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, LUM001) and volixibat (formerly SHP626, LUM002) 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.[1]
  - This action is hypothesized to moderate the accumulation of cytotoxic bile acids in the liver, thereby moderating 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 (sBA), serum 7-α-hydroxy-cholesten-3-one (7αC4; 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 18–65 years) with a body mass index (BMI) of 25–35 kg/m^2.
- Participants were randomized to receive maralixibat (10, 20, 50 or 100 mg once daily [QD] or 50 mg twice daily [BID]), volixibat (10 or 20 mg QD) or placebo, for 7 days.
- Participants consumed a low-fiber diet (< 10 mg per day) for 2 days before randomization and during the 7-day treatment period.

Outcomes and Analyses

- 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 day 6 and 7 (combined average).
- Stool softness (assessed using the Bristol Stool Chart[2]) and frequency of bowel movements were monitored.
- Treatment-emergent adverse events (TEAEs) were monitored.

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 50 mg BID than with 100 mg QD.
- Volixibat 20 mg/day had similar fBA excretion effects to 50 mg/day of maralixibat.

Pharmacodynamic Endpoints

- 7αC4 levels generally increased with increasing doses of maralixibat; the greatest change was with 50 mg BID (**Figure 2**).
- sBA levels were not elevated at baseline and did not change with maralixibat and volixibat treatment, as expected.

Safety Outcomes

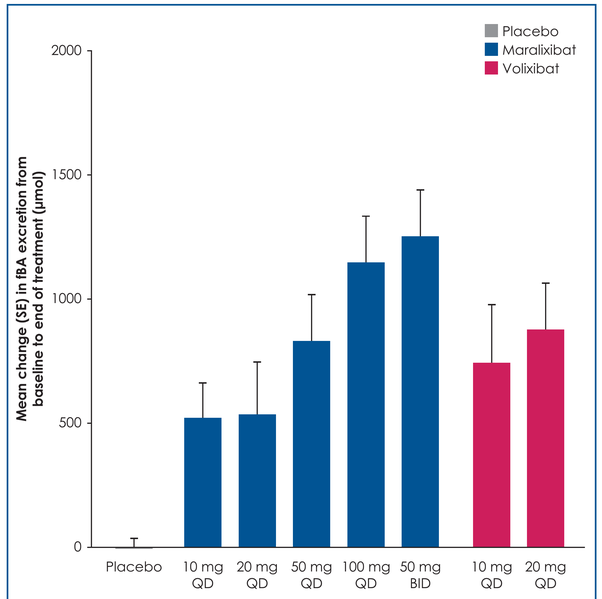
- Incidence of TEAEs was not dose-dependent and was similar between maralixibat and volixibat (**Table 2**).
- The proportions of participants with TEAEs were higher in both the maralixibat and volixibat groups than in the placebo group, due to the expected increase in instances of diarrhea.
  - No TEAEs were severe or serious.
  - No adverse events led to drug discontinuation.
- The only TEAEs occurring in over 10% of the study population were headache and diarrhea.
- Frequency of bowel movements and stool softness were increased at the end of treatment in both the combined maralixibat and volixibat groups, compared with placebo, in line with the mechanism of action.

Table 1. Demographics and baseline characteristics

	Placebo	Maralixibat						Volixibat			Overall
		10 mg QD	20 mg QD	50 mg QD	100 mg QD	50 mg BID	All doses	10 mg QD	20 mg QD	All doses	
n	14	10	10	10	10	10	50	10	10	20	84
Mean age, years (SD)	38.2 (9.32)	45.4 (11.18)	32.2 (8.92)	36.4 (12.87)	38.5 (9.87)	39.4 (12.66)	38.4 (11.58)	37.5 (6.74)	43.7 (14.40)	40.6 (11.39)	38.9 (11.11)
Race, n (%)											
White	7 (50.0)	6 (60.0)	3 (30.0)	7 (70.0)	7 (70.0)	6 (60.0)	29 (58.0)	6 (60.0)	5 (50.0)	11 (55.0)	47 (56.0)
Black	6 (42.9)	4 (40.0)	7 (70.0)	3 (30.0)	3 (30.0)	4 (40.0)	21 (42.0)	4 (40.0)	4 (40.0)	8 (40.0)	35 (41.7)
Multiple[a]	1 (7.1)	0	0	0	0	0	0	0	1 (10.0)	1 (5.0)	0
Mean fBA excretion, µmol (SD)	246 (113.6)	201 (176.9)	138 (91.7)	192 (235.8)	230 (231.5)	199 (147.9)		161 (129.6)	263 (287.7)		
Mean serum 7αC4, ng/mL (SD)	20 (11.3)	22 (24.0)	14 (5.9)	26 (19.8)	16 (14.7)	23 (17.4)		26 (38.1)	13 (13.4)		

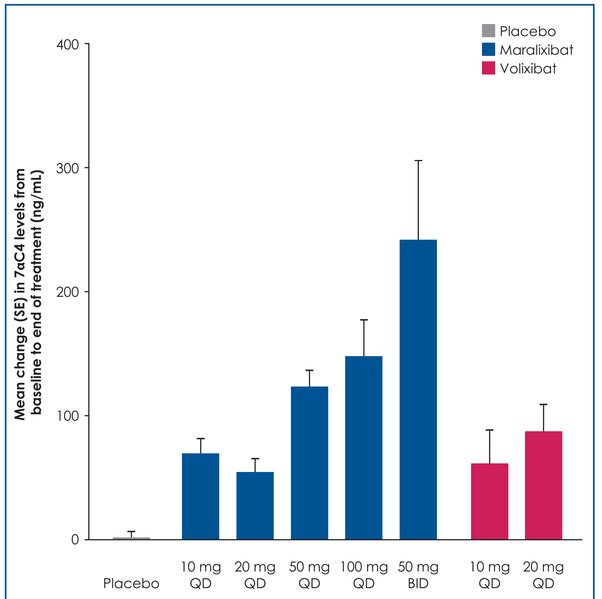
BID, twice daily; QD, once daily, SD, standard deviation; n, number of participants.
[a]Black and white.

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



BID, twice daily; fBA, fecal bile acid; QD, once daily, SE, standard error.

Figure 2. Mean change from baseline to end of treatment in serum 7αC4 levels across doses of maralixibat, volixibat and placebo



7αC4, 7-α-hydroxy-cholesten-3-one; BID, twice daily; QD, once daily, SE, standard error.

Table 2. Summary of TEAEs

	Placebo	Maralixibat						Volixibat			Overall
		10 mg QD	20 mg QD	50 mg QD	100 mg QD	50 mg BID	All doses	10 mg QD	20 mg QD	All doses	
Any TEAE, n (%) m	6 (42.9) 10	9 (90.0) 16	8 (80.0) 28	10 (100) 29	10 (100) 28	10 (100) 23	47 (94.0) 124	10 (100) 20	10 (100) 23	20 (100) 43	73 (86.9) 177
Related to study drug, n (%) m	6 (42.9) 8	9 (90.0) 16	8 (80.0) 28	10 (100) 29	10 (100) 28	10 (100) 23	47 (94.0) 124	10 (100) 20	10 (100) 23	20 (100) 43	73 (86.9) 175
Leading to drug withdrawal, n (%) m	0	0	0	0	0	0	0	0	0	0	0
Diarrhea, n (%) m	5 (35.7) 7	9 (90.0) 16	7 (70.0) 16	10 (100) 25	10 (100) 19	9 (90.0) 20	45 (90.0) 96	10 (100) 18	10 (100) 18	20 (100) 36	70 (83.3) 139
Headache, n (%) m	1 (7.1) 1	0	2 (20.0) 3	1 (10.0) 1	2 (20.0) 2	0	5 (10.0) 6	1 (10.0) 1	2 (20.0) 2	3 (15.0) 3	9 (10.7) 10

BID, twice daily; m, number of events; n, number of participants; QD, once daily, TEAE, treatment-emergent adverse event.

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,[3,4] 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.**

Disclosures

Pamela Vig holds a management position at Mirum Pharmaceuticals, Patrick Martin, Lee Jennings and George Apostol are employees of Takeda Pharmaceutical Company Ltd. Patrick Martin is a stock shareholder of Shire Pharmaceuticals (now a member of the Takeda group of companies). William Smith has no conflicts of interest to declare.

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