Author’s response to reviews

Title: Safety, tolerability and pharmacodynamics of apical sodium-dependent bile acid transporter inhibition with volixibat in healthy adults and patients with type 2 diabetes mellitus: a randomised placebo-controlled trial

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Comment 1: Was fatty liver excluded for study participants? Were ultrasound, transient elastography or any other type of liver imaging part of the study?

Response: No liver imaging or histology was performed during screening of patients. Therefore, it is possible that participants had hepatic steatosis.

Details of all exclusion criteria are provided in the supplementary material (Additional file 1), which was submitted along with the manuscript. At screening, all values for haematology and for clinical chemistry tests of blood and urine had to be within the normal range or showing no clinically relevant deviations. Also, participants were excluded if there was evidence of an uncontrolled, clinically significant hepatic abnormality (including cholestasis) in the judgement of the PI.
To address this comment, we have updated the methods (lines 1–5, page 8) as follows to make it clear that the possibility of fatty liver could not be excluded:

‘The screening visit did not involve a liver biopsy or imaging of the liver. Therefore, the presence of hepatic steatosis or NASH cannot be ruled out among participants in this study. However, individuals with abnormal haematology or clinical chemistry test results were excluded, as were individuals who had evidence of any clinically significant hepatic abnormality (including cholestasis) in judgement of the principal investigator. Complete inclusion and exclusion criteria are provided in Additional file 1.’

Comment 2: To which extent did antidiabetic medication impact PK/PD of the drug?

Response: This question cannot be answered by this study. Subjects with diabetes were discontinued from anti-diabetic medications for 14 days before dosing (this is stated on lines 1–2 of page 6). Metformin is eliminated from the body by the kidneys and has a half-life of 6 hours, meaning that roughly 94% of the drug is removed from the body in 24 hours. The duration of action of the sulfonylureas (18–72 hours) is generally of greater importance than the individual half-lives of these drugs. Thus, the washout of 14 days for the anti-diabetic medication before starting volixibat means that the impact of anti-diabetic medication on the PK/PD of volixibat cannot be directly addressed by this study.

However, in this study and two further phase 1 studies, including a recently published ADME study (https://link.springer.com/article/10.1007/s13318-017-0429-7), PK parameters could not be calculated because serum concentrations of volixibat were below the lower limit of quantification (this is stated on lines 11–13 on Page 11), indicating that the drug is minimally absorbed. The ADME study also showed that volixibat is not metabolized. These findings indicate the absorption of volixibat is unlikely to be affected by other drugs. A minimally absorbed drug is a desirable choice for patients with liver disease.

To address this comment as far as possible with the available data, we have updated the methods (lines 15–23, page 18; reference 55, lines 3–6, page 28) to include the following paragraph:

‘In this study and two further phase 1 studies, PK parameters could not be calculated because serum concentrations of volixibat were below the lower limit of quantitation, indicating that the drug is minimally absorbed. One of these studies, a disposition study of radiolabelled volixibat, also demonstrated that volixibat is not metabolized; it is eliminated unchanged from the body almost exclusively via faecal excretion. These findings suggest that other medications (e.g. anti-diabetic drugs) are unlikely to affect the absorption of volixibat. In patients with NASH, who often need to receive several pharmacotherapies for associated comorbidities, a low potential for
drug–drug interactions would be beneficial. Further preclinical and clinical studies are needed to explore the potential for drug–drug interactions in the gut or those arising from inhibition of ASBT.’

Comment 3: You state that the participants were not allowed to take any other medication. This is hard to believe given the study population. What about ACE inhibitors, statins, beta blockers? - If this was unallowed, please comment on potential drug-drug interactions.

Response: During the study, patients with T2DM were allowed to take all medications other than anti-diabetic medications or medications that significantly alter blood glucose. T2DM patients were given dietary advice and provided with a blood glucose monitor. Blood glucose was measured daily, and HBa1c and lipid levels were monitored throughout the study. Healthy individuals had to discontinue all medications during the study, but the PI could permit a limited amount of acetaminophen for the treatment of headache/pain.

Based on this comment, we realize that this information should be included in the manuscript for clarity and have updated the methods (lines 17–23, page 7) to include the following description:

‘With the exception of the anti-diabetic medications, use of all other medications were allowed during the study in patients with T2DM (chronic medication: statins [n = 7], angiotensin converting enzyme inhibitors [n = 3], beta-blockers [n = 1], proton pump inhibitors [n = 1]); anti-diabetic medication was restarted on day 29. In HVs, a limited amount of acetaminophen could be used for the treatment of headaches and other pain at the discretion of the principal investigator, but other medications were not permitted except for the treatment of adverse events (AEs) following consultation with the sponsor.’

This study did not assess DDIs so currently we can only speculate on the potential for such effects. As mentioned in response to Comment 2 (above), volixibat is minimally absorbed, is not metabolized, and any influence of increased presence of bile acids in the gut on the bioavailability of other compounds is hypothetical, suggesting that clinically significant effects on the metabolism of other drugs (or vice versa) are unlikely. However, DDI studies are needed to confirm this assertion.

The authors’ response letter has been included as a supplementary file.