Weight loss and nausea in patients receiving semaglutide for the treatment of obesity

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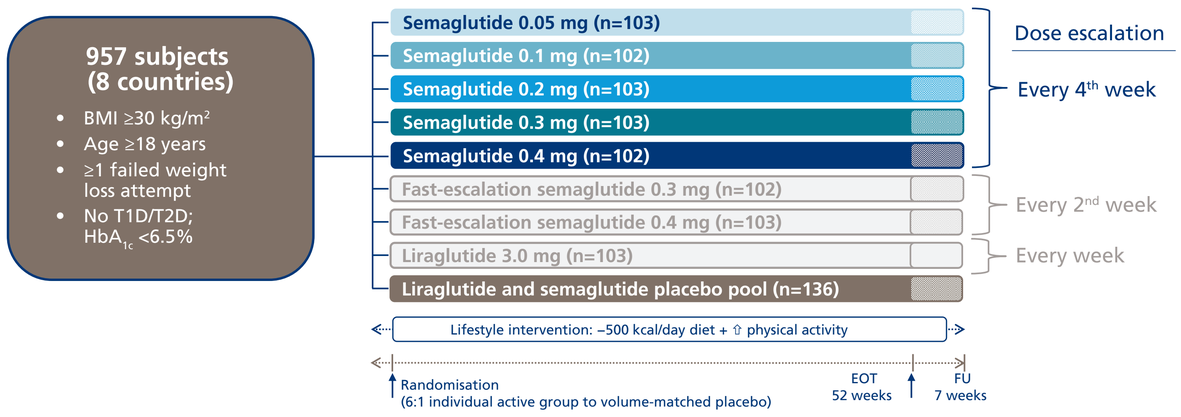
Background

- Dose-dependent nausea is a known potential side effect of glucagon-like peptide 1 (GLP-1) receptor agonists used for the treatment of type 2 diabetes (T2D) or obesity.[1]
- The GLP-1 analogue liraglutide is indicated both for T2D at doses of 1.2 or 1.8 mg/day and for weight management at a higher dose of 3.0 mg/day. Previous data for liraglutide suggested that those who experienced nausea or vomiting at the 3.0 mg dose experienced greater weight loss than those who did not.[2]
- Semaglutide is a GLP-1 analogue indicated for T2D at doses up to 1.0 mg/week, and is under clinical development for weight management at higher doses.
- Previous pooled data from studies of semaglutide in T2D have shown only a minor contribution of nausea or vomiting to the weight loss observed at T2D dosing levels.[3]
- In a recent phase 2 study (NCT02453711) of semaglutide for weight management,[4] high levels of dose-dependent weight loss were observed over 1 year of treatment with semaglutide 0.05–0.4 mg/day, with dose-related gastrointestinal (GI) symptoms—chiefly nausea—as the most common adverse event.
- The association between weight loss and nausea on semaglutide treatment for weight management was assessed in an exploratory post hoc analysis from this phase 2 study.

Methods

- This was a multinational, double-blind, placebo- and active-controlled (liraglutide 3.0 mg daily), phase 2, dose-finding randomised clinical trial investigating the 1-year safety and efficacy of 0.05, 0.1, 0.2, 0.3 or 0.4 mg subcutaneous once-daily doses of semaglutide in combination with diet and lifestyle intervention for treatment of people with obesity (body mass index ≥30 kg/m^2) without diabetes (NCT02453711; **Figure 1**).
  - The study design and subject characteristics are fully described elsewhere.[4]
- Semaglutide was initiated at 0.05 mg/day and escalated to the next dosing level every 4 weeks until reaching the final randomised dose. Doses of 0.3 or 0.4 mg/day were also escalated on an exploratory 2-weekly schedule.
- Each dosing arm (semaglutide or liraglutide) was randomised 6:1 to receive active drug or a placebo matched for injection volume and escalation schedule. All placebo groups were pooled for analysis.
- The incidence of nausea was assessed by treatment group and study visit using observed data.
- Percentage weight change from baseline was estimated for each treatment group by study visit according to the prespecified primary analytical methodology for the study, using an analysis of covariance (ANCOVA) model with treatment, region and sex as factors and baseline body weight as covariate.
  - All available data were used in the ANCOVA model. For the end-of-treatment visit at week 52, data included both on-treatment subjects and those with early discontinuation for any reason who subsequently returned for weight assessment at week 52.
  - For visits prior to week 52, available data were for those on treatment only.
  - Missing data at each time point assessed were imputed from the placebo pool using a jump-to-reference multiple imputation approach.
- ANCOVA-estimated weight changes at week 52 were assessed separately in those who did or did not experience nausea and/or vomiting on treatment.
- Data are presented for the five semaglutide groups on 4-weekly escalation and the pooled placebo group only.
- This was a post hoc exploratory assessment using descriptive statistics. Hypothesis testing was not performed.

Figure 1: Trial design (NCT02453711)



BMI, body mass index; EOT, end of treatment; FU, follow-up; T1D/T2D, type 1 or type 2 diabetes.

Results

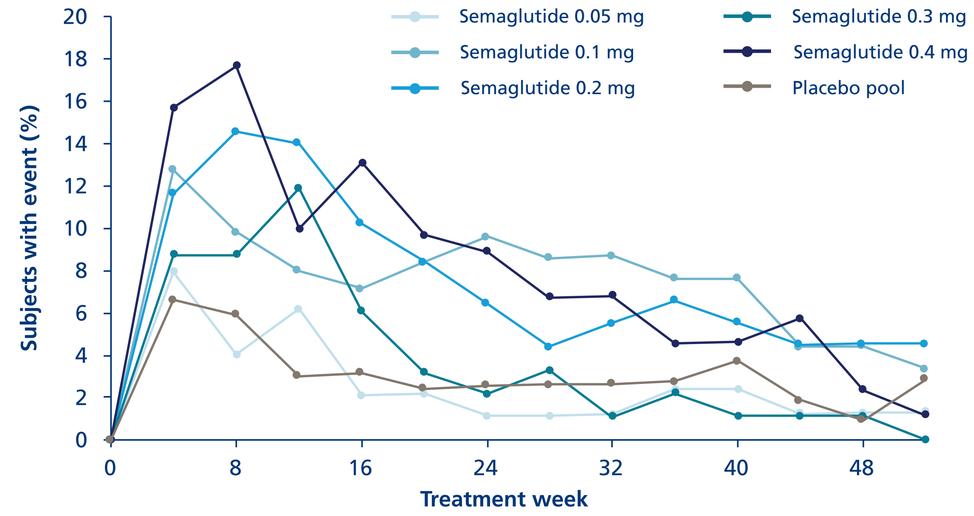
- Of 957 subjects randomised in the study, data are presented for 649 who received semaglutide on a 4-weekly escalation schedule, or placebo (**Figure 1**).
- The overall incidence of GI adverse events was higher on semaglutide (62–82%) compared with placebo (38%), and GI events were most frequent at the highest semaglutide dose (**Table 1**).
  - The majority of events in each treatment group were of mild or moderate severity.
- Discontinuation of treatment for GI events was greater on semaglutide at all doses compared with placebo, but was low across all treatment arms (**Table 1**).
- The most common GI-related adverse event in all treatment arms was nausea (31–48% on semaglutide vs 18% on placebo).
- Nausea episodes were most frequent during the period of dose escalation, with peak levels in all treatment groups seen between weeks 4 and 12 that were dose proportional. Thereafter, the incidence rate declined to broadly comparable levels across treatment groups by week 52 (**Figure 2**).
- By contrast, ANCOVA-estimated weight loss on semaglutide remained dose proportional across all visits and was ongoing at week 52, particularly at the highest dose of 0.4 mg/day (**Figure 3**).
- Overall weight loss was comparable across semaglutide dosing groups between those with and without nausea or vomiting on treatment (**Figure 4**).

Table 1: Overview of gastrointestinal adverse events on treatment

n (%)	0.05 mg (n=103)	0.1 mg (n=102)	0.2 mg (n=103)	0.3 mg (n=103)	0.4 mg (n=102)	Placebo pool (n=136)
Any GI AE	64 (62)	72 (71)	72 (70)	72 (70)	84 (82)	52 (38)
Nausea (overall, any severity)*	32 (31)	42 (41)	45 (44)	43 (42)	49 (48)	24 (18)
Mild	28 (27)	32 (31)	37 (36)	40 (39)	43 (42)	22 (16)
Moderate	4 (4)	14 (14)	15 (15)	8 (8)	12 (12)	4 (3)
Severe	2 (2)	2 (2)	0	1 (1)	4 (4)	0
Vomiting (overall, any severity)*	8 (8)	18 (18)	24 (23)	11 (11)	18 (18)	6 (4)
Mild	5 (5)	10 (10)	16 (16)	8 (8)	12 (12)	4 (3)
Moderate	2 (2)	9 (9)	11 (11)	4 (4)	9 (9)	2 (1)
Severe	1 (1)	2 (2)	1 (1)	1 (1)	1 (1)	0
Discontinuation for any GI AE	6 (6)	5 (5)	3 (3)	4 (4)	13 (13)	2 (1)

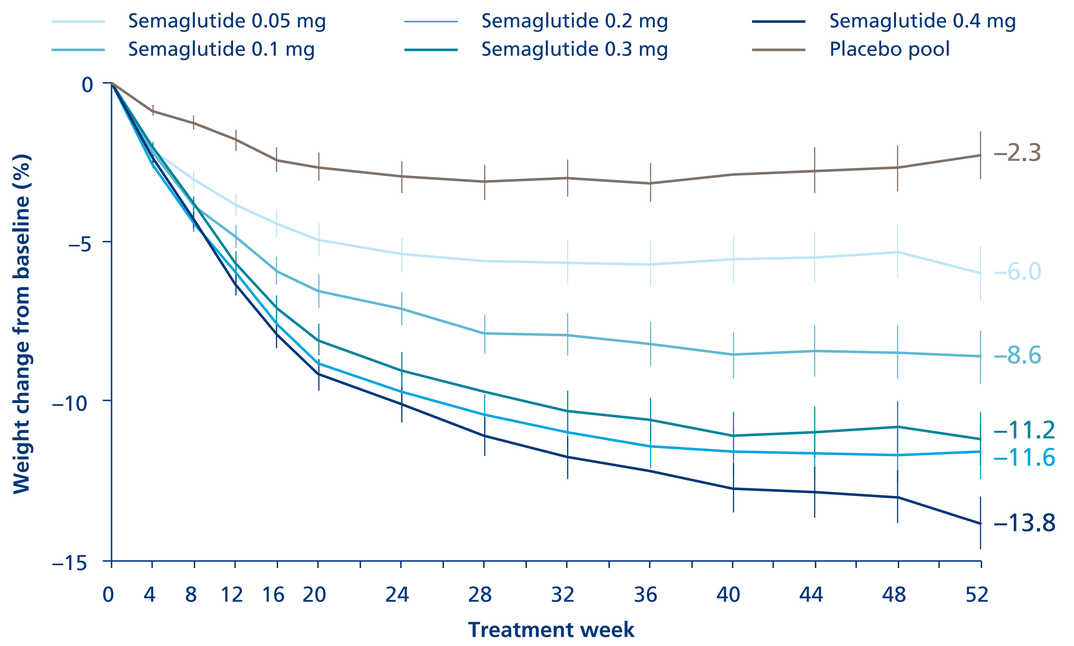
*Subjects with >1 event of differing severities are counted once overall and once for each severity that applies.
AE, adverse event; GI, gastrointestinal.

Figure 2: Incidence of nausea by treatment group and week



Semaglutide 0.05 mg	n= 103	99	96	88	84	77
Semaglutide 0.1 mg	n= 102	102	98	93	92	89
Semaglutide 0.2 mg	n= 103	103	98	91	90	88
Semaglutide 0.3 mg	n= 103	103	99	92	90	87
Semaglutide 0.4 mg	n= 102	102	99	89	87	85
Placebo pool	n= 136	135	127	115	107	105

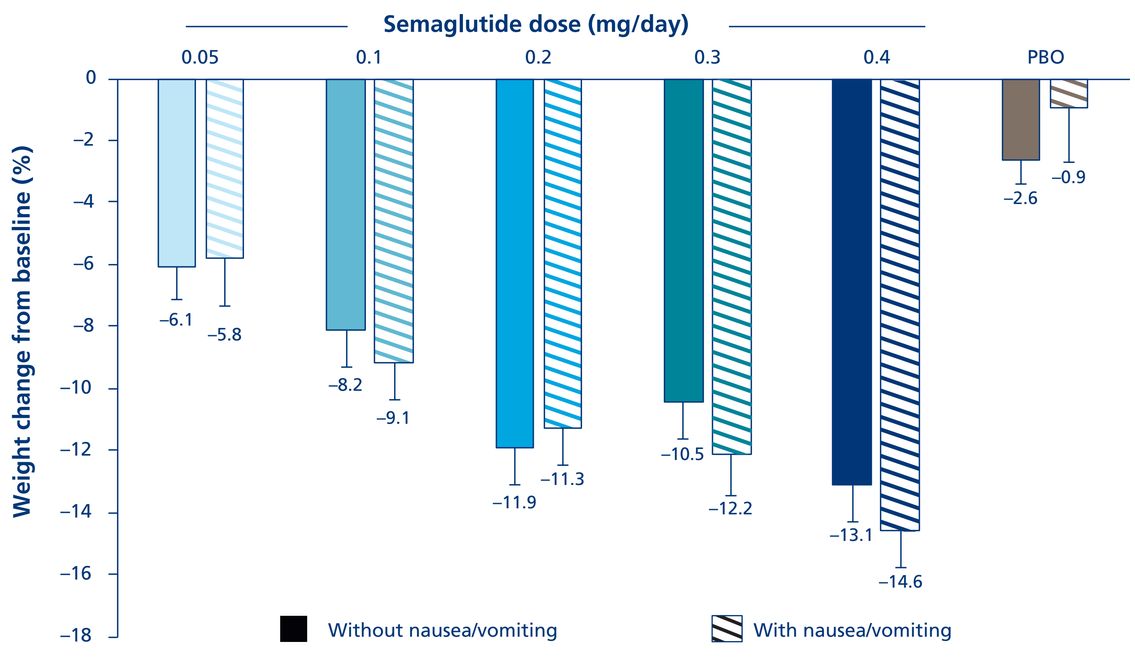
Figure 3: Estimated percentage change from baseline in body weight by treatment group and week



Estimated mean data (ANCOVA, J2RMI for missing data) ± standard error of the mean.
ANCOVA, analysis of covariance; J2RMI, jump-to-reference multiple imputation.

Key result

Figure 4: Estimated percentage change in body weight from baseline to week 52 in those with or without at least one episode of nausea or vomiting on treatment



Mean estimated (ANCOVA, J2RMI for missing data) change from baseline + standard error of the mean.
ANCOVA, analysis of covariance; J2RMI, jump-to-reference multiple imputation; PBO, pooled placebo group.

Conclusions

- Nausea was common among people receiving once-daily subcutaneous semaglutide for weight management, but was of predominantly mild severity and mostly occurred early on treatment during semaglutide dose escalation. Discontinuation of treatment for GI events was uncommon but highest at the highest dose of semaglutide.
- There was no obvious temporal association between nausea and weight loss: most nausea occurred within the first few weeks then declined, while weight loss remained ongoing through end of treatment at week 52.
- Dose-dependent, ANCOVA-estimated weight loss at week 52 was comparable for each semaglutide dose between those who did and those who did not experience nausea.

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References:
(**1**) Bettge K, et al. Diabetes Obes Metab 2017;19:336–47.
(**2**) Lean MEJ, et al. Int J Obes (Lond) 2014;38:689–97.
(**3**) Ahrén B, et al. Diabetes Obes Metab 2018;20:2210–9.
(**4**) O'Neil PM, et al. Lancet 2018;392:637–49.