Dose-dependent fecal bile acid excretion with apical sodium-dependent bile acid transporter inhibitors maralixibat and volixibat in a dose-ranging phase 1 study in overweight and obese adults

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Background

- Maralixibat (formerly SHP625, LUMO01) and volixibat (formerly SHP626, LUMO02) are minimally absorbed, selective inhibitors of the ileal apical sodium-dependent bile acid transporter (ASBT).
- Both are in development for cholestatic liver disease.
- ASBT inhibition reduces intestinal absorption of bile acids and increases fecal bile acid (FBA) excretion.
- This action is hypothesized to moderate the accumulation of cytotoxic bile acids in the liver, thereby modulating serum bile acid levels.

Objectives

- The primary objective of this study was to explore dose-dependent effects of maralixibat and volixibat on FBA excretion.
- The secondary objectives were:
  - to evaluate the pharmacodynamic properties of multiple doses of maralixibat and volixibat, using serum bile acid (BAs), serum 7α-hydroxy-cholesten-3-α-one (7C4), a biomarker of bile acid synthesis, and stool assessments; to evaluate safety and tolerability.

Methods

Study Design and Participants

- This was a phase 1, blinded, placebo-controlled, dose-ranging study (NCT02475317).
- Eligible participants were healthy adults (aged 18-45 years) with a body mass index (BMI) of 25-35 kg/m².
- Participants were randomized to receive maralixibat (10, 20, 50 mg once daily [QD]) or placebo, for 7 days.
- Participants consumed a low-fiber diet (<10 mg per day) for 2 days prior to randomization and during the 7-day treatment period.

Outcomes and Analysis

- Assessments of FBA excretion were based on mean change in total FBA concentration from baseline (average value from day-2 up to dosing on day 1) to days 1 and 7 (combined average).

Results

Disposition, Demographics and Baseline Characteristics

- Of 84 enrolled participants, all were male and all completed the study.
- Participant demographics and baseline characteristics are described in Table 1.

Fecal Bile Acid Excretion

- Mean FBA excretion increased up to the highest tested dose of 100 mg/day of maralixibat and 20 mg/day of volixibat from baseline to end of treatment (Figure 1).
- At the highest doses of maralixibat, increases in FBA excretion were numerically higher with 100 mg QD than with 100 mg BID.
- Volunteers 20 mg/day had similar FBA excretion effects to 50 mg/day of maralixibat.

Pharmacodynamic Endpoints

- 7C4 levels generally increased with increasing doses of maralixibat; the greatest change was with 50 mg QD (Figure 2).
- BA levels were not elevated at baseline and did not change with maralixibat and volixibat treatment, as expected.

Safety Outcomes

- Incidence of TEAEs was dose-dependent and was similar between maralixibat and volixibat (Table 2).
- No TEAEs were severe or serious.
- Safety outcomes were similar between doses and study drugs (maralixibat and volixibat); there were no drug discontinuations.

Conclusions

- Maralixibat and volixibat increased FBA excretion in a dose-dependent fashion.
- Safety outcomes were similar between doses and study drugs (maralixibat and volixibat); there were no drug discontinuations.
- Rates of GI TEAEs following ASBT inhibition were higher than observed in previous studies in patients with cholestatic liver disease,3 likely due to greater bile flow in healthy individuals.
- The pharmacodynamic profiles of maralixibat and volixibat support further clinical development in patients with cholestatic liver disease up to the maximum tested doses.

References

1. Takeda Pharmaceuticals, Lexington, MA, USA. 2. Takeda Pharmaceuticals, Zug, Switzerland. 3. New Orleans Center for Clinical Research, UT Medical Center, Knoxville, TN, USA. 4. Mirum Pharmaceuticals, Foster City, CA, USA.

Acknowledgments

This study was supported by Takeda Pharmaceuticals, Ltd. The authors’ financial disclosures and the DrugBank database are available at http://www.drugbank.ca. The authors thank their patients who volunteered for this study, the staff at their institutions, and the trial teams for their support and assistance.

Table 1. Demographics and baseline characteristics

<table>
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<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Maralixibat</th>
<th>Volixibat</th>
<th>Overall</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>38.2 (9.32)</td>
<td>45.4 (11.18)</td>
<td>32.2 (8.92)</td>
<td>36.4 (12.75)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>37.5 (6.74)</td>
<td>43.7 (14.40)</td>
<td>46.0 (11.39)</td>
<td>38.9 (11.11)</td>
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<tr>
<td>White</td>
<td>7 (50.0)</td>
<td>6 (60.0)</td>
<td>3 (30.0)</td>
<td>7 (70.0)</td>
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<tr>
<td>Black</td>
<td>6 (42.9)</td>
<td>4 (40.0)</td>
<td>3 (30.0)</td>
<td>7 (70.0)</td>
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<tr>
<td>Multipl*</td>
<td>1 (7.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Mean FBA excretion, µmol (SD)</td>
<td>244 (113.6)</td>
<td>201 (178.9)</td>
<td>138 (117.9)</td>
<td>192 (235.8)</td>
</tr>
<tr>
<td>Mean serum 7C4, ng/mL (SD)</td>
<td>20 (11.3)</td>
<td>22 (24.0)</td>
<td>14 (5.9)</td>
<td>26 (19.8)</td>
</tr>
</tbody>
</table>

* BID, twice daily; QD, once daily; SD, standard deviation; no, number of participants; *black and white.

Figure 1. Mean change from baseline to end of treatment in fecal bile acid excretion across doses of maralixibat, volixibat and placebo.

Figure 2. Mean change from baseline to end of treatment in serum 7C4 levels across doses of maralixibat, volixibat and placebo.