Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity

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Aim: The aim of this trial was to investigate the mechanism of action for body weight loss with semaglutide.

Materials and methods: This randomised, double-blind, placebo-controlled, two-period cross-over trial investigated the effects of 12 weeks of treatment with once-weekly subcutaneous semaglutide, dose-escalated to 1.0 mg, in 30 subjects with obesity. Ad libitum energy intake, ratings of appetite, thirst, nausea and well-being, control of eating, food preference, resting metabolic rate, body weight and body composition were assessed.

Results: After a standardised breakfast, semaglutide, compared with placebo, led to a lower ad libitum energy intake during lunch (−1255 kJ; \( P < .0001 \)) and during the subsequent evening meal (\( P = .0401 \)) and snacks (\( P = .0034 \)), resulting in a 24% reduction in total energy intake across all ad libitum meals throughout the day (−3036 kJ; \( P < .0001 \)). Fasting overall appetite suppression scores were improved with semaglutide vs placebo, while nausea ratings were similar. Semaglutide was associated with less hunger and food cravings, better control of eating and a lower preference for high-fat foods. Resting metabolic rate, adjusted for lean body mass, did not differ between treatments. Semaglutide led to a reduction from baseline in mean body weight of 5.0 kg, predominantly from body fat mass.

Conclusion: After 12 weeks of treatment, ad libitum energy intake was substantially lower with semaglutide vs placebo with a corresponding loss of body weight observed with semaglutide. In addition to reduced energy intake, likely mechanisms for semaglutide-induced weight loss included less appetite and food cravings, better control of eating and lower relative preference for fatty, energy-dense foods.

KEYWORDS
Body composition, Energy regulation, GLP-1 analogue, Glucagon-like peptide-1, Randomised trial, Semaglutide, Type 2 diabetes, Visual analogue scale
obese, with or without diabetes.\textsuperscript{6–10} Furthermore, activation of GLP-1 receptors in the human brain helps to regulate appetite and food reward.\textsuperscript{11} Animal studies have shown that a GLP-1RA, liraglutide, can access specific areas of the brain involved in appetite regulation.\textsuperscript{11,12} Combined, these studies indicate a central mechanism for liraglutide-mediated weight loss due to the direct activation of discrete sites within the hypothalamus.

Semaglutide is a human GLP-1 analogue currently in development for the treatment of T2D, with a similar structure to liraglutide. Semaglutide has 94\% structural homology with native human GLP-1\textsuperscript{13} with three important modifications: an amino acid substitution at position 8 makes semaglutide less susceptible to degradation by dipeptidyl peptidase-4; lysine acylation of the peptide backbone with a spacer and C-18 fatty di-acid chain at position 26 provides strong, specific binding to albumin; and another amino acid substitution at position 34 prevents C-18 fatty di-acid binding at the wrong site.\textsuperscript{13} These modifications give semaglutide an extended half-life of approximately one week,\textsuperscript{13} making it suitable for once-weekly administration.\textsuperscript{14–15} Once-weekly administration may improve patient compliance and quality of life,\textsuperscript{16,17} compared with first-generation GLP-1RAs that require once-/twice-daily dosing.\textsuperscript{18} Semaglutide is associated with dose-dependent reductions in HbA1c and body weight in individuals with diabetes.\textsuperscript{19} As a GLP-1RA, the trial of the effect of semaglutide on appetite control may provide additional clarity concerning the role of GLP-1 receptors in this process.

The primary aim of this trial was to investigate the role of semaglutide compared with placebo on body weight loss in subjects with obesity by evaluating the effect of semaglutide on \textit{ad libitum} energy intake. In addition, further aspects of homeostatic (\textit{ad libitum} energy intake after lunch, appetite ratings and energy expenditure) and hedonic (food preference and food cravings) regulation of energy balance were assessed. This trial also evaluated glucose and lipid metabolism, and gastric emptying in the same subjects; these data will be reported elsewhere.

2 | MATERIALS AND METHODS

2.1 | Trial design

This was a single-centre, randomised, double-blind, placebo-controlled, two-period crossover trial (NCT02079870, EudraCT number: 2013-000012-24) (Figure S1). The trial was conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines\textsuperscript{20} and the Declaration of Helsinki.\textsuperscript{21}

2.2 | Trial population

Eligible subjects were \textgeq 18 years of age, with a body mass index (BMI) of 30 to 45 kg/m\textsuperscript{2}, HbA1c < 6.5\% and stable body weight (< 3 kg change during the 3 months prior to screening). Key exclusion criteria were: diagnosis of type 1 or 2 diabetes; history of chronic/idiopathic acute pancreatitis; personal/family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; previous surgical treatment for obesity; smoking or use of any nicotine products; use of any medication that could interfere with trial results; or anticipated change in lifestyle (eg, eating, exercise or sleeping pattern) during the trial. Written informed consent was obtained from all participants before any trial-related activities commenced.

2.3 | Interventions

The trial consisted of two 12-week crossover treatment periods, separated by a wash-out period of 5 to 7 weeks. Eligible subjects were randomised 1:1 to one of two treatment sequences: semaglutide–placebo or placebo–semaglutide. Subjects received either semaglutide (1.34 mg/mL) or matching placebo administered subcutaneously (s.c.) once-weekly. The starting dose was 0.25 mg (4 weeks), escalating to 0.5 mg (4 weeks) and then 1.0 mg (4 weeks). Subjects received a fifth dose (administered at the clinic) of 1.0 mg at the last visit of each treatment period and assessments were conducted. Subjects attended the clinic for each dose escalation and were reminded, by text message or telephone, to administer the remaining doses at home.

2.4 | Endpoints

The primary endpoint was \textit{ad libitum} energy intake during a lunch meal (5 hours after a standardised breakfast meal) after 12 weeks of treatment. Secondary endpoints included: \textit{ad libitum} energy intake during a subsequent evening meal and from an evening snack box; total day-time \textit{ad libitum} energy intake until midnight; duration of \textit{ad libitum} lunch; ratings of appetite parameters, thirst, nausea and well-being before and after a standardised breakfast meal; palatability of \textit{ad libitum} meals; energy expenditure (resting metabolic rate [RMR] and respiratory quotient [RQ]); control of eating and food cravings over the past week; food preference; body weight; and body composition (fat and fat-free mass). In addition, the multiple-dose pharmacokinetics (PK), and safety and tolerability of semaglutide were investigated.

2.5 | Assessments

At the end of each 12-week treatment period, subjects attended an in-house stay. On Day 1 of their stay, subjects were standardised with regard to meals, physical activity and sleep. The last dose of trial drug was administered in the evening.

On Day 2, a 5-hour standardised breakfast meal test was performed (macronutrient composition: approximately 30 energy percentage [E\%] fat, 15 E\% protein, 55 E\% carbohydrate); meals were served at \textapprox 8:00 AM. Following this test, a homogeneous \textit{ad libitum} lunch was served in excess (Appendix S1) and meal duration was recorded. At \textapprox 6:00 PM, subjects were given a self-served \textit{ad libitum} evening meal. For both lunch and evening meals, subjects were instructed to eat until pleasantly satiated; food consumption was measured. At \textapprox 7:00 PM, subjects received their evening snack box comprised of four food categories (four items of 100 g each: high-fat and sweet; low-fat and sweet; high-fat and non-sweet; low-fat and non-sweet; individualised by preference), which they were allowed to
Body weight was measured prior to subjects entering the Bodpod tite parameters (Appendix S1).10 Palatability (taste, visual appearance, recorded. keep until midnight. The consumption of each food category was
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| 2.6 | Statistical analysis |
Based on a previous trial,10 30 subjects were needed to provide a power of 80% to detect a treatment difference in energy intake of 500 kJ at a significance level of 5%, assuming a dropout rate of about 15%. The primary endpoint was analysed in a linear mixed model on original outcome values, including treatment and period as fixed effects and subject as a random effect. Statistical analysis of the primary endpoint was performed for the full analysis set (FAS; all randomised subjects who were exposed to ≥1 dose of trial product). Energy intake, duration of ad libitum lunch and COEQ endpoints were analysed as per the primary endpoint. The ad libitum evening snack box energy intake also included interaction between treatments, with high-/low-fat and sweet/non-sweet food categories as fixed effects. Furthermore, treatment differences were estimated for the two food categories of high-fat combined and the two categories of low-fat combined, using a linear mixed model. Treatment period, and interactions between treatments and high-/low-fat food categories were fixed effects; subject was a random effect. A similar approach was used for sweet/non-sweet food categories. Endpoints for the LFPT28 were analysed in a statistical model similar to that used for energy intake of the evening snack box with the same four food categories. Body weight, body composition and palatability assessments of the ad libitum lunch, evening meal and evening snack box were summarised descriptively. For VAS profiles of appetite, thirst, nausea and well-being, the fasting rating and mean postprandial increase in rating were analysed as per the main analysis of the primary endpoint. For the mean postprandial increase in ratings, the fasting ratings were added as a covariate. Palatability was analysed post hoc using a linear mixed model: treatment and treatment period were fixed effects; subject was a random effect. Treatment difference in RMR was estimated post hoc using a linear mixed model; treatment, treatment period and subject were fixed effects. Treatment difference in RQ was similarly estimated. Treatment difference in RMR was also estimated with lean body mass as a covariate. All statistical analyses were two-sided and on a 5% significance level. The primary endpoint was controlled for type 1 error. Other analyses were not controlled for multiplicity.

3 | RESULTS

3.1 | Trial population
Thirty subjects were randomised to once-weekly semaglutide or placebo, and 28 completed both treatment periods of the trial. Two female subjects took contraceptives during both treatment periods. Two subjects withdrew during treatment period 1 while receiving semaglutide due to gastrointestinal (GI) AEs. Baseline characteristics are shown in Table S1. Mean age, body weight and BMI were 42 years, 101.3 kg and 33.8 kg/m², respectively. Two-thirds of subjects were male.
3.2 | Ad libitum energy intake and macronutrient composition

Ad libitum energy intake at lunch was approximately 35% lower with semaglutide vs placebo (primary endpoint; estimated treatment difference (ETD) [95% confidence interval (CI)], -1255 kJ [-1707; -804]; $P < .0001$) (Figure 1A). In addition, ad libitum food intake and meal duration were significantly lower with semaglutide vs placebo (Table 1). Lower ad libitum energy and food intake were also observed at subsequent evening meals and the evening snacks (Figure 1A and Table 1). Total energy intake across all ad libitum meals was approximately 24% lower with semaglutide vs placebo (ETD [95% CI] -3036 kJ [-4209; -1864]; $P < .0001$) (Figure 1A). Energy intake of food categories in the ad libitum evening snack box showed an approximately 35% lower intake from high-fat and non-sweet foods with semaglutide vs placebo ($P = .0184$) (Figure 1B). Macronutrient compositions of foods consumed in the ad libitum evening meal and evening snack box were similar between treatments.
3.3 | Appetite, thirst, nausea and well-being

At the standardised breakfast meal, the fasting overall appetite suppression score was higher with semaglutide vs placebo, indicating less appetite with semaglutide ($P = .0023$). Overall appetite suppression scores remained higher at all time-points with semaglutide, with the difference increasing towards the end of the 5-hour postprandial period (Figure 2A). In general, VAS ratings of individual appetite parameters indicated less appetite with semaglutide vs placebo (Figure 2B and C). Ratings for thirst, nausea and well-being were similar between treatments (Figure 2C).

Postprandial increases from fasting VAS ratings showed greater increases in satiety with semaglutide vs placebo; however, differences in the overall incremental appetite suppression score were not significant (Figure S4). Postprandial increases from fasting ratings in nausea, thirst and well-being were comparable between treatments.

3.4 | Palatability

Palatability ratings were similar between treatments for both ad libitum lunch and evening meal, except for taste of the ad libitum lunch (ETD [95% CI] $-8.5$ mm $[-16.5; \ -0.4]$; $P = .0398$) and visual appearance of the ad libitum evening meal (ETD [95% CI] $-7.4$ mm $[-14.6; \ -0.2]$; $P = .0432$). Mean ratings of all parameters were above 50 mm for all meals regardless of treatment.

3.5 | Energy expenditure

RMR was lower following 12 weeks of treatment with semaglutide vs placebo (ETD $-602$ kJ/24 h $[-959; \ -245]$; $P = .0019$), while there was no significant difference in RQ (ETD $-0.03$ $[-0.06; \ 0.00]$; $P = .0698$). When adjusted for lean body mass, the difference in RMR was not significant between treatments (ETD RMR, $-508$ kJ/24 h $[-1061; \ 46]$; $P = .0704$).

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**TABLE 1** Energy and food intake during ad libitum meals and duration of ad libitum lunch

<table>
<thead>
<tr>
<th>FAS</th>
<th>N</th>
<th>Estimated mean [95% CI]</th>
<th>ETD $^1$ [95% CI]</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Energy intake (kJ)</td>
<td></td>
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</tr>
<tr>
<td>Placebo</td>
<td>28</td>
<td>28</td>
<td>3634 [3132; 4136]</td>
<td></td>
</tr>
<tr>
<td>Semaglutide 1.0 mg</td>
<td>30</td>
<td>28</td>
<td>2378 [1876; 2881]</td>
<td>1255 [1707; -804]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Food intake (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>28</td>
<td>28</td>
<td>645 [556; 735]</td>
<td></td>
</tr>
<tr>
<td>Semaglutide 1.0 mg</td>
<td>30</td>
<td>28</td>
<td>424 [334; 514]</td>
<td>-221 [-301; -142]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration (min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>28</td>
<td>28</td>
<td>12.2 [10.5; 13.9]</td>
<td></td>
</tr>
<tr>
<td>Semaglutide 1.0 mg</td>
<td>30</td>
<td>28</td>
<td>10.7 [9.0; 12.4]</td>
<td>1.5 [-2.4; -0.6]</td>
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</table>

Ad libitum evening meal

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<thead>
<tr>
<th>FAS</th>
<th>N</th>
<th>Estimated mean [95% CI]</th>
<th>ETD $^1$ [95% CI]</th>
<th>$P$ value</th>
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<tr>
<td>Placebo</td>
<td>28</td>
<td>28</td>
<td>4214 [3618; 4809]</td>
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<tr>
<td>Semaglutide 1.0 mg</td>
<td>30</td>
<td>28</td>
<td>3461 [2865; 4057]</td>
<td>753 [-1469; -36.6]</td>
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<tr>
<td></td>
<td></td>
<td>Food intake (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>28</td>
<td>28</td>
<td>557 [481; 634]</td>
<td></td>
</tr>
<tr>
<td>Semaglutide 1.0 mg</td>
<td>30</td>
<td>28</td>
<td>446 [369; 522]</td>
<td>112 [-201; -22.3]</td>
</tr>
</tbody>
</table>

Ad libitum evening snack box

<table>
<thead>
<tr>
<th>FAS</th>
<th>N</th>
<th>Estimated mean [95% CI]</th>
<th>ETD $^1$ [95% CI]</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>28</td>
<td>28</td>
<td>4573 [3967; 5178]</td>
<td></td>
</tr>
<tr>
<td>Semaglutide 1.0 mg</td>
<td>30</td>
<td>28</td>
<td>3545 [2939; 4150]</td>
<td>1028 [-1684; -372]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Food intake (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>28</td>
<td>28</td>
<td>257 [223; 290]</td>
<td></td>
</tr>
<tr>
<td>Semaglutide 1.0 mg</td>
<td>30</td>
<td>28</td>
<td>200 [166; 233]</td>
<td>57.3 [-94.0; -20.6]</td>
</tr>
</tbody>
</table>

Total intake during ad libitum meals

<table>
<thead>
<tr>
<th>FAS</th>
<th>N</th>
<th>Estimated mean [95% CI]</th>
<th>ETD $^1$ [95% CI]</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>28</td>
<td>28</td>
<td>12421 [11214; 13627]</td>
<td></td>
</tr>
<tr>
<td>Semaglutide 1.0 mg</td>
<td>30</td>
<td>28</td>
<td>9384 [8178; 10591]</td>
<td>3036 [-4209; -1864]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Food intake (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>28</td>
<td>28</td>
<td>1459 [1315; 1604]</td>
<td></td>
</tr>
<tr>
<td>Semaglutide 1.0 mg</td>
<td>30</td>
<td>28</td>
<td>1069 [925; 1213]</td>
<td>391 [-505; -276]</td>
</tr>
</tbody>
</table>

Abbreviation: FAS, full analysis set.

$^1$ Semaglutide 1.0 mg – placebo.
A. Overall appetite suppression score during the standardised breakfast; B, visual analogue scale (VAS) ratings of appetite during a standardised breakfast and C, fasting VAS ratings. CI, confidence interval; ETD, estimated treatment difference. Overall appetite suppression score = \( \frac{\text{satiety} + \text{fullness} + (100 - \text{hunger}) + (100 - \text{prospective food consumption})}{4} \). 100 indicates less appetite; 0 indicates more appetite. Error bars represent 95% CI.
3.6 | Control of eating and food cravings

The COEQ indicated less hunger, better control of eating and meal portion size, less food cravings, particularly for savoury foods, and lower ratings for the pleasantness of food for semaglutide vs placebo (Figure 3).

3.7 | Food preference

LFPT indicated lower explicit liking for high-fat and non-sweet foods with semaglutide vs placebo ($P = .0016$). Differences between treatments in implicit liking for other food categories were not significant. Ratings of implicit wanting were lower for high-fat and non-sweet foods ($P = .0203$) and higher for low-fat and sweet foods ($P = .0401$) with semaglutide vs placebo (Table S2).

3.8 | Body weight and body composition

After 12 weeks of treatment with semaglutide, a change from baseline in mean body weight of $-5.0$ kg was observed, vs $+1.0$ kg with placebo. A three-fold greater loss of mean fat over lean body mass was observed with semaglutide vs placebo (Figure 4).

3.9 | PK endpoints

The PK profile for semaglutide was as expected, supporting compliance with the treatment regimen during the trial (mean $[\text{coefficient of variation (CV)}]$ AUC$_{0-168h}$: 4467 [17.7] nmol $\times$ h/L; $C_{\text{max}}$: 32.0 [19.1] nmol/L; $t_{\text{max}}$: 33.2 [59.8] hours). Mean trough values (CV) for individual semaglutide dosages were: 0.25 mg, 4.64 (22.5) nmol/L; 0.5 mg, 10.25 (23.3) nmol/L; 1.0 mg, 19.73 (21.9) nmol/L.

3.10 | Safety

AEs were reported more frequently with semaglutide vs placebo. All AEs were mild or moderate in severity; no serious AEs were reported. The most common AEs were GI events. Two AEs led to withdrawal from the trial during semaglutide treatment. No severe or blood glucose-confirmed symptomatic hypoglycaemic events were reported. Observed systolic and diastolic blood pressure were stable throughout the trial for subjects receiving either treatment; at week 12, observed mean changes from baseline were within 2 mm Hg.

**FIGURE 3** Results of the Control of Eating Questionnaire (COEQ). CI, confidence interval; ETD, estimated treatment difference. Results for the open-ended question “Which one food makes it difficult for you to control eating?” (question 15) not shown. Error bars represent 95% CI.

**FIGURE 4** A, Absolute mean body weight change and B, estimated mean change in body composition. Body weight and body composition were measured on distinct days. Error bars represent standard error of the mean.
This trial investigated the mechanism of body weight loss with semaglutide in subjects with obesity. The results suggest that the significantly lower energy intake provides a plausible mechanism to explain the decrease in body weight associated with semaglutide treatment. Not only was energy intake during ad libitum lunch (primary endpoint) substantially lower with semaglutide vs placebo (approximately −35%), the same pattern also held true for subsequent ad libitum evening meal and evening snack box, demonstrating no compensatory effect due to a reduced lunch intake earlier in the day. Total ad libitum energy intake across all meals on the test day was reduced by 24%. A reduction in body weight of approximately 5.0 kg over 12 weeks was observed with semaglutide, consistent with previous findings. Energy expenditure appeared to be lower with semaglutide vs placebo, though not statistically significant after correcting for lean body mass, suggesting that semaglutide-associated weight loss was not attributable to increased energy expenditure. Given recent findings regarding the association between energy intake and changes in weight, it is not possible to ascertain to what degree reductions in energy intake led to the 5.0 kg loss of body weight. Since RMR did not increase with semaglutide, it can be inferred that the whole of the body weight loss was most likely caused by a reduction in energy intake. However, RMR represents only one dimension of energy expenditure and the impact of semaglutide on the thermogenic effect or physical activity is unknown.

It should be noted that the reduction in energy intake was observed during/after body weight loss, despite known counter-regulatory effects during a period with an energy deficit. In terms of body composition, a three-fold greater reduction in body fat vs lean body mass was observed with semaglutide, indicating no unintentional excess loss of lean body mass.

The effect on energy intake is consistent with previous data from non-clinical27 and clinical studies with other GLP-1RAs, as well as studies with native GLP-1, with the reduction in energy intake correlating with reduction in body weight. However, the effects with semaglutide appear to be greater than those of other GLP-1RAs, consistent with larger weight reductions observed in larger semaglutide trials of longer duration, however, caution is required when drawing an indirect comparison between trials.

Furthermore, by accessing specific areas of the brain relevant for appetite regulation, GLP-1RAs (eg, liraglutide) may mediate weight loss via direct activation of discrete sites within the hypothalamus. This may help explain how treatment with semaglutide led to reduced appetite and food cravings, and better control of eating. The COEQ, which assessed control of eating and food cravings, demonstrated less hunger, better control of eating and less food cravings, particularly for savoury foods, compared with placebo. These effects probably reflect both direct and indirect effects of semaglutide treatment on body weight and fat mass. The LFPT, which assessed food reward (explicit liking and implicit wanting), showed a relatively lower liking and wanting of high-fat, non-sweet foods compared with placebo, consistent with results of the COEQ. The LFPT results also corroborated actual ad libitum energy intake from the same food categories of the evening snack box, suggesting that the lower intake of fatty, energy-dense food may be the result of semaglutide-mediated reduction in preference for such foods.

Semaglutide treatment was not associated with significant changes in nausea vs placebo, either in the fasted state or postprandially. Mean palatability ratings of all meals were above 50 mm for both treatments, meaning that meals were generally well liked.

Combined, these results suggest that the lower energy intake and body weight loss with semaglutide was a general effect on both homeostatic and hedonic systems of appetite control, rather than a response caused by nausea or food aversion.

Overall, semaglutide was well tolerated. No new safety concerns were identified, in line with other GLP-1RAs and longer-term semaglutide trials. By having subjects act as their own control, the crossover design of this trial can be considered a major strength of our overall findings. With regard to changes in weight and body composition, however, this trial could be conversely limited by the crossover design. During the wash-out period, body weight in subjects receiving semaglutide likely had recovered before crossing over to placebo, but may not have had sufficient time to reach pre-treatment levels; which might have contributed to the small weight gain observed with placebo.

In conclusion, data after 12 weeks of treatment indicate that semaglutide-induced weight loss is probably caused by the reduced energy intake associated with reductions in appetite, and is not the result of increased energy expenditure. Other mechanisms include improvements in the control of eating, fewer food cravings and a lower relative preference for fatty, energy-dense foods. Furthermore, semaglutide-induced weight loss was associated with proportionally greater losses of body fat than lean body mass.

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Conflict of interest

JB and CG received research grants from Novo Nordisk for the current study. JB received personal fees from Novo Nordisk, outside the submitted work. GF declares no relevant conflict of interest. MBA, AF, TK, and JH are employees of Novo Nordisk. MBA, AF, and TK are shareholders of Novo Nordisk.

Author contributions

JB, AF, CG, and JH contributed to the study design; CG, MBA, and JH contributed to the collection or handling of data; all authors contributed to the analysis or interpretation of data; literature searches were conducted by JB and JH; JB, GF, MBA, AF, CG, and JH contributed to the writing, reviewing, and editing of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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