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

Poster 5038

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Introduction

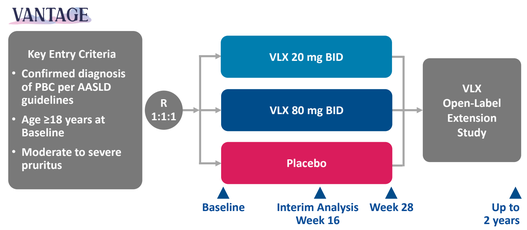
- Primary biliary cholangitis (PBC) is a chronic, progressive, immune-mediated condition leading to destruction of small intrahepatic bile ducts.[1,2]
- The estimated prevalence of PBC is 1.9 to 40.2 per 100,000 persons. Women are predominantly affected, with a sex ratio of 9:1.[1]
- Key clinical features and complications of PBC 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 of PBC and greatly impact overall quality of life (QoL).[2]
  - Cholestatic pruritus affects up to 80% of individuals with PBC and is thought to result in part from accumulation of toxic bile acids (BAs).[1,2]
- Newer therapies for PBC aim to prevent disease progression; however, they are not designed to address all symptoms, including pruritus.[3]
- Volixibat (VLX) is a minimally absorbed ileal BA transporter inhibitor that interrupts enterohepatic recirculation.[4]
  - By inhibiting BA uptake in the small intestine, volixibat leads to increased BA elimination in feces and reductions in the systemic BA pool.[5-7]

Objective

- To report the interim analysis, including dose selection, for the phase 2b, randomized, multicenter, double-blind, placebo-controlled study evaluating the efficacy and safety of volixibat in treating cholestatic pruritus in adults with PBC (VANTAGE; NCT05050136).[8]

Methods

Figure 1. Phase 2 Study Design[8]



Primary Endpoint
- Mean change in daily itch scores using the Adult Itch-Reported Outcome (ItchRO)[a] questionnaire from Baseline to Week 28

Select Secondary Endpoints[b]
- Incidence of AEs
- Change in key laboratory parameters: ALP, total bilirubin, and sBA
- Change in QoL using PBC-40

[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.

- Interim analysis was conducted when approximately 12 participants per treatment arm completed Week 16 or prematurely discontinued study drug.

Results

Baseline Characteristics Were Balanced Between Treatment Arms

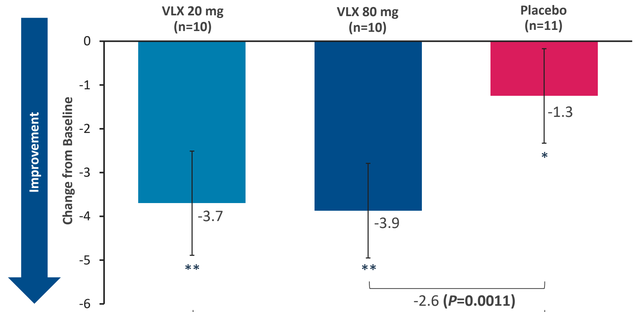
Table 1. Key Demographics and Baseline Characteristics

Parameter[a]	VLX 20 mg (n=10)	VLX 80 mg (n=10)	Placebo (n=11)	Total (N=31)
Age, y	53.9 (15.8)	52.3 (5.9)	62.1 (9.7)	56.3 (11.7)
Sex, female, n (%)	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)

[a]Continuous variables present mean (SD). Categorical variables present count (%). [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: symptoms (7-35), itch (3-15), fatigue (11-55), cognition (6-30), 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.[9]

Statistically Significant Reductions in Pruritus Were Observed With Both Doses of Volixibat Compared With Placebo

Figure 2. Pruritus Score (Adult ItchRO) MMRM Analysis[a]

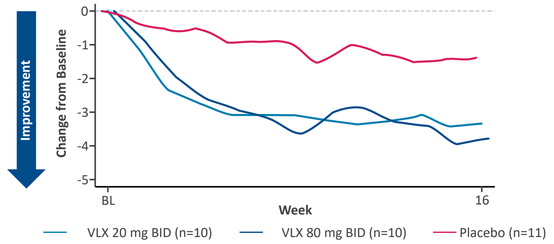


[a]LS mean (95% CI) change from Baseline to the average of the last 12 weeks of treatment. LS means and *P* values were calculated using an MMRM model. Within-group *P* values are depicted as * ≤0.05, ** ≤0.0001.

- Significant improvements in pruritus were observed for volixibat 20 mg and 80 mg groups compared with Baseline (*P*<0.0001 for both).

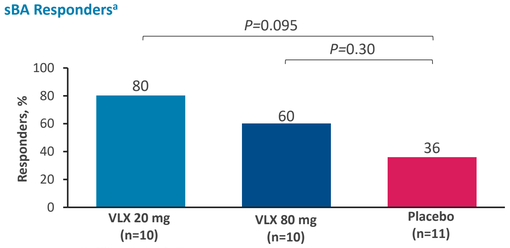
Rapid Reductions in Pruritus Were Observed After Treatment With Volixibat Starting at Week 1 and Were Maintained Over Time

Figure 3. Average Pruritus Score (Adult ItchRO) Over 16 Weeks



A Higher Proportion of Participants Who Received Volixibat Showed sBA Response Compared With Those Who Received Placebo

Figure 4. sBA Responders[a]



[a]sBA responders were defined as those with ≥50% reduction from Baseline.

Improvements in QoL Were Observed After Treatment With Volixibat

Table 2. PBC-40 Domain Scores

PBC-40 domains[a]	VLX 20 mg (n=8)	VLX 80 mg (n=9)	Placebo (n=7)
Symptoms	0.5 (-1.0, 3.0)	2.0 (-2.0, 3.0)	2.0 (-1.0, 2.0)
Itch	**-2.5*** (-6.5, -2.0)	**-3.0*** (-6.0, -1.0)	0.0 (0.0, 1.0)
Fatigue	**-5.0†** (-9.0, -3.0)	-4.0 (-7.0, 0.0)	1.0 (-3.0, 4.0)
Cognitive	-3.0 (-4.5, -0.5)	**0.0*** (-1.0, 0.0)	-3.0 (-4.0, -2.0)
Emotional	**-2.5*** (-4.5, -1.0)	0.0 (-2.0, 1.0)	1.0 (0.0, 2.0)
Social	-4.5 (-9.0, -1.0)	-1.0 (-4.0, 3.0)	-2.0 (-5.0, 1.0)

[a]Median (Q1, Q3) change from Baseline to Week 16. *P* values from 2-sample t-test comparing active versus placebo. *P<0.05. †P<0.01.

No New Safety Signals Were Observed, With a Similar Incidence of AEs Observed Between Volixibat Treatment Groups

Table 3. Summary of TEAEs[a]

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)	1 (2.6)
TEAEs leading to drug interruption[b]	4 (36.4)	1 (9.1)	1 (6.3)	6 (15.8)

[a]Safety analysis set included primary and secondary cohorts, double-blind period.

- Diarrhea was reported in up to 77% (17 of 22) of pooled participants receiving volixibat.
  - Diarrhea was mild in severity and led to 1 discontinuation.
- No clinically relevant changes were observed in total bilirubin, ALT, AST, or ALP with volixibat treatment compared with placebo.
- Serious TEAEs were suicide attempt and syncope (n=1) in the volixibat 20 mg group, drug-induced liver injury due to ibuprofen and alcohol (n=1) in the volixibat 80 mg group, and small intestine obstruction (n=1) in the placebo group.
- TEAEs Grade ≥3 included suicide attempt and syncope (n=1), and hyperbilirubinemia and liver function test increased (n=1) in the volixibat 20 mg group, drug-induced liver injury due to ibuprofen and alcohol (2 events; n=1) in the volixibat 80 mg group, and small intestine obstruction in the placebo group (n=1).
- TEAEs related to study drug Grade ≥3 were hyperbilirubinemia and liver function test increased (n=1) in the volixibat 20 mg group.
- TEAEs leading to premature discontinuation of study drug included diarrhea (n=1) in the volixibat 20 mg group and dermatomyositis (n=1) in the placebo group.

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 were observed with volixibat.
- Numerically greater reductions in sBA 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.

Abbreviations

AASLD, American Association for the Study of Liver Diseases; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BA, bile acid; BID, twice daily; ItchRO, Itch-Reported Outcome; LS, least squares; MMRM, mixed model repeated measures; PBC, primary biliary cholangitis; PBC-40, primary biliary cholangitis 40-item questionnaire; QoL, quality of life; R, randomized; sBA, serum bile acid; TEAE, treatment-emergent adverse event; VLX, volixibat.

Disclosures

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