A randomised, phase II, placebo- and active-controlled dose-ranging study of semaglutide for treatment of obesity in subjects without diabetes

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Introduction: The global rise in the prevalence of obesity and its comorbidities is a major public health challenge. The incretin GLP-1 regulates both insulin secretion and appetite, and significant weight loss has been observed among subjects treated with the GLP-1 receptor agonists liraglutide (LIRA) and semaglutide (SEMA). The use of SEMA for treatment of obesity in subjects without diabetes was evaluated in a phase 2 clinical trial.

Methods: a multinational, randomised, double-blinded, dose-ranging study (NCT02453711) of SEMA versus placebo (PBO) and an active LIRA control (3 mg), each with dietary and physical activity counselling. Eligible subjects were adults with obesity (BMI ≥30 kg/m^2) without diabetes and with at least one previous non-surgical attempt at weight loss. Participants were randomised to receive PBO or active treatment with either once-daily subcutaneous SEMA at doses of 0.05, 0.1, 0.2, 0.3, or 0.4 mg (starting at 0.05 mg and escalating every 4 weeks to target dose) or with once-daily subcutaneous LIRA 3 mg (weekly escalation from 0.6 mg), in a 6:1 active:PBO ratio. Each active group had a PBO counterpart of matching injection volume and escalation schedule; all PBO groups were pooled for analysis. Two additional faster-escalation SEMA groups are not presented here. The primary endpoint was change in body weight (%) from baseline (BL) to week 52 (ANCOVA model; region, sex, and BL body weight as covariates).

Results: A total of 957 subjects (35% male) were randomised and treated (102–103 per active arm; 136 pooled PBO). Mean (range) BL characteristics were: age 47 (18–86) years, weight 111 (70–244) kg, and BMI 39 (30–80) kg/m^2. Overall, 93% (892/957) had body weight data at Week 52 (81% on drug, 12% discontinued). Estimated mean weight losses from BL to Week 52 were –2.3% (PBO) and –7.8% (LIRA 3 mg), vs –6.0% (0.05 mg; *P*=0.001 vs PBO), –8.6% (0.1 mg), –11.6% (0.2 mg), –11.2% (0.3 mg) and –13.8% (0.4 mg; *P*<0.0001 vs PBO for 0.1–0.4 mg). All comparisons remained significant after adjustment for multiple testing. Mean weight loss for 0.2–0.4 mg were all *P*<0.01 (unadjusted) vs LIRA 3 mg. Weight loss ≥5% occurred in an estimated 23% (PBO) and 66% (LIRA 3 mg) vs 54% (0.05 mg), 67% (0.1 mg), 75% (0.2 mg), 81% (0.3 mg), and 83% (0.4 mg) of subjects (all *P*<0.0001 vs PBO). Weight loss ≥10% occurred in an estimated 10% (PBO) and 34% (LIRA 3 mg) vs 19% (SEMA 0.05 mg; *P*=NS vs PBO), 37% (0.1 mg), 56% (0.2 mg), 58% (0.3 mg), and 65% (0.4 mg) of subjects (*P*<0.0001 vs PBO for 0.1–0.4 mg). All SEMA doses were generally tolerated; there were no new safety concerns observed. The most common adverse events on SEMA were dose-related gastrointestinal events as seen previously with GLP-1 receptor agonists.

Conclusions: In combination with dietary and physical activity counselling, all SEMA doses from 0.05 to 0.4 mg daily were tolerated and resulted in dose-related reductions in body weight that were superior to PBO among people with obesity without diabetes.