Changes in SF-36 scores among subjects receiving semaglutide for treatment of obesity

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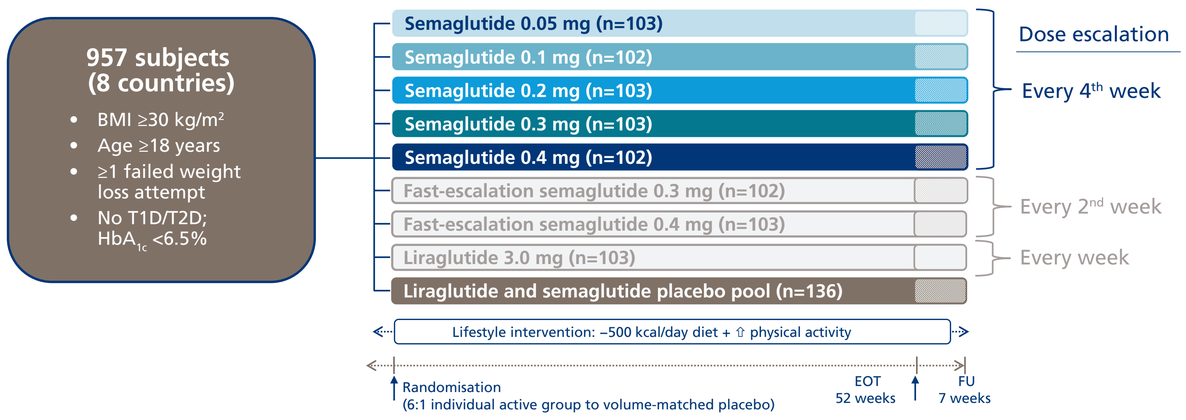
Background

- For people with obesity, improvement of physical and mental functioning is an important goal, which can most easily be measured by self-assessment.[1]
  - » Improved functioning may also aid in weight management.
- Semaglutide is a glucagon-like peptide-1 analogue which is indicated in type 2 diabetes at weekly doses of 0.5–1.0 mg, and is under clinical development for weight management at a higher dose.
- In a recent phase 2 study (NCT02453711) of semaglutide for weight management,[2] dose-dependent weight changes of –6.0% to –13.8% were observed in subjects with obesity 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% for those who received placebo.
- In order to assess the effect of various doses of semaglutide on the physical and mental functioning of subjects in this phase 2 study, patient-reported outcome measures were administered in the form of questionnaires to a subset of English-speaking US subjects in the trial.
- Here, we present the results of a post hoc analysis of the physical functioning (PF) and mental component summary (MCS) scores of the 36-Item Short Form survey (SF-36v2®; acute)[3] recorded by subjects in the study.

Methods

- This was a randomised, double-blind, placebo- and active-controlled, phase 2 dose-finding trial, designed to investigate the safety and efficacy of 0.05, 0.1, 0.2, 0.3 or 0.4 mg subcutaneous semaglutide administered once daily for 52 weeks, in combination with diet and lifestyle counselling for weight management in people with obesity, without diabetes (NCT02453711).[2]
  - » Semaglutide was initiated at 0.05 mg/day in each dose group, then incrementally escalated to final dose every 4 weeks (q4w).
  - » Each dosing group (semaglutide and liraglutide control) was randomised 6:1 to receive active drug or an injection volume-matched placebo on the same dosing schedule. All placebo groups were pooled for analysis.
  - » Two exploratory groups, which were dose escalated every 2 weeks, and the active control group (liraglutide 3.0 mg/day), are not presented here.
  - » The trial design is illustrated in **Figure 1**; details of the design of the trial have been reported in greater detail elsewhere.[2]
- For the primary analysis, percentage weight change from baseline was estimated for each treatment group at each study visit using an analysis of covariance (ANCOVA) model with treatment, region and sex as factors and baseline body weight as covariate.
  - » For the end-of-treatment visit at week 52, data included both subjects who were on treatment and those who discontinued for any reason and subsequently returned for weight assessment at week 52.
  - » Missing data were imputed from the placebo pool using a jump-to-reference multiple imputation (J2RMI) approach.
- The SF-36v2® questionnaire was administered at baseline and week 52 to a subset of English-speaking subjects who had received treatment at centres in the United States.
- Estimated treatment differences vs placebo for change from baseline to week 52 in PF and MCS scores and associated 95% confidence intervals were calculated for each dosing group using the same ANCOVA model (baseline score as covariate), with J2RMI as for the primary weight analysis.

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

Baseline characteristics and disposition

- Baseline characteristics were generally balanced across treatment groups (**Table 1**).
- Overall, body weight data were available at week 52 for 92% of the trial subjects in the six treatment groups discussed here, of whom 81% were on treatment and 12% were off treatment at week 52 (**Table 2**).

Table 1: Baseline characteristics

Baseline characteristics	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 (N=136)
Age, years	47 (18–73)	45 (21–72)	44 (22–71)	47 (20–77)	48 (20–74)	46 (20–76)
Male, n (%)	36 (35.0)	36 (35.3)	37 (35.9)	37 (35.9)	36 (35.3)	48 (35.3)
White race, n (%)	88 (85.4)	76 (74.5)	72 (69.9)	74 (71.8)	71 (69.6)	97 (71.3)
Weight, kg	111 (73–184)	111 (76–176)	114 (75–199)	112 (79–196)	113 (75–244)	114 (77–213)
Body mass index, kg/m²	39 (30–59)	40 (30–74)	40 (30–62)	40 (30–62)	40 (30–80)	40 (31–62)
Waist circumference, cm	117 (88–160)	117 (85–155)	119 (91–167)	118 (87–159)	119 (83–187)	119 (92–180)

All characteristics are mean (range) unless otherwise indicated.

Table 2: Overall disposition at week 52

Overall disposition	
Randomised and exposed, n	649
On drug at week 52, n (%)	525 (81)
Discontinued trial drug, n (%)	124 (19)
• Discontinued and retrieved at week 52	75 (12)
• Discontinued and withdrew	49 (7)
Weight assessment at week 52, n (%)	600 (92)

- 35% of subjects in the semaglutide q4w groups and 35% of subjects in the placebo group completed the SF-36v2® questionnaire at baseline (**Table 3**).

Table 3: Baseline SF-36v2® scores

SF-36v2® category, mean (SD)	0.05 mg (N=38)	0.1 mg (N=31)	0.2 mg (N=31)	0.3 mg (N=36)	0.4 mg (N=43)	Placebo (N=48)
Mental component summary score	54.4 (9.3)	56.6 (4.6)	55.6 (6.6)	55.7 (8.0)	53.1 (7.4)	54.9 (7.2)
Physical functioning score	43.7 (10.0)	46.6 (9.9)	46.5 (8.1)	47.4 (8.5)	44.9 (9.2)	47.7 (7.3)

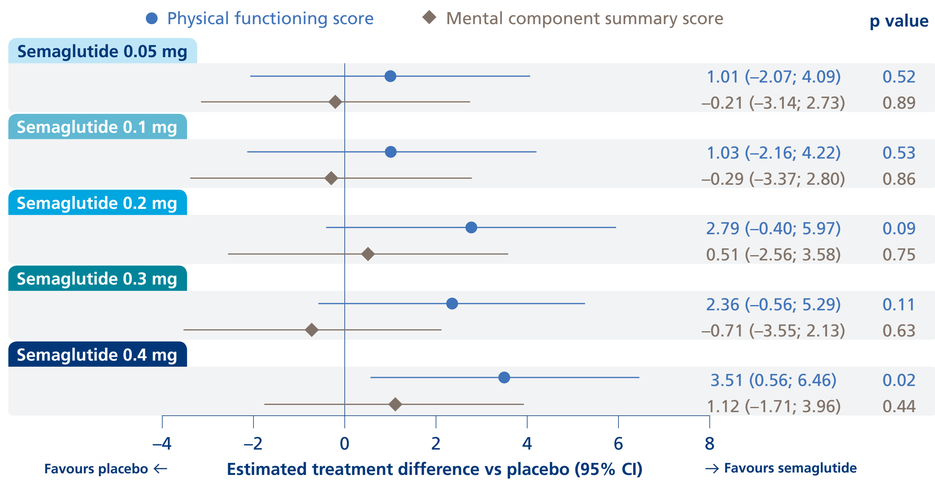
SD, standard deviation; SF-36v2®, 36-Item Short Form survey.

Relationship between semaglutide dose and patient-reported outcomes

- Of the 227 subjects who completed the SF-36v2® at baseline, 171 (75%) also completed the questionnaire at week 52.
- Estimated treatment differences vs placebo for the PF score appeared to increase with rising semaglutide dose (**Figure 2**).
  - » At the highest semaglutide dose of 0.4 mg/day, the treatment difference was statistically significant (p=0.02) and exceeded the minimum clinically important difference defined in the SF-36v2® manual (>3.0 points).[4]
- No significant treatment differences or dose-related trends were observed for the MCS score (**Figure 2**).

Figure 2: Change from baseline to week 52 in SF-36v2® physical functioning score and mental component summary score in the semaglutide dose groups, compared with placebo

Key result

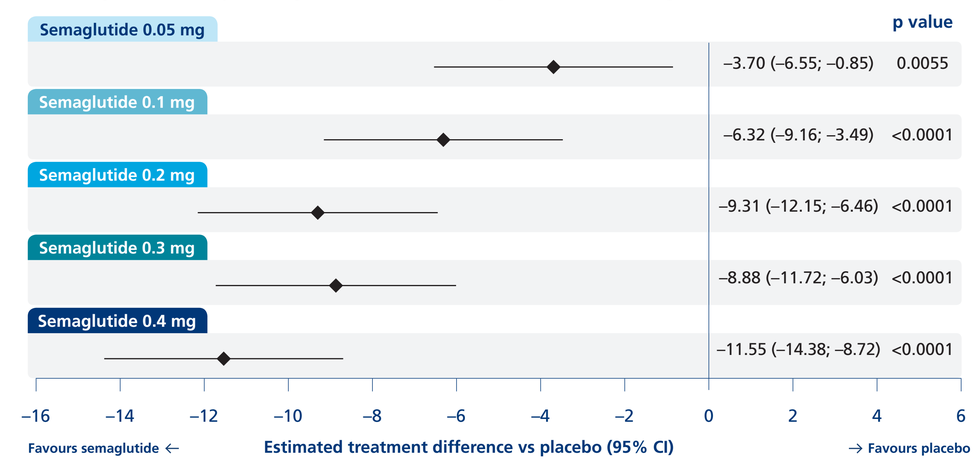


At week 52, 37 subjects in the placebo group, 27 receiving 0.05 mg semaglutide, 23 in the 0.1 mg group, 20 in the 0.2 mg group, 31 in the 0.3 mg group, and 33 in the 0.4 mg group completed the SF-36v2® questionnaire. Results should be interpreted with caution due to the sample sizes.
CI, confidence interval; SF-36v2®, 36-Item Short Form survey.

Weight loss

- Overall dose-related estimated weight changes on semaglutide ranged from –6.0% of baseline at 0.05 mg/day to –13.8% at 0.4 mg/day, vs –2.3% on placebo (N=649; **Figure 3**).

Figure 3: Change in body weight in the semaglutide dose groups compared with placebo

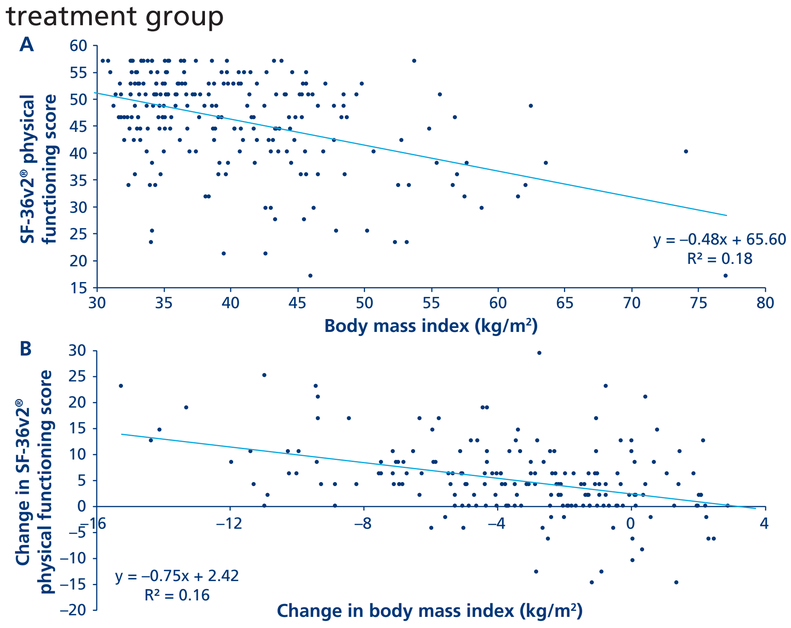


Confidence intervals and p values adjusted for multiple comparisons (Dunnett's method).
CI, confidence interval.

Relationship between baseline weight, weight change and PF

- There was an inverse correlation between body mass index (BMI) and PF score at baseline, with subjects who had a higher BMI tending to have lower PF (**Figure 4A**).
- A similar correlation was noted at week 52 between change in BMI and change in PF score from baseline, with greater improvement in PF score associated with greater reductions in BMI (**Figure 4B**).
- The slopes of the regression lines for the association between change in BMI and change in PF score were broadly comparable across the five semaglutide dosing groups and placebo pool (data not shown).

Figure 4: Scatter plot of (A) BMI vs SF-36v2® physical functioning score at baseline and (B) change in BMI vs change in SF-36v2® physical functioning score from baseline to week 52, irrespective of treatment group



BMI, body mass index; SF-36v2®, 36-Item Short Form survey.

Conclusions

- In this study of semaglutide for weight management in people with obesity, without diabetes, semaglutide dose-related improvements in the PF domain of SF-36v2® were noted at end of treatment. At the highest dose of 0.4 mg/day, this improvement was statistically significant and exceeded the minimum clinically important difference (>3.0 points).[4]
- There was a baseline correlation between higher BMI and poorer PF, as assessed by the SF-36v2® instrument.
- This improvement in PF score appeared to be driven by weight loss, with a correlation observed between PF score change and BMI change from baseline at week 52 that was broadly similar irrespective of treatment group.

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