HbA_{1c} changes in subjects with obesity without diabetes receiving semaglutide for weight management

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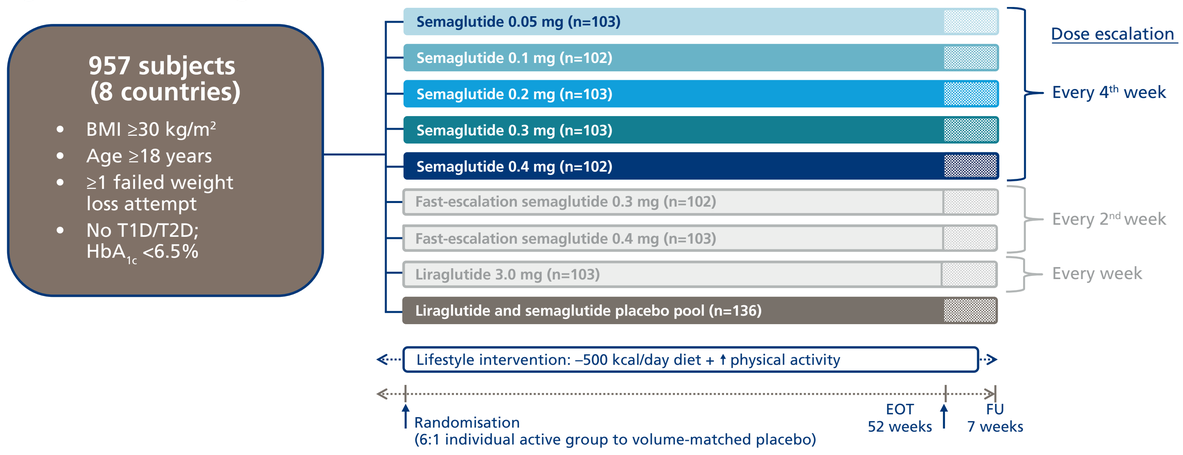
Background

- Elevated HbA_{1c} within the prediabetes range (5.7–6.5%) is common in people with obesity and is associated with an increased risk of developing type 2 diabetes (T2D).[1]
- Semaglutide, a human glucagon-like peptide 1 (GLP-1) analogue, was recently approved at subcutaneous doses up to 1.0 mg weekly to treat T2D. It is currently being investigated at higher doses for weight management.
- A recent phase 2 trial (NCT02453711) in people with obesity without diabetes showed mean weight changes of –6.0% to –13.8% of baseline body weight in those who received once-daily subcutaneous semaglutide for 52 weeks at final doses between 0.05 mg and 0.4 mg/day, compared with –2.3% on placebo.[2]
  - » Treatment effects for HbA_{1c} (for which mean changes in semaglutide dose groups ranged from –0.13% to –0.29%), fasting plasma glucose (–0.29 mmol/L in the 0.05 mg group to –0.43 mmol/L in the 0.4 mg group) and body weight appeared to be dose-dependent.
- In this post hoc analysis we aimed to evaluate the effect of various doses of semaglutide or placebo in individuals with normal and elevated HbA_{1c} (within the prediabetes range) at baseline.

Methods

- The design of this phase 2 randomised, double-blind, active- and placebo-controlled trial is shown in **Figure 1**.
- Further details of the study design have been reported elsewhere.[2]

Figure 1: Trial design (NCT02453711)



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

- Adults with obesity (body mass index ≥30 kg/m²) and without T2D (screening HbA_{1c} <6.5%) were enrolled.
- At each dose, individuals were randomised to either active treatment or placebo (6:1) alongside site-specific, standard-of-care counselling on diet and physical activity for weight loss; all placebo groups were pooled for analysis.
- Semaglutide dose was escalated sequentially every 4 weeks (q4w), or every 2 weeks (q2w; exploratory only).
  - » As the current analysis was intended to explore whether the effects of semaglutide on HbA_{1c} were dose proportional, data from the liraglutide 3.0 mg/day arm and the exploratory analyses of higher doses of q2w semaglutide were not included.
- HbA_{1c} was categorised at baseline into normal (<5.7%) or elevated (≥5.7%) subgroups, and assessed at week 52 (end of treatment) in those still on randomised treatment. Body weight at week 52 was assessed both in those still on treatment and those off treatment who returned for a week 52 assessment.
- Progression from normal to elevated HbA_{1c}, and vice versa, were summarised by treatment group using observed data.
- Treatment differences vs placebo for absolute changes from baseline in HbA_{1c} and percentage body weight were estimated overall and by baseline HbA_{1c} subgroup using an analysis of covariance with treatment, region and sex as factors, and baseline HbA_{1c} or body weight as covariate. Missing data at week 52 were imputed from the placebo group using a jump-to-reference multiple imputation (J2RMI) approach; data from this analysis are presented here.

Results

Baseline characteristics and disposition

- 649 individuals were randomised to receive semaglutide on a q4w schedule (n=513) or placebo (n=136).
  - » At baseline, 431 (66%) had normal HbA_{1c} and 217 (33%) had elevated HbA_{1c} within the prediabetes range.
  - » One individual in the 0.1 mg semaglutide group had missing baseline HbA_{1c} data.
  - » Of the 648 individuals with HbA_{1c} data available at baseline, 524 (81%) individuals on treatment had HbA_{1c} data available at week 52.
- Baseline characteristics according to treatment group are presented in **Table 1**.

Table 1: Baseline characteristics for individuals who received semaglutide escalated on a q4w schedule or placebo

Characteristic	Placebo (N=136)	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)
Age, years	46 (20–76)	47 (18–73)	45 (21–72)	44 (22–71)	47 (20–77)	48 (20–74)
Male, n (%)	48 (35)	36 (35)	36 (35)	37 (36)	37 (36)	36 (35)
BMI, kg/m²	40 (31–62)	39 (30–59)	40 (30–74)	40 (30–62)	40 (30–62)	40 (30–80)
Body weight, kg	114.19 (77–213)	111.29 (73–184)	111.31 (76–176)	114.49 (75–199)	111.51 (79–196)	113.20 (75–244)
HbA_{1c}, %	5.54 (4.8–6.5)	5.51 (4.7–6.4)	5.45 (4.3–6.4)	5.41 (4.2–6.2)	5.51 (4.3–7.0)	5.47 (4.4–6.6)
FPG, mmol/L	5.50 (4.2–8.0)	5.48 (4.2–7.3)	5.48 (4.3–7.0)	5.41 (4.2–11.1)	5.48 (4.3–8.5)	5.40 (4.3–8.9)

All characteristics are mean (range) unless otherwise indicated. The majority of individuals completed 52 weeks of treatment: 103 (76%) in the placebo arm, 77 (75%) in the 0.05 mg arm, 88 (86%) in the 0.1 mg arm, 87 (85%) in the 0.2 mg arm, 88 (85%) in the 0.3 mg arm and 82 (80%) in the 0.4 mg arm.
BMI, body mass index; FPG, fasting plasma glucose; q4w, escalated every 4 weeks.

Changes in HbA_{1c}

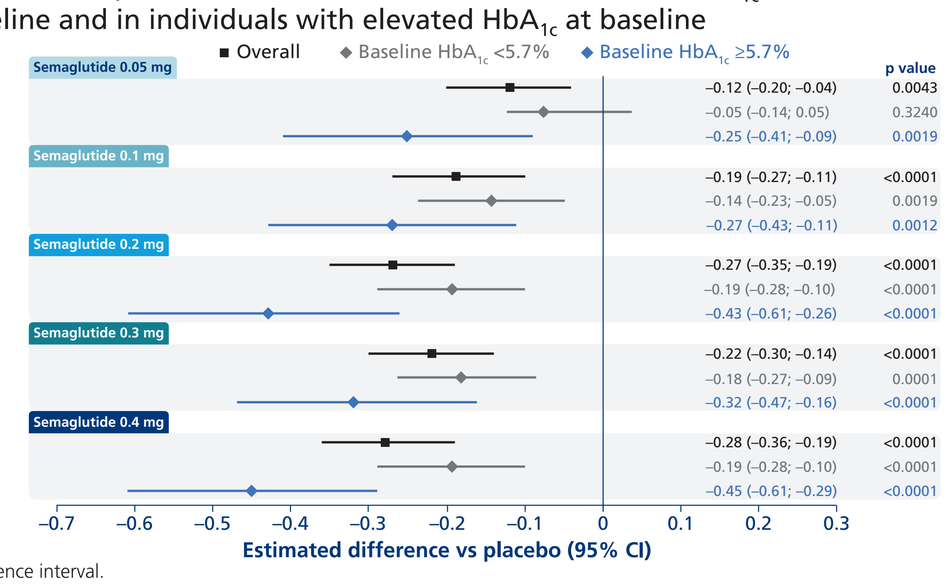
- Larger changes in HbA_{1c} were observed in the semaglutide arms, compared with placebo (**Figure 2**):
  - » Individuals who received semaglutide experienced a decrease in HbA_{1c} over time. These effects appeared to be dose related in both baseline HbA_{1c} groups.
  - » This relationship was more pronounced for individuals with prediabetes range HbA_{1c} at baseline.

Changes in body weight by baseline HbA_{1c}

- Mean estimated percentage body weight changes, for semaglutide vs placebo, were dose related and ranged between –3.70% (95% confidence interval [CI] –6.55; –0.85) and –11.55% (95% CI –14.38; –8.72), respectively (**Figure 3**).
- There was no observed difference in weight loss between individuals with normal HbA_{1c} at baseline and those with elevated HbA_{1c} at baseline; the observed weight loss effect was equally strong regardless of HbA_{1c} status at baseline.

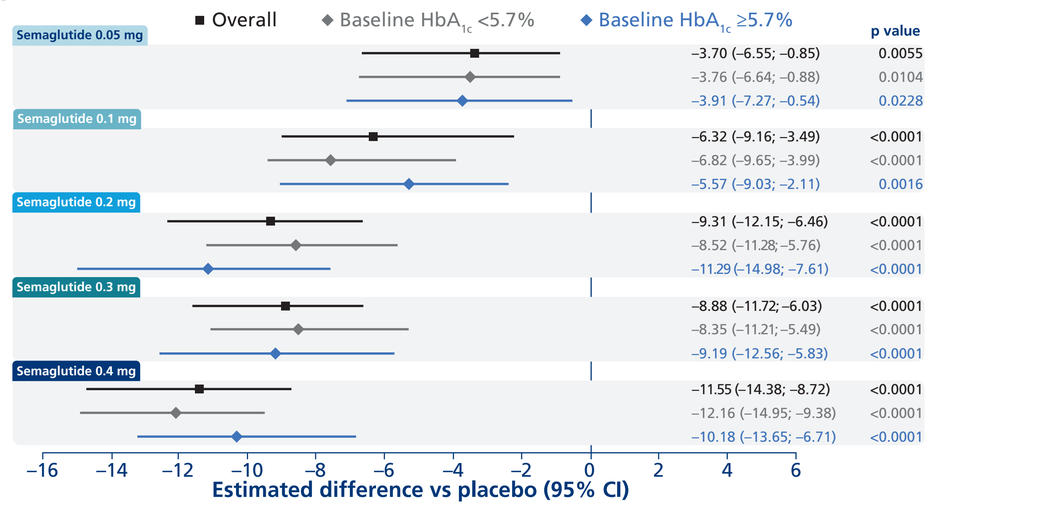
Key result

Figure 2: Change in HbA_{1c} levels in the semaglutide dose groups compared with placebo, overall, in individuals with normal HbA_{1c} at baseline and in individuals with elevated HbA_{1c} at baseline



CI, confidence interval.

Figure 3: Change in body weight in the semaglutide dose groups compared with placebo, overall, in individuals with normal HbA_{1c} at baseline and in individuals with elevated HbA_{1c} at baseline

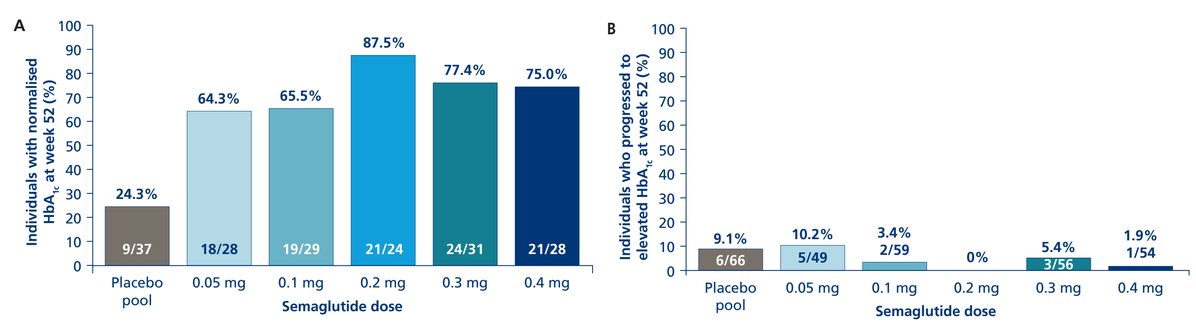


CI, confidence interval.

Changes in HbA_{1c} status

- Few individuals across treatment groups progressed from normal HbA_{1c} to elevated HbA_{1c} during the 52 weeks (**Figure 4**).
- A majority of individuals who received semaglutide (64.3–87.5%) improved HbA_{1c} level from the prediabetes range to the normal range, whereas this was the case for the minority of individuals who received placebo (24.3%).

Figure 4: Individuals who A) improved from elevated HbA_{1c} (prediabetes range) at baseline to normal HbA_{1c} at week 52 and B) deteriorated from normal HbA_{1c} at baseline to elevated HbA_{1c} at week 52



N=total observed at week 52 in the indicated subgroup. Results should be interpreted with caution due to the sample sizes.

Safety and initiation of antidiabetes medications

- Treatment was generally well tolerated, with no severe or documented symptomatic hypoglycaemic episodes reported in these groups.[2]
- The most common adverse events were gastrointestinal events, primarily nausea, which was dose related, as seen previously for GLP-1 receptor agonists.[2]
- Four individuals (0.6%) initiated a drug for a primary indication of "diabetes", "prediabetes" or "impaired glucose tolerance" during the study.
  - » These included three in the placebo pool (two who received metformin and one who received metformin and insulin glargine) and one in the 0.4 mg semaglutide arm, who received metformin.
- Medications which can be used to treat T2D were also initiated with the intention of treating obesity (n=4 who each received liraglutide, two of whom were in the placebo pool, one had discontinued 0.1 mg semaglutide and one was receiving 0.05 mg semaglutide) and polycystic ovarian syndrome (n=1 in the 0.05 mg semaglutide group, who also received metformin).

Conclusion

- Those randomised to semaglutide experienced a greater decrease in HbA_{1c} compared with placebo, which appeared to be dose related.
  - » The dose relationship was more pronounced for individuals with elevated HbA_{1c} at baseline, compared with those who had normal HbA_{1c} at baseline.
- Weight loss was dose related and appeared to be similar in individuals with normal HbA_{1c} and elevated HbA_{1c} at baseline.
  - » About a third of individuals had elevated baseline HbA_{1c}, and most of those treated with semaglutide achieved normal levels by week 52.
- The effect of semaglutide on HbA_{1c} in patients without diabetes will be investigated further as part of the phase 3 trial programme.

This trial was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT02453711).
Presenter O Mosenzon reports grants and other financial support from Novo Nordisk and Bristol-Myers Squibb, and other financial support from Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, Janssen, Novartis and AstraZeneca.
The authors acknowledge the medical writing assistance of John Munro of Articulate Science Ltd.
Presented at the 26th European Congress on Obesity, 28 April–01 May 2019, Glasgow, Scotland.

References: (**1**) Tabák AG, et al. Lancet 2012;379:2279–90.
(**2**) O'Neil PM, et al. Lancet 2018;392:637–49.