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Safety, tolerability and efficacy of volixibat, an apical sodium-dependent bile acid transporter inhibitor, in adults with non-alcoholic steatohepatitis: 24-week interim analysis results from a phase 2 study

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INTRODUCTION

- Non-alcoholic steatohepatitis (NASH) is a potentially severe form of non-alcoholic fatty liver disease[1] that may progress to cirrhosis, liver failure or liver cancer.[2]
- NASH has an estimated prevalence of 1.5–6.5% in the general population, with a higher prevalence in individuals with diabetes and those with obesity.[3]
- Abnormal cholesterol metabolism and accumulation of free cholesterol in the liver contribute to the pathogenesis of NASH.[4]
- Volixibat (SHP626; formerly LUM002), a highly selective inhibitor of the apical sodium-dependent bile acid transporter, is hypothesized to indirectly stimulate the hepatic production of bile acid from free cholesterol by the inhibition of bile acid reuptake.[5] This may have beneficial metabolic, anti-inflammatory, anti-steatotic and anti-fibrotic effects.[5,6]
- Consistent with this hypothesis, volixibat reduced serum cholesterol levels in overweight or obese adults in a phase 1 study.[5]
- Here we report the 24-week interim results of a 48-week phase 2 study investigating the safety, tolerability and efficacy of volixibat in adults with NASH.

OBJECTIVES

- To examine the effect of volixibat on liver histology compared with that of placebo (primary objective) and to assess the effect of volixibat on hepatic steatosis and serum alanine aminotransferase (ALT) concentration (secondary objectives).

METHODS

Study design and participants

- This was a multicentre, phase 2, double-blind, randomized, placebo-controlled, parallel-group, proof-of-concept, dose-finding study (ClinicalTrials.gov identifier: NCT02787304).
- Participants were aged 18–80 years, had at least 5% steatosis (determined by magnetic resonance imaging-derived proton density fat fraction [MRI-PDFF]) and histological confirmation of NASH without cirrhosis (fibrosis [F] stage 0–3) with a NASH activity score (NAS) of at least 4 and at least 1 point in each component, assessed by a central NASH Clinical Research Network pathologist.
- Participants were randomized in a 1:1:1:1 ratio to receive oral placebo or volixibat 5 mg, 10 mg or 20 mg once daily for 48 weeks, stratified by baseline NAS and the presence of type 2 diabetes (T2DM).

Outcomes and analyses

- A prespecified interim analysis (IA) was conducted when 80 participants had received 24 weeks of treatment.
- For the IA, a clinically important effect was defined as an absolute reduction from baseline to week 24 in steatosis of at least 5% (assessed by MRI-PDFF) or a reduction of at least 20% from baseline in serum ALT concentration.
- The probability of a clinically important effect on MRI-PDFF or ALT concentration was also calculated from the posterior distribution of Bayesian hierarchical models, with a probability of 0.1 or less considered to be low.
- Bile acid synthesis was assessed via serum 7-alpha-hydroxy-4-cholesten-3-one (C4) concentration, as an exploratory pharmacodynamic outcome.
- Lipid panels included fasting total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride levels.
- Liver biopsies were conducted during the screening period, or within 6 months before the first visit, and after 48 weeks of treatment to determine NAS and stage of fibrosis.
- The primary efficacy endpoint of the study was a binary response indicating whether a participant responded at week 48 with a reduction of at least 2 points, without worsening fibrosis, from baseline NAS.
- Safety and tolerability assessments were conducted in the safety analysis set (SAS), which included all randomized participants who received at least one dose of volixibat or placebo and had at least one post-baseline safety assessment.

RESULTS

Demographics and baseline characteristics

- The SAS included 196 participants with a mean (standard deviation [SD]) age of 53.1 (12.8) years. Most participants were female (60.2%), white (89.3%) and had a body mass index (BMI) in the obese range (73.5%). Mean (SD) BMI was 34.5 (6.3) kg/m^2.
- At baseline, 43.4% of participants had T2DM, mean (SD) NAS was 5.2 (1.1) and mean (SD) MRI-PDFF was 18.5 (8.2).
- Demographics and baseline characteristics, including serum cholesterol and LDL-C levels, were generally well balanced between the treatment groups (Table 1).

Interim analysis of efficacy at week 24

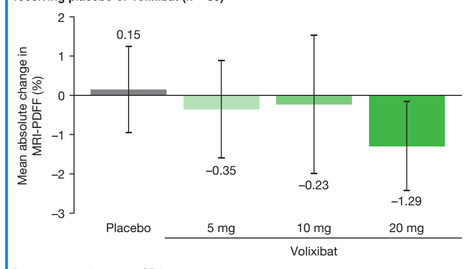
- In the 80 participants treated up to week 24, the probability of a clinically important effect on MRI-PDFF and ALT concentration was 0.1 or less for all volixibat doses, resulting in early termination of the study due to lack of efficacy.
- Absolute change in MRI-PDFF from baseline to week 24 was similar for all doses of volixibat and placebo; none of the volixibat doses achieved the prespecified 5% or more decrease in MRI-PDFF (Figure 1).
- None of the volixibat groups achieved the prespecified 20% or more reduction in ALT concentration from baseline to week 24 (Figure 2).
- Subgroup analysis by sex, presence of T2DM, NAS and stage of fibrosis did not reveal a significant improvement for MRI-PDFF or ALT concentration with any volixibat dose.

Table 1. Demographics and baseline characteristics of the safety analysis set

	Placebo (n = 49)	Volixibat 5 mg (n = 49)	Volixibat 10 mg (n = 49)	Volixibat 20 mg (n = 49)
Age [years], mean (SD)	53.4 (11.75)	52.8 (14.13)	53.0 (11.84)	53.2 (13.61)
Sex, n (%)				
Female	32 (65.3)	27 (55.1)	34 (69.4)	25 (51.0)
Race, n (%)				
White	41 (83.7)	46 (93.9)	47 (95.9)	41 (83.7)
Stage of fibrosis, n (%)				
0	11 (22.4)	7 (14.3)	7 (14.3)	8 (16.3)
1a	12 (24.5)	13 (26.5)	8 (16.3)	9 (18.4)
1b	7 (14.3)	7 (14.3)	7 (14.3)	6 (12.2)
1c	0 (0.0)	3 (6.1)	2 (4.1)	1 (2.0)
2	7 (14.3)	6 (12.2)	6 (12.2)	7 (14.3)
3	12 (24.5)	13 (26.5)	18 (36.7)	18 (36.7)
T2DM, n (%)				
Yes	21 (42.9)	22 (44.9)	21 (42.9)	21 (42.9)
NAS, mean (SD)	5.2 (0.96)	5.2 (1.01)	5.2 (1.26)	5.1 (1.11)
MRI-PDFF [%], mean (SD)	18.829 (8.7765)	20.360 (7.5965)	17.832 (8.7204)	17.013 (7.6557)
Serum ALT concentration [U/L], mean (SD)[a]	59.48 (60.277)	68.14 (37.173)	70.80 (45.153)	62.72 (37.823)
Serum cholesterol [mg/dL], mean (SD)	183.0 (45.09)	179.1 (37.01)	187.2 (35.99)	188.8 (45.14)
Serum LDL-C [mg/dL], mean (SD)	104.3 (39.37)	100.8 (32.91)	108.9 (31.31)	115.0 (37.08)
Serum C4 concentration [ng/mL], mean (SD)[b]	42.85 (33.192)	39.92 (29.733)	39.20 (36.362)	37.00 (42.856)

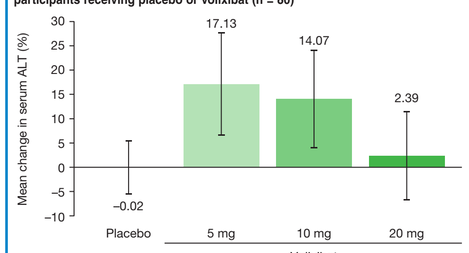
[a]Interim analysis set (n = 80).
[b]Pharmacodynamic analysis set (n = 182).
ALT, alanine aminotransferase; C4, 7-alpha-hydroxy-4-cholesten-3-one; LDL-C, low-density lipoprotein cholesterol; MRI-PDFF, magnetic resonance imaging-derived proton density fat fraction; NAS, non-alcoholic fatty liver disease activity score; SD, standard deviation; T2DM, type 2 diabetes.

Figure 1. Absolute change in MRI-PDFF from baseline to week 24 in participants receiving placebo or volixibat (n = 80)



Data are presented as mean ± SEM.
MRI-PDFF, magnetic resonance imaging-derived proton density fat fraction; SEM, standard error of the mean.

Figure 2. Change in serum ALT concentration from baseline to week 24 in participants receiving placebo or volixibat (n = 80)

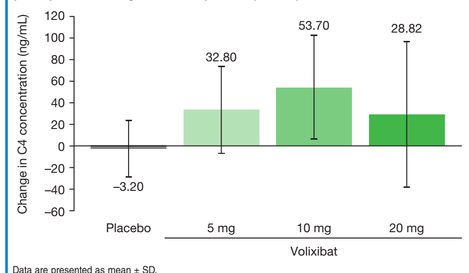


Data are presented as mean ± SEM.
ALT, alanine aminotransferase; SEM, standard error of the mean.

Exploratory pharmacodynamic analysis at week 24

- Mean serum C4 concentrations increased from baseline to week 24 in all volixibat groups, with no meaningful change in the placebo group (Figure 3).

Figure 3. Change in serum C4 concentration from baseline to week 24 in participants receiving volixibat or placebo (n = 128)



Data are presented as mean ± SD.
C4, 7-alpha-hydroxy-4-cholesten-3-one; SD, standard deviation.

Lipid panel results at week 24 and week 48

- In the SAS, mean cholesterol and LDL-C levels decreased from baseline to week 24 and 48 in all volixibat groups, with no meaningful changes in the placebo group (Table 2).
- The greatest reduction in cholesterol and LDL-C levels from baseline was observed in participants who received volixibat 20 mg.

Liver histology at week 48

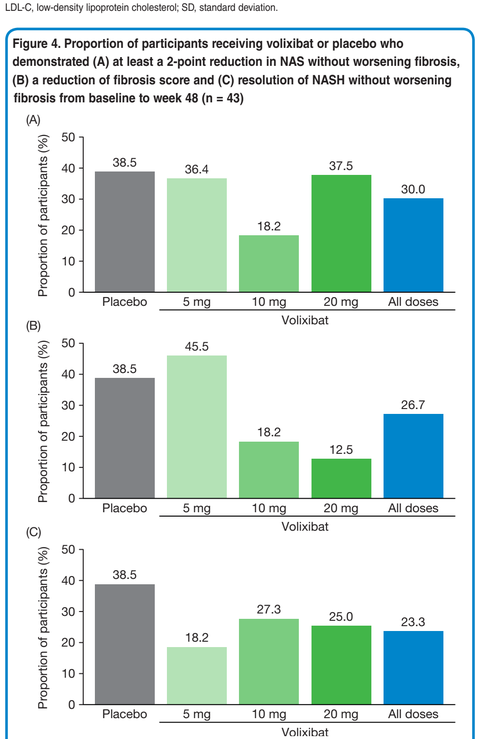
- Owing to early termination of the study, the primary efficacy endpoint could not be statistically evaluated.

Table 2. Change in serum cholesterol and LDL-C levels from baseline to week 24 and week 48 in participants receiving volixibat or placebo

	Placebo	Volixibat 5 mg	Volixibat 10 mg	Volixibat 20 mg
Change in cholesterol levels [mg/dL], mean (SD)				
Baseline to week 24 (n = 140)	1.0 (24.64)	−9.0 (20.17)	−12.7 (30.85)	−22.5 (32.29)
Baseline to week 48 (n = 69)	4.7 (30.38)	−13.4 (32.06)	−19.1 (38.26)	−7.6 (26.94)
Change in LDL-C levels [mg/dL], mean (SD)				
Baseline to week 24 (n = 140)	−1.4 (18.97)	−11.4 (21.09)	−15.0 (26.90)	−22.5 (27.36)
Baseline to week 48 (n = 69)	−0.8 (26.12)	−13.4 (27.38)	−19.5 (31.78)	−9.0 (22.37)

LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

Figure 4. Proportion of participants receiving volixibat or placebo who demonstrated (A) at least a 2-point reduction in NAS without worsening fibrosis, (B) a reduction of fibrosis score and (C) resolution of NASH without worsening fibrosis from baseline to week 48 (n = 43)



NAS, non-alcoholic steatohepatitis activity score; NASH, non-alcoholic steatohepatitis

- At study termination, paired liver biopsies (baseline and 48 weeks) were available for 43 participants.
- A reduction of at least 2 points in NAS without worsening fibrosis was observed in a lower proportion of the pooled volixibat group (30.0%) than of the placebo group (38.5%; Figure 4A).
- A decrease in fibrosis score was observed in a lower proportion of the pooled volixibat group (26.7%) than of the placebo group (38.5%; Figure 4B).
- A lower proportion of the pooled volixibat group (23.3%) than of the placebo group (38.5%) experienced resolution of NASH (defined as absence of ballooning and absent or mild inflammation, with or without steatosis) without worsening fibrosis (Figure 4C).
  - In the subgroup of participants at fibrosis stage F0/1 at baseline, a greater proportion of the volixibat 10 mg group (50.0%) experienced resolution of NASH than of the placebo group (37.5%) or the volixibat 5 mg (20.0%) and 20 mg (20.0%) groups.
  - In the subgroup of participants at fibrosis stage F2/3 at baseline, a greater proportion of the placebo group (40.0%) experienced resolution of NASH than any of the volixibat groups (5 mg, 16.7%; 10 mg, 14.3%; 20 mg, 33.3%).
- There was no apparent dose–response relationship between volixibat and any liver histological parameters (Figure 4).

Safety and tolerability

- Treatment-emergent adverse events (TEAEs) occurred in 88.4% of participants receiving volixibat and 75.5% of participants receiving placebo; most were mild or moderate in severity.
- TEAEs in the pooled volixibat group were predominantly gastrointestinal disorders (82.3%) and included diarrhoea (73.5%), abdominal pain (17.0%), nausea (10.9%) and vomiting (5.4%).
- TEAEs leading to discontinuation of treatment occurred in 13.6% of the pooled volixibat group and 2.0% of the placebo group. Diarrhoea was the most commonly reported TEAE leading to discontinuation in the pooled volixibat group, with most events occurring within the first 2 weeks of dosing.
- There were no deaths or serious TEAEs related to volixibat.

CONCLUSIONS

- As none of the volixibat doses met the prespecified efficacy endpoints relating to a reduction of steatosis on MRI-PDFF or a reduction of ALT concentration at the 24 week IA, the study was terminated.
- Volixibat treatment decreased cholesterol and LDL-C levels from baseline at week 24 and week 48.
- There was no histological benefit after 48 weeks of volixibat treatment, although the number of participants assessed was small.
- Increased C4 levels indicate that inhibition of bile acid reuptake results in a compensatory increase in bile acid synthesis from cholesterol in the liver; however, this was not associated with an improvement in liver health in patients with NASH, as measured by a reduction in steatosis or ALT concentration after 24 weeks of treatment.

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