A Phase 1 dose-ranging study assessing fecal bile acid excretion by volixibat, an apical sodium-dependent bile acid transporter inhibitor, and coadministration with loperamide (PBO)

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Background

- Cholestatic liver diseases result from a disruption to normal bile acid (BA) homeostasis, with systemic and intracellular retention of BAs eventually leading to liver injury.
- The apical sodium-dependent BA transporter (ASBT) plays a key role in the enterohepatic circulation of BAs, mediating their reabsorption in the intestines and helping to recycle them back to the liver.1,2
- ASBT inhibitors reduce BA reabsorption and increase fecal BA (fBA) excretion, thus moderating the toxic accumulation of BAs in the liver and offering a potential pharmacological therapy for the treatment of cholestatic liver diseases.2,3
- Volibegat (VLX) is a minimally absorbed ASBT inhibitor in clinical development for the treatment of primary sclerosing cholangitis and intracholestatic cholestasis of pregnancy.

Aim

- To assess the safety and tolerability of VLX, the pharmacodynamic (PD) impact of a range of VLX dose regimens, and the pharmacokinetics (PK) of VLX alone and in combination with loperamide (PBO).

Methods

Study design

- This was a single-center, placebo (PBO)-controlled, single-blind, multiple-dose, dose-ranging study in healthy adults.
- Participants were randomized to one of five cohort groups to receive either VLX 5 mg twice daily (BID), VLX 20 mg once daily (QD), VLX 20 mg BID, VLX 40 mg BID, or VLX 80 mg BID, and each cohort underwent four treatment periods (Figure 1).

Results

- A total of 60 participants were enrolled and included in the analyses (n = 12 per cohort).
- Baseline characteristics were similar across all cohorts: the mean age of participants was 37.2 (95% CI: 5.5) years; 58.3% were male; 50.0% were black/African American and 46.7% were white; the mean body mass index was 26.36 (3.38) mg/m².

Pharmacodynamic results

Changes in fecal bile acids

- Median fBA excretion at Baseline (defined as Day 5 PBO treatment) for BAs ranged from 127 pmol to 456 pmol.
- At Day 12, all doses of VLX were associated with increases in fBA excretion compared with Baseline (Figure 2).

- At Day 12, all doses of VLX were associated with increased fBA excretion versus QD dosing.
- All dosing regimens of VLX were associated with an increase in the frequency of bowel movements relative to PBO, which was mitigated with the addition of PLO to VLX dosing. Dose dependency was not observed.
- All dosing regimens of VLX were associated with an increase in the Bristol Stool Score for stool consistency relative to PBO, indicative of low levels of diarrhea. Dose dependency was not observed.
- Changes in f7C4 and lipids levels
- Mean Baseline (defined as study Day 5 [PBO treatment]) f7C4 ranged from 1.0 (0.3) pmol to 1.2 (0.3) pmol.

Vitamin D metabolites

- At Day 12, all doses of VLX were associated with increases in 25(OH)D in a dose-dependent manner (Figure 3).

Conclusions

- VLX was well tolerated at all doses and regimens studied.
- Although VLX BID versus QD dosing cannot be directly compared at each dose level given the chosen regimens, all BID doses increased fBA excretion versus QD, and higher doses increased BA synthesis as demonstrated by increased 7αC4.
- Standard LOP dosing, prophylactic and/or PRN, was well tolerated and addressed the expected, transient, low-grade gastrointestinal disturbance during initial VLX dosing, without a drug-drug interaction.
- As a minimally absorbed drug, VLX is unlikely to be subject to drug-drug interactions through other concomitant medications.
- Even after a relatively short dosing duration, the large increases in fBA excretion and their effects on BA trafficking and synthesis support the further study of a range of VLX doses in patients with cholestatic liver disease.

Pharmacokinetic interactions

- As VLX was minimally absorbed, PK parameters were difficult to assess due to very low plasma concentrations and a high degree of variation. This resulted in limited prediction of linear PK, making it difficult to draw definitive conclusions.
- LOP mean plasma Cmax and AUC were decreased by 11–21% and 8–35%, respectively, in some cohorts, after VLX + LOP administration versus PBO + LOP. However, there was no correlation between VLX dose and the magnitude of reductions in LOP exposure. The decrease in LOP exposure was the opposite of what might be expected for a drug-drug interaction via CYP3A4 and P-gp.

Safety and tolerability

- Safety outcomes were similar across all cohorts.
- All TEAEs in the World Health Organization Common Terminology Criteria for Adverse Events Grade 1 or 2; there were no Grade 3 or higher TEAEs, and no serious AEs were reported.

The most commonly reported TEAEs were gastrointestinal disorders, the majority of which were Grade 1, and no dose-dependent differences were noted.

- Diarrhea (Grade 1 or 2 in severity) occurred in most participants, the majority (> 80%) of which were Grade 1, and resolved prior to or with administration of LOP.
- Other commonly reported gastrointestinal TEAEs were constipation (Grade 1) and abdominal pain (14 participants [23.3%]).
- Transient, non-dose-dependent increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were noted, with the majority of ALT increases, and all AST increases, being Grade 1, all were asymptomatic, and most resolved while the participant remained on the study drug.
- Such changes could be a marker of PD effect in healthy subjects, similar to effects seen with cholestasis-lowering agents, such as statins and other drugs that increase BA excretion, either with bile acid sequestrants or bile salt sequestrants.

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Figure 1. Study design

Figure 2. Fold change from Baseline in fBA excretion by cohort at Day 12

Figure 3. Change from Baseline in 25(OH)D by cohort at Day 12

Table 1. Pharmacokinetic parameters by dose cohort

Table 2. Lipid and lipoprotein levels by treatment period