the safety and efficacy of volixibat for the treatment of PBC in patients with or without ongoing OCA treatment.

Abbreviations

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BA, bile acid; BID, twice daily; EOT, end of treatment; GGT, gamma-glutamyl transferase; IBAT, ileal bile acid transporter; OCA, obeticholic acid; PBC, primary biliary cholangitis; PIS-Itch, Patient Impression of Severity of Itch; PRO, patient-reported outcome; QD, once daily; sBA, serum bile acid; TEAE, treatment-emergent adverse event; UDCA, ursodeoxycholic acid; VLX, volixibat; WI-NRS; Worst Itch Numeric Rating Scale.

Disclosures

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References

1. Pandit S, et al. Primary Biliary Cholangitis. In: *StatPearls [Internet]*. **2.** Patel A, et al. *J Clin Exp Hepatol*. 2016;6:311-318. **3.** Trivella J, et al. *Hepatol Commun*. 2023;7:e0179. **4.** Düll MM, et al. *Clin Liver Dis*. 2022;26:727-745. **5.** Lindor KD, et al. *Hepatology*. 2019;69:394-419. **6.** Nevens F, et al. *N Engl J Med*. 2016;375:631-643. **7.** Kowdley KV, et al. *Hepatology*. 2018;67:1890-1902. **8.** Hirschfield GM, et al. *Gastroenterology*. 2015;148:751-761.e8. **9.** Siebers N, et al. *Eur J Drug Metab Pharmacokinet*. 2018;43:91-101. **10.** Newsome PN, et al. *J Hepatol*. 2020;73:231-240. **11.** Palmer M, et al. *BMC Pharmacol Toxicol*. 2018;19:10. **12.** Duan S, et al. *Biomed Pharmacother*. 2022;152:113154.

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