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

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Background

- Cholestatic liver diseases result from a disruption to normal bile acid (BA) homeostasis, with systemic and intrahepatic retention of BAs eventually leading to liver injury.[1,2]
- 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.[2,3]
- 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 cholestasis.[2,3]
- Volixibat (VLX) is a minimally absorbed ASBT inhibitor in clinical development for the treatment of primary sclerosing cholangitis and intrahepatic cholestasis of pregnancy.

Aim

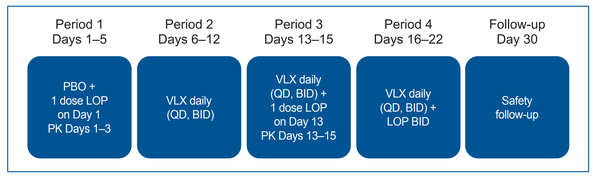
- To assess the safety and tolerability of VLX, the pharmacodynamic (PD) impact of a range of VLX dose regimens, and the pharmacokinetics (PK) of VLX alone and in combination with loperamide (LOP).

Methods

Study design

- This was a single-center, placebo (PBO)-controlled, single-blind, multiple-dose/regimen, parallel-group, dose-finding 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**).

Figure 1. Study design



BID, twice daily; LOP, loperamide; PBO, placebo; PK, pharmacokinetic; QD, once daily; VLX, volixibat

Study population

- Eligible participants were healthy male or non-pregnant, non-lactating female adults (18–55 years of age) with a body mass index ≥ 18 and ≤ 32 kg/m^2.

Data analyses

Pharmacodynamic assessments

- Primary objective: to evaluate the effects of a range of VLX QD or BID dose regimens on fBA excretion *versus* PBO.
- Secondary objective: to determine the effects of VLX with and without concomitant LOP on bowel movement frequency and stool consistency (Bristol Stool Score Chart) *versus* PBO.
- Exploratory objective: to evaluate the effects of VLX with and without concomitant LOP on 7 α-hydroxy-4-cholesten-3-one (7αC4) synthesis (a biomarker of BA synthesis[3]) *versus* PBO.
- Exploratory objective: to assess the effects of VLX with and without concomitant LOP on a full lipid panel *versus* PBO.

Pharmacokinetic assessments

- Primary objective: to evaluate the effects of VLX on the PK of a single 4 mg dose of LOP.
- Secondary objective: to assess the plasma concentrations and, if feasible, the PK of VLX.

Safety assessments

- Secondary objective: to assess the safety and tolerability of VLX with and without concomitant LOP *versus* PBO, including treatment-emergent adverse events (TEAEs) and clinical laboratory tests.

Statistical methods

Pharmacodynamic assessments

- fBA data were collected on Days 5, 9, and 12, and mean daily fBA excretion on Day 5 (PBO treatment) was compared with Days 9 and 12 (VLX monotherapy) across cohorts using a mixed-model analysis of variance (ANOVA); 95% confidence interval (CI) of the least squares (LS) mean difference was calculated.
- Additionally, the fold change from Day 5, defined as the ratio of the two values, was assessed and is presented here at Days 9 and 12.
- Change from Baseline (defined as Day 5, PBO treatment) at Day 12 for pre-dose 7αC4 values were examined.

Pharmacokinetic assessments

- Geometric LS mean ratios and 90% CIs were calculated for the maximum serum concentration (C_{max}), area under the curve (AUC) up to the last measurable concentration (AUC_{last}), and AUC from time zero to infinity (AUC_{inf}) of LOP with VLX *versus* without VLX, and a mixed-model ANOVA was used to assess cohorts.
- PK parameters were calculated for VLX, if feasible.

Safety and tolerability

- All analyses were performed using the safety analysis set (all participants assigned to the study drug who took at least one dose).
- Participants were analyzed according to the study drug actually received.
  - A TEAE was defined as an adverse event (AE) that was not present prior to treatment with the study drug but appeared following treatment or was present at treatment initiation but worsened during treatment; overall TEAEs were summarized.

Results

Enrolment and participant demographics

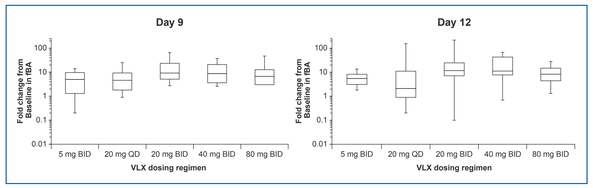
- A total of 60 participants were enrolled and included in the analyses (n = 12 per cohort).
- Baseline characteristics were similar across all cohorts: the mean age of participants was 37.2 (9.65) years of age; 58.3% were male; 50.0% were black/African American and 46.7% were white; the mean body mass index was 26.36 (3.38) mg/m^2.

Pharmacodynamic results

Changes in fecal bile acid

- Median fBA excretion at Baseline (defined as study Day 5 [PBO treatment] for fBA) ranged from 127 µmol to 456 µmol.
- At Days 9 and 12, all doses were associated with an increase in fBA excretion compared with Baseline (**Figure 2**).

Figure 2. Fold change from Baseline in fBA excretion by cohort at a) Day 9 and b) Day 12[a]



[a]Baseline for fBA was defined as Day 5. Thus, the summaries above present the data at 4 and 7 days after Baseline
BID, twice daily; fBA, fecal bile acid; QD, once daily; VLX, volixibat

- After 1 week, BID dosing of VLX was associated with greater increases in fBA excretion *versus* QD dosing.

Bowel movement frequency and stool consistency

- 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 LOP 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 7αC4 and lipid levels

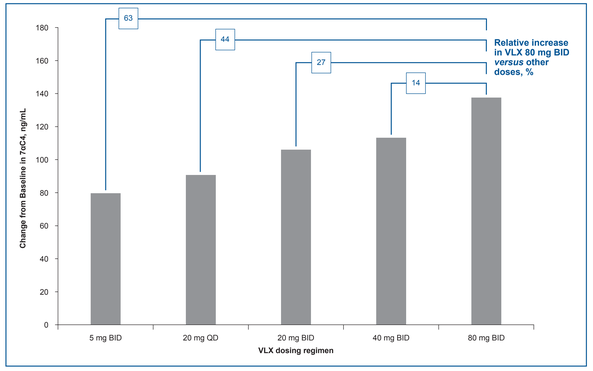
- Mean Baseline (defined as study Day 5 [PBO treatment]) 7αC4 ranged from 9.4 ng/mL to 15.2 ng/mL (**Table 1**).
- At Day 12, all doses of VLX were associated with increases in 7αC4 in a dose-dependent manner (**Table 1 and Figure 3**).

Table 1. 7αC4 and low-density lipoprotein by cohort[a]

Parameters	VLX dosing regimen				
	5 mg BID (n = 12)	20 mg QD (n = 12)	20 mg BID (n = 12)	40 mg BID (n = 12)	80 mg BID (n = 12)
7αC4, mean (ng/mL)					
Baseline	10.4	10.7	9.4	15.2	8.8
Day 12	90.0	101.4	115.5	128.4	146.5
Change from Baseline to Day 12	79.6	90.7	106.0	113.2	137.6
Low-density lipoprotein, mean (mmol/L)					
Baseline	3.2	3.1	3.1	2.8	2.5
Change from Baseline to Day 12	–1.2	–1.1	–1.0	–1.2	–1.0

[a]High-density lipoprotein levels were relatively unchanged
7αC4, 7 alpha-hydroxy-4-cholesten-3-one; BID, twice daily; QD, once daily; VLX, volixibat

Figure 3. Change from Baseline in 7αC4 by cohort at Day 12[a]



[a]Baseline for fBA was defined as Day 5. Thus, the summary represents the data at 7 days after Baseline
7αC4, 7 alpha-hydroxy-4-cholesten-3-one; BID, twice daily; fBA, fecal bile acid; QD, once daily; VLX, volixibat

- Mean Baseline (defined as study Day 1 [PBO treatment]) low-density lipoprotein values were similar across groups (**Table 1**).
  - At Day 12, mean decreases were observed for low-density lipoprotein compared with Baseline. Dose dependency was not observed.

Pharmacokinetic results

Volixibat pharmacokinetic results

- VLX was minimally absorbed with low to undetectable plasma concentrations.
  - VLX geometric mean plasma C_{max} increased in a dose-dependent manner and was 0.10 ng/mL (standard error [SE] 0.11) and 0.14 ng/mL (SE 0.22) for VLX 40 mg BID and 80 mg BID, respectively, consistent with previous VLX PK results.

Loperamide pharmacokinetic results

- LOP PK parameters half-life ($t_{½}$), AUC_{inf}, oral clearance (CL/F), and apparent volume of distribution (V_z/F) were consistent with expectations, with AUC extrapolated from time to infinity ($AUC_{\%extrap}$) < 20% for most participants.

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 large CIs for geometric LS mean ratios, thus precluding any definitive conclusions.
- LOP mean plasma C_{max} 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 apparent decrease in LOP exposure. The decrease in LOP exposure was the opposite of what might be expected for a drug–drug interaction via Cytochrome P450.

Safety and tolerability

- Safety outcomes were similar across all cohorts.
- All TEAEs in the study were 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 (16 participants [26.7%]) 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 cholesterol-lowering agents, such as statins and other treatments, that increase BA excretion, including other ASBT inhibitors and BA sequestrants like cholestyramine.
- One TEAE led to discontinuation from the study due to Grade 2 hematochezia that was considered possibly related to the study drug; however, the participant had a history of hematochezia prior to study participation. In addition, another participant elected to discontinue the study drug due to an asymptomatic Grade 2 ALT increase (stopping criteria not met) but completed all study visits.

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 clear effects on BA trafficking and synthesis support the further study of a range of VLX doses in patients with cholestatic liver disease.**

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