Semaglutide provides sustained reductions in body weight over 2 years in subjects with type 2 diabetes (SUSTAIN 6)

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Background and aims: Semaglutide, a glucagon-like peptide-1 analogue in development for the treatment of type 2 diabetes (T2D), has demonstrated superior body weight loss vs placebo and active comparators across the SUSTAIN phase 3a clinical trial programme. Excess weight is often a concomitant complication in patients with T2D and is associated with increased cardiovascular risk.
Materials and methods: SUSTAIN 6 was a 2-year cardiovascular outcomes trial that was conducted in 3,297 subjects with T2D at high risk of cardiovascular events. The primary outcome was a composite of the first occurrence of CV death, non-fatal myocardial infarction or non-fatal stroke. Secondary endpoints included glycaemic and weight-related endpoints. Key inclusion criteria were subjects ≥50 years old with established cardiovascular disease (previous cardio-, cerebro-, or peripheral-vascular disease), chronic heart failure (New York Heart Association class II or III), or chronic kidney disease (stage 3 or higher) or ≥60 years old with at least one cardiovascular risk factor. Subjects were randomised to once-weekly, s.c. semaglutide 0.5 or 1.0 mg, or volume-matched placebo, added to standard of care, without any lifestyle intervention, for 104 weeks.
Results: At baseline, overall mean body weight, age, duration of diabetes and HbA_{1c} were 92.1 kg, 65 years, 13.9 years and 8.7%, respectively. Semaglutide significantly reduced the risk of the primary composite outcome vs placebo (hazard ratio, 0.74; 95% CI, 0.58-0.95; p<0.001 for non-inferiority with a margin of 1.8). Treatment with semaglutide, vs placebo, led to significantly reduced body weight, BMI and waist circumference at 2 years vs placebo (p<0.001; Table). BW loss plateaued at Week 44 and was sustained throughout the remainder of the trial until Week 104. The proportion of subjects achieving ≥5% and ≥10% reduction in body weight was more than two-fold greater with semaglutide vs placebo. For semaglutide 0.5 and 1.0 mg, 77% and 81% of subjects, respectively, had no weight gain at 2 years, compared with 52% and 53% of subjects receiving placebo 0.5 and 1.0 mg, respectively. A dose-response effect with semaglutide was observed for body weight reduction.
Conclusion: Semaglutide treatment, added to standard of care, led to clinically meaningful and sustained reductions in body weight, BMI and waist circumference at 2 years in subjects with T2D at high cardiovascular risk.

Table. Body weight-related endpoints: Change from baseline at Week 104

	Overall mean at baseline	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo 0.5 mg	Placebo 1.0 mg
Number of randomised subjects		826	822	824	825
Body weight, kg					
	92.1	−3.6	−4.9	−0.7	−0.5
ETD vs placebo [95% CI]	-	−2.87* [−3.47; −2.28]	−4.35* [−4.94; −3.75]		
BMI, kg/m²					
	32.8	−1.3	−1.8	−0.2	−0.2
ETD vs placebo [95% CI]	-	−1.06* [−1.28; −0.85]	−1.59* [−1.80; −1.37]		
Waist circumference, cm					
	110.2	−2.7	−4.2	−0.6	−0.9
ETD vs placebo [95% CI]	-	−2.17* [−2.82; −1.53]	−3.25* [−3.89; −2.60]		
Weight loss category, n (%)					
≥5%		297 (36)*	383 (47)*	144 (18)	154 (19)
≥10%		109 (13)*	168 (20)*	47 (6)	54 (7)

*p<0.0001. *Post-hoc* defined endpoint. Data are in trial, including all scheduled assessments from randomisation to last subject-site contact or death, estimated mean changes from baseline, and treatment differences with CIs from mixed models for repeated measures. For weight loss categories, data are observed proportions; p-values are from logistic regressions where missing data were imputed as predictions from a mixed model for repeated measures. BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference.

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