Oral semaglutide reduces appetite and energy intake and improves control of eating in subjects with type 2 diabetes

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Background and aims

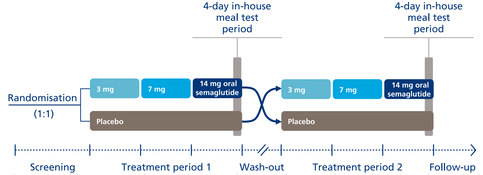
- Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue that has previously been shown to increase fullness, and reduce hunger and energy intake in subjects with obesity after subcutaneous administration.[1]
- An oral formulation of semaglutide has been developed, in which semaglutide is co-formulated with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC).[2]
- This trial was conducted to evaluate the extent to which oral semaglutide affects appetite and energy intake in subjects with type 2 diabetes (T2D).

Materials and methods

Trial design

- Phase 1, placebo-controlled, double-blind, two-period crossover trial conducted at a single site in the UK.
- There were two treatment periods (Figure 1); after the first 12 weeks of treatment, subjects crossed over to whichever treatment they did not previously receive for a further 12 weeks.
- At the end of each treatment period was a 4-day in-house meal test period, during which subjects received a standardised breakfast (standard on day 2, fat-rich on day 4), lunch and evening meal (both *ad libitum* on day 2), and *ad libitum* evening snack box on day 2.

Figure 1 Trial design.



Eligibility criteria

- Male or female, aged 18–75 years, T2D ≥90 days, treated with diet and exercise and/or stable dose of metformin ≥30 days, HbA_{1c} 6.0–9.0%, body mass index 20–38 kg/m^2, and stable body weight (<3 kg body weight change during 3 months prior to screening).

Assessments

- Appetite and palatability ratings were measured using a 100 mm visual analogue scale (VAS)[3] on days 2 and 4 of the standardised meal test periods.
- Control of eating and cravings were evaluated using the Control of Eating Questionnaire (CoEQ)[4] on day 3 of the standardised meal test periods.
- Changes in body weight and composition were assessed by air displacement plethysmography in both treatment periods; data are reported for treatment period 1 only, due to a possible rebound effect in subjects crossing-over from oral semaglutide to placebo.

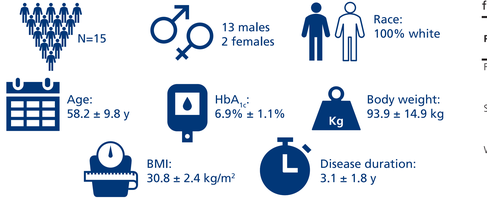
Statistical analysis

- The difference between oral semaglutide and placebo for each outcome was estimated together with the corresponding two-sided 95% confidence interval (CI) and P value for the test of no difference.
- Safety endpoints (adverse events [AE]) were analysed descriptively.

Results

- Fifty-three subjects were screened, of whom 15 were enrolled; two subjects withdrew before the end of the trial. Baseline characteristics are shown in Figure 2.

Figure 2 Baseline characteristics.



Data are mean ± standard deviation unless otherwise stated. BMI, body mass index.

Energy intake

- ***Ad libitum* energy intake** was lower when receiving oral semaglutide vs placebo at each meal, leading to a **38.9% lower total daily energy intake** (Figure 3).

Appetite and palatability

- There were **no significant differences** between treatments in **overall appetite** ratings pre-meal (in a fasting state) or during the standard breakfast (data not shown).
- After the fat-rich breakfast, there were **statistically significant differences** in favour of oral semaglutide vs placebo for the **mean postprandial overall appetite score** as well as all four individual mean postprandial ratings of appetite (satiety, fullness, hunger and prospective food consumption; Figure 4).
  - **Mean postprandial increment for fullness** after a fat-rich breakfast was **significantly greater** during treatment with oral semaglutide vs placebo.
- **Palatability** (taste, visual appearance and overall pleasantness) of the standard breakfast, *ad libitum* lunch and evening meal, and evening snack box appeared **similar** for oral semaglutide and placebo.
- No mean VAS scores of <50 mm were reported for palatability with either treatment, indicating **no food aversion**.

Figure 3 *Ad libitum* energy intake (*ad libitum* meals [lunch, evening meal and snack box] on day 2 of the in-house meal test period).

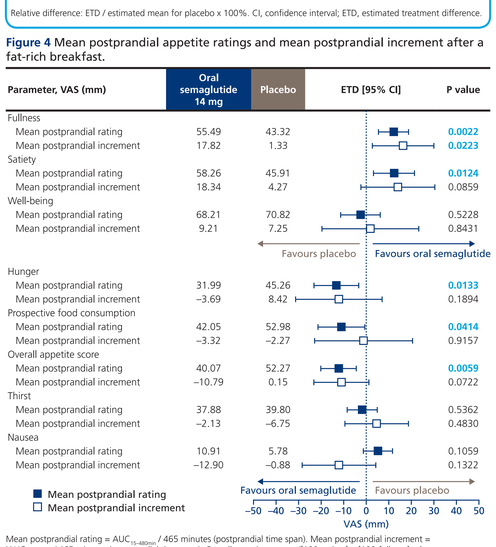
Key results

Energy intake, kJ	Oral semaglutide 14 mg	Placebo	ETD [95% CI]	Relative difference	P value
Lunch meal	2133	3331		–35.9%	0.0257
Evening meal	2620	4546		–42.4%	0.0263
Snack box	3237	5210		–37.9%	0.0058
Total daily intake	7991	13087		–38.9%	0.0001

Relative difference: ETD / estimated mean for placebo x 100%. CI, confidence interval; ETD, estimated treatment difference.

Figure 4 Mean postprandial appetite ratings and mean postprandial increment after a fat-rich breakfast.

Parameter, VAS (mm)	Oral semaglutide 14 mg	Placebo	ETD [95% CI]	P value
Fullness				
Mean postprandial rating	55.49	43.32		0.0022
Mean postprandial increment	17.82	1.33		0.0223
Satiety				
Mean postprandial rating	58.26	45.91		0.0124
Mean postprandial increment	18.34	4.27		0.0859
Well-being				
Mean postprandial rating	68.21	70.82		0.5228
Mean postprandial increment	9.21	7.25		0.8431
Hunger				
Mean postprandial rating	31.99	45.26		0.0133
Mean postprandial increment	–3.69	8.42		0.1894
Prospective food consumption				
Mean postprandial rating	42.05	52.98		0.0414
Mean postprandial increment	–3.32	–2.27		0.9157
Overall appetite score				
Mean postprandial rating	40.07	52.27		0.0059
Mean postprandial increment	–10.79	0.15		0.0722
Thirst				
Mean postprandial rating	37.88	39.80		0.5362
Mean postprandial increment	–2.13	–6.75		0.4830
Nausea				
Mean postprandial rating	10.91	5.78		0.1059
Mean postprandial increment	–12.90	–0.88		0.1322



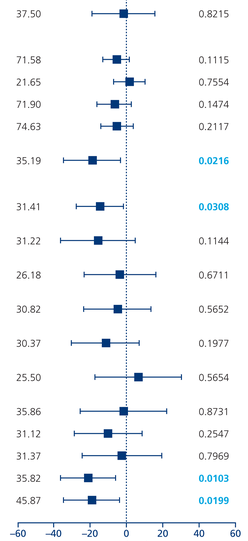
Mean postprandial rating = $AUC_{15-480min}$ / 465 minutes (postprandial time span). Mean postprandial increment = $iAUC_{15-480min}$ / 465 minutes (postprandial time span). Overall appetite score = ([100-satiety] + [100-fullness] + hunger + prospective food consumption) / 4. AUC, area under the curve; CI, confidence interval; ETD, estimated treatment difference; iAUC, incremental area under the curve; VAS, visual analogue scale.

Control of eating and cravings

- Control of eating (evaluated with the CoEQ) assessed after a standard breakfast indicated **fewer food cravings, better control** of eating and **less difficulty resisting food** when receiving oral semaglutide vs placebo (Figure 5).

Figure 5 Control of Eating Questionnaire scores.

CoEQ item*, VAS (mm)	Oral semaglutide 14 mg	Placebo	ETD [95% CI]	P value
1. How hungry have you felt?	29.59	41.24		0.0618
2. How full have you felt?	68.07	62.22		0.4983
3. How strong was your desire to eat sweet foods?	29.67	45.60		0.0862
4. How strong was your desire to eat savoury (non-sweet) foods?	35.70	37.50		0.8215
5. How happy have you felt?	65.83	71.58		0.1115
6. How anxious have you felt?	22.91	21.65		0.7554
7. How alert have you felt?	65.10	71.90		0.1474
8. How contented have you felt?	69.32	74.63		0.2117
9. During the last 7 days how often have you had food cravings?	15.94	35.19		0.0216
10. How strong have any food cravings been?	16.64	31.41		0.0308
11. How difficult has it been to resist any food cravings?	15.23	31.22		0.1144
12. How often have you eaten in response to food cravings?	22.27	26.18		0.6711
13. Cravings for chocolate or chocolate flavoured foods	25.89	30.82		0.5652
14. Cravings for other sweet foods	18.60	30.37		0.1977
15. Cravings for fruit or fruit juice	31.92	25.50		0.5654
16. Cravings for dairy foods	34.07	35.86		0.8731
17. Cravings for starchy foods	20.87	31.12		0.2547
18. Cravings for savoury foods	28.76	31.37		0.7969
19. Difficulty in controlling eating	14.66	35.82		0.0103
21. Difficulty in resisting this food during last 7 days	26.52	45.87		0.0199



*Question 20 was open-ended and thus not rated using the VAS. CI, confidence interval; CoEQ, Control of Eating Questionnaire; ETD, estimated treatment difference; VAS, visual analogue scale.

Body weight and composition

- For subjects who received oral semaglutide in treatment period 1, a rebound in body weight was observed during the wash-out period.
- Weight loss with oral semaglutide was due to a **reduction in whole body fat mass**; whole body lean mass was not substantially affected (Table 1).

Table 1 Change from baseline in body composition at the end of treatment period 1.

	Oral semaglutide 14 mg		Placebo	
	N	Mean ± SD	N	Mean ± SD
Whole body fat mass, kg	7	–2.7 ± 2.5	7	–1.2 ± 3.0
Whole body lean mass, kg	7	–0.2 ± 2.3	7	0.0 ± 1.1
Fat percentage, %	7	–2.0 ± 2.0	7	–0.9 ± 2.4
Body weight, kg	7	–2.9 ± 4.2	7	–1.2 ± 3.1

SD, standard deviation.

Safety

- **More AEs** were reported in subjects when receiving oral semaglutide vs placebo (93 events in 14 [93.3%] subjects vs 51 events in 13 [92.9%] subjects, respectively).
- Typical of the GLP-1 receptor agonist class, **gastrointestinal AEs** were most frequently reported.
- Most AEs during oral semaglutide treatment were considered possibly related to trial product.
- There was **one serious AE** (acute myocardial infarction) during oral semaglutide treatment, considered possibly related to trial product and leading to withdrawal. This serious AE was severe; all other AEs reported were of mild or moderate severity. **No deaths** were reported.

Conclusions

***Ad libitum* energy intake** throughout the day was **lower** during treatment with oral semaglutide vs placebo, resulting in a **greater reduction in body weight** after 12 weeks of treatment, mainly driven by a reduction in whole body fat mass.

Hunger was reduced, and satiety and fullness increased during treatment with oral semaglutide vs placebo after a fat-rich breakfast, whereas there was no difference in appetite after a standard breakfast.

Control of eating was improved during treatment with oral semaglutide compared with placebo. This did not appear to be related to increased food aversion.

This trial was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT02773381).
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