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

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INTRODUCTION

• Non-alcoholic steatohepatitis (NASH) is a potentially severe form of non-alcoholic liver disease that may progress to cirrhosis, liver failure or liver cancer.
• NASH has an estimated prevalence of 5-10% in the general population, with a higher prevalence in individuals with diabetes and those with obesity.
• Abnormal cholesterol metabolism and accumulation of free fatty acids in the hepatocytes contribute to NASH.
• Volixibat (SHP626; formerly LUM002), a highly selective inhibitor of the apical sodium-dependent bile acid transporter (ASBT), reduces hepatic bile acid concentrations.
• This is associated with decreased hepatic production of bile acid from free cholesterol by the inhibition of ASBT.
• This may have beneficial metabolic, anti-inflammatory, anti-atherogenic and anti-fibrotic effects.
• Consistent with this hypothesis, volixibat reduced serum cholesterol levels in patients 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, parallel-group, proof-of-concept, double-dummy, placebo-controlled, 24-week trial (ClinicalTrials.gov identifier: NCT02787394).
• Participants aged 18–65 years, had at least 5% steatosis (determined by magnetic resonance imaging-derived proton density fat fraction [MRI-PDFF]) and a liver histology consistent with NASH without cirrhosis (F0–4 stage) 0–3, with a NAS score (NASH) of at least 4 at least 1 point in each component.
• Participants were randomized in 1:1:1:1 ratio to receive volixibat 5 mg, 10 mg, 20 mg or placebo once daily for 24 weeks (Table 1).

Outcomes and analyses

• A prespecified interim analysis (IA) was conducted when 69 participants had received 24 weeks of treatment.
• For the IA, a clinically important effect on MRI-PDFF and ALT concentration was defined, or for all volixibat doses, resulting in early termination of the study due to lack of efficacy.
• A decrease in MRI-PDFF and ALT concentration at week 24 was compared with the placebo group (Figure 1).

RESULTS

Demographics and baseline characteristics

• The SAS included 160 participants with a median (interquartile range) age of 54 (43–63) years, most participants were female (69.3%), and had a body mass index (BMI) in the obese range (35.3%).
• At baseline, 43.4% of participants had TIDM, mean (SD) NAS was 5.2 (1.1) and mean (SD) MRI-PDFF was 18.5 (3.7).
• 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 IA participants treated up to week 24, a probability of a clinically important effect on MRI-PDFF and ALT concentration was defined, or for all volixibat doses, resulting in early termination of the study due to lack of efficacy.
• A decrease in MRI-PDFF and ALT concentration at week 24 was compared with the placebo group (Figure 2).

Subgroup analysis by sex, presence of T2DM, NAS and stage of fibrosis did not

• None of the volixibat groups achieved the prespecified 20% or more reduction in MRI-PDFF (Figure 1).
• A decrease in fibrosis score was observed in a lower proportion of the pooled volixibat group (38.5%) than of the placebo group (56.7%; Figure 3).

Liver histology at week 48

• On the basis of the interim analysis of the study, the primary efficacy endpoint could not be evaluated.

CONCLUSIONS

• 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 postbaseline safety assessment.

DISCLOSURES

• All authors have contributed to writing as authors, editors or reviewers. They have voluntarily provided information on relationships with companies or organizations indicated in the acknowledgments section.

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REFERENCES


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