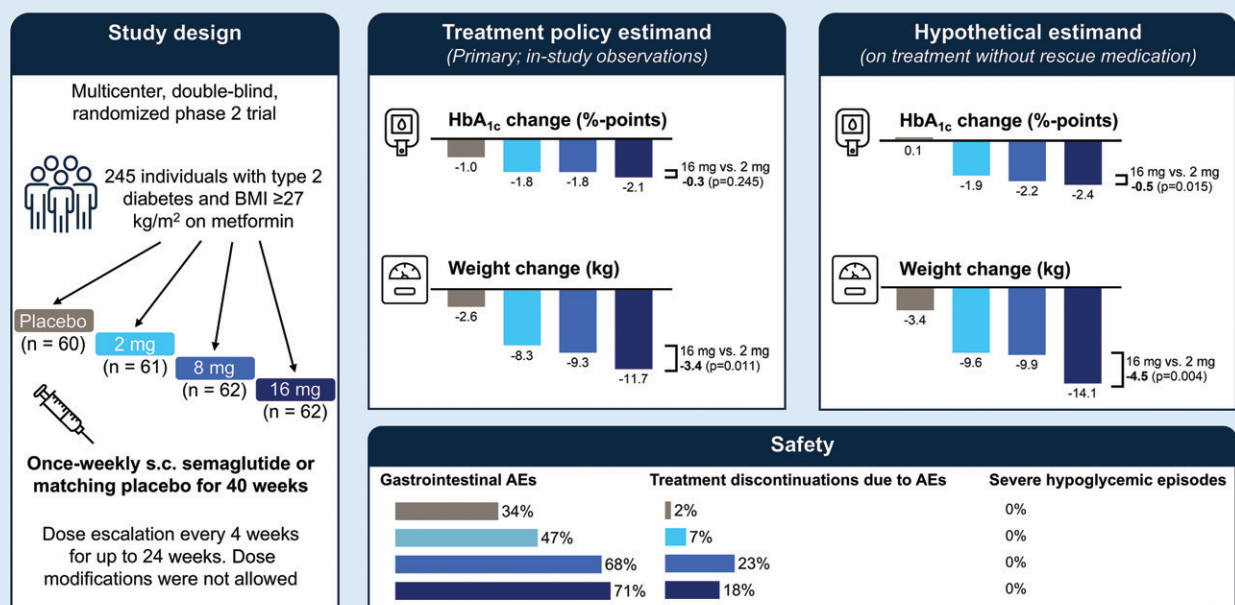


High-Dose Semaglutide (Up to 16 mg) in People With Type 2 Diabetes and Overweight or Obesity: A Randomized, Placebo-Controlled, Phase 2 Trial

Vanita R. Aroda, Nils B. Jørgensen, Bharath Kumar, Ildiko Lingvay, Anne Sofie Laulund, and John B. Buse, for the trial investigators

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Conclusion: In people with type 2 diabetes and overweight or obesity, higher weekly semaglutide doses (8 mg and 16 mg s.c.), exceeding the approved 2 mg, provided modest additional glycemic control. The higher doses led to slightly more weight loss; however, gastrointestinal side effects were also more prevalent compared with currently approved dose of 2 mg.

ARTICLE HIGHLIGHTS

• Why did we undertake this study?

Studies demonstrate a dose-response relationship for glucagon-like peptide 1 receptor agonists on glycemic and weight loss efficacy, even within narrow dose ranges. As managing gastrointestinal tolerability of semaglutide has improved, it is relevant to explore whether exceeding the approved dose yields greater efficacy.

• What is the specific question(s) we wanted to answer?

Do higher semaglutide doses (up to 16 mg/week) have additional glucose-lowering and weight loss effects in people with type 2 diabetes and overweight or obesity?

• What did we find?

Higher semaglutide doses showed little additional glucose-lowering effect, with additional weight loss, at the expense of poorer tolerability.

• What are the implications of our findings?

Based on data from this study, use of higher semaglutide doses (2 mg/week) for glycemic control in type 2 diabetes is not supported.



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Vanita R. Aroda,¹ Nils B. Jørgensen,² Bharath Kumar,³ Ildiko Lingvay,⁴ Anne Sofie Laulund,² and John B. Buse,⁵ for the trial investigators*

OBJECTIVE

Studies have demonstrated dose-dependent efficacy of glucagon-like peptide 1 receptor agonists for glycemic control and body weight. The aim of this trial was to characterize the dose-dependent effects of semaglutide (up to 16 mg/week) in people with type 2 diabetes and overweight or obesity.

RESEARCH DESIGN AND METHODS

In this parallel-group, participant- and investigator-blinded, phase 2 trial, 245 individuals with type 2 diabetes and BMI ≥ 27 kg/m² on metformin were randomized to weekly semaglutide (2, 8, or 16 mg s.c.) or placebo for 40 weeks. Doses were escalated every 4 weeks, followed by a maintenance period. Dose modifications were not allowed. Primary and secondary efficacy end points included change from baseline to week 40 in HbA_{1c} and body weight, respectively.

RESULTS

Estimated treatment difference between 16 and 2 mg was -0.3 percentage points (%-points) (95% CI -0.7 to 0.2 ; $P = 0.245$) for HbA_{1c} change and -3.4 kg (-6.0 to -0.8 ; $P = 0.011$) for weight change for the treatment policy estimand and -0.5% -points (-1.0 to -0.1 ; $P = 0.015$) and -4.5 kg (-7.6 to -1.4 ; $P = 0.004$), respectively, for the hypothetical estimand. Dose-response modeling confirmed these findings. Treatment-emergent adverse events (AEs) and treatment discontinuations due to AEs, primarily gastrointestinal, were more frequent in the semaglutide 8 and 16 mg groups than in the 2 mg group. No severe hypoglycemic episodes were reported.

CONCLUSIONS

Higher semaglutide doses for type 2 diabetes and overweight or obesity provide modest additional glucose-lowering effect, with additional weight loss, at the expense of more AEs and treatment discontinuations. A study for evaluating high-dose semaglutide in obesity is currently underway.

Diabetes and overweight or obesity are among the fastest growing global health problems, with prevalences predicted to rise significantly (1–3). Type 2 diabetes and obesity share pathophysiological mechanisms, with obesity often being a primary

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*A list of the trial investigators can be found in the supplementary material online.

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driver (4). Weight loss affects mechanisms that contribute to hyperglycemia (5), and glycemic control is essential for preventing long-term complications of type 2 diabetes (6).

The multidimensional effects of glucagon-like peptide 1 receptor agonists (GLP-1RA) on glycemic control, weight, and cardiovascular risk have resulted in broadened prescribing indications, guideline recommendations, and clinical use. Greater improvements in glycemic control and weight reduction have been demonstrated with semaglutide, a once-weekly injectable GLP-1RA, than with several other GLP-1RA (7–10) and glucose-lowering agents (11,12). Semaglutide has also shown cardiovascular benefits in individuals with established cardiovascular disease, alongside type 2 diabetes or overweight or obesity (13,14).

In early trials, the dose range of semaglutide was limited due to tolerability concerns. Results from the phase 2 program showed that 75% of participants reported gastrointestinal adverse events (AEs) at a dose equivalent to 1.6 mg/week (15), a proportion considered unacceptable, despite the higher efficacy. Consequently, in the phase 3 program, doses of 0.5 and 1.0 mg/week were investigated. However, data from the phase 2 obesity program using slower dose escalations showed additional weight loss benefits of doses up to 2.8 mg/week and a favorable risk-benefit profile for higher doses (16). Furthermore, a pooled analysis of four trials showed that tolerability improved over time, demonstrating that sensitivity to gastrointestinal AEs decreased with prolonged exposure (17). This justified testing higher doses in the SUSTAIN FORTE study (18), which showed similar safety and tolerability of 2.0 and 1.0 mg/week, with 2.0 mg/week providing superior glycemic control and weight reduction.

Given the dose-dependent effects and improved management of tolerability within the GLP-1RA class, the aim of this trial was to characterize the dose-dependent effects of subcutaneous semaglutide at doses up to 16 mg weekly (2 mg, 8 mg, 16 mg, and pooled placebo) in individuals with type 2 diabetes and overweight or obesity (BMI ≥ 27 kg/m²).

RESEARCH DESIGN AND METHODS

Study Design

This randomized, multicenter, double-blind, placebo-controlled, parallel-group phase 2

trial (clinical trial reg. no. NCT05486065, ClinicalTrials.gov) was conducted at 82 sites across Greece, Hungary, Poland, and U.S., with participants enrolled at 75 sites. The protocol was approved by appropriate health authorities according to local regulations and by independent ethics committees or institutional review boards. The trial adhered to the Declaration of Helsinki and the International Council for Harmonisation good clinical practice guidelines. Protocol deviations were unlikely to compromise patient safety significantly and did not affect the trial conclusions.

Participants

Eligible participants were aged 18–64 years with type 2 diabetes (diagnosed ≥ 180 days before screening), HbA_{1c} 7.0%–10.5% (53–91 mmol/mol), and BMI ≥ 27.0 kg/m² and were on a stable dose of metformin for ≥ 90 days before screening. Key exclusion criteria were recent diabetes or obesity medication use, uncontrolled and potentially unstable diabetic retinopathy or maculopathy, renal impairment, recent cardiovascular events or planned revascularization, history of pancreatitis, and expected lifestyle changes. Detailed inclusion and exclusion criteria can be found in Supplementary Material.

Randomization and Masking

Participants were randomized (3:1:3:1:3:1) to semaglutide (2, 8, or 16 mg s.c.) or matching placebo, with stratification by HbA_{1c} at screening ($<8.5\%$, $\geq 8.5\%$). The randomization and treatment allocation were carried out with use of a web-based system. The placebos were volume matched within dose levels. Participants and investigators were blinded to treatment allocation within dose levels.

Procedures

Dosing started at 0.29 mg weekly, with escalation every 4 weeks, and reached 2, 8, or 16 mg over 12, 20, or 24 weeks, respectively, followed by a 16- to 28-week maintenance period (Supplementary Fig. 1). The doses used during the dose escalation period were 0.29, 0.58, 1.06, 2.02, 4.03, 8.06, and 16.13 mg, respectively. The target doses administered were 2.02, 8.06, and 16.13 mg; the dose arms are referred to as 2 mg, 8 mg, and 16 mg throughout this article. Dose modifications (e.g., downtitration, pause in titration) were not allowed. If a participant could not tolerate the dose

(e.g., persistent severe nausea, vomiting or diarrhea events) they were discontinued from the trial. The doses of 2, 8, and 16 mg were chosen to allow differentiation of efficacy and safety at different higher dose levels, and 16 mg was assessed to be both tolerable and safe based on preclinical and clinical data. The maximum treatment duration was 40 weeks, followed by a 9-week follow-up period. Injections could be administered to the abdomen, upper arm, or thigh. The injections were performed with the NovoPen 4 with semaglutide 9.6 mg/mL. One, two, and three injections were needed for 2 mg (1×0.21 mL), 8 mg (2×0.42 mL), and 16 mg (3×0.56 mL), respectively (additional information in Supplementary Fig. 1). The participants continued metformin with no changes in dose or frequency, unless glycemic rescue medication was needed or a safety concern arose. The criteria for initiating rescue medication were persistent and unacceptable hyperglycemia (HbA_{1c} $>8.5\%$ [69 mmol/mol]), applied from weeks 12 to 40, allowing time for dose escalation and effects from treatment.

Outcomes

The primary end point was change from baseline to week 40 in HbA_{1c} (percentage points [%-points]). Confirmatory secondary end point included change from baseline to week 40 in body weight (kilograms). Supportive secondary end points included the number of treatment-emergent AEs and the number of severe hypoglycemic episodes up to week 49 (end of study) (19).

Further assessments included attainment of targets for HbA_{1c} ($<6.5\%$, $<5.7\%$) and body weight ($\geq 5\%$, $\geq 10\%$ of body weight lost) at week 40, change from baseline to week 40 in body weight (% change), pulse, hs-CRP, systolic and diastolic blood pressure, waist circumference, and lipid profile, as well as safety outcomes from baseline to week 49 (end of study).

Statistical Analyses

A sample size of 240 participants (60 in each active treatment group and pooled placebo group) was considered adequate to achieve sufficient precision on the dose-response relationship for the treatment policy estimand (primary estimand) with the primary and confirmatory secondary end points (additional details available in Supplementary Material). For all analyses,

the three placebo arms were pooled into one placebo group.

Two estimand strategies were used for the identified intercurrent events, use of rescue medication and treatment discontinuation: a treatment policy estimand (primary; akin to an intention-to-treat analysis) and a hypothetical estimand (also called trial product estimand; if treatment was taken as intended and without rescue medication). The hypothetical estimand therefore quantifies the achievable difference in treatment effects between the different treatment regimens and, hence, reflects the drug efficacy.

The treatment policy estimand was based on the full analysis set, including all randomly assigned participants according to the planned randomized treatments, and the in-study observation period. The hypothetical estimand was based on the full analysis set and the on-treatment-without-rescue-medication observation period.

ANCOVA with treatment, stratification factor, and sex as fixed effects and baseline value as a covariate was used for the primary and confirmatory secondary end points. Missing data at week 40 were imputed using multiple imputation. The multiple imputation was conducted with the “jump to reference” method for the treatment policy estimand, with the assumption that data were missing not at random (MNAR), and sequential conditional linear regression for the hypothetical estimand, with the assumption that data were missing at random. A total of 500 complete data sets were generated and analyzed separately with ANCOVA. The estimated means and variances were combined with use of Rubin rules (20).

To characterize the dose-response relationship of once-weekly semaglutide with change in HbA_{1c} (%-points) and change in body weight (kilograms) at week 40 for each estimand, four dose-response candidate models were fitted separately, a maximum effect (E_{\max}) model, a sigmoidal E_{\max} model, a linear + E_{\max} model, and a linear log-dose model. The model with the best fit was ultimately used, based on convergence and Akaike information criterion value. In fitting the model, the estimated means were weighted by their inverse of the estimated variance.

Attainment of HbA_{1c} and body weight targets was analyzed with logistic regression, based on the same factors and covariates, and imputed data, as for the main

analyses. Change in pulse was analyzed in the same way as the primary end point.

Post hoc analyses of further end points (hs-CRP, blood pressure, waist circumference, and lipid profile) were performed for the hypothetical estimand with mixed-effects repeated-measures models. Summaries of safety outcomes were presented descriptively and based on the safety analysis set including all participants exposed to randomized treatment, according to the treatment received. Adjustment for multiplicity was not done. Statistical analyses were done with SAS software, version 9.4.

Data and Resource Availability

Data will be shared with researchers who submit a research proposal approved by the independent review board. Information about data access request proposals can be found at novonordisk-trials.com.

RESULTS

Study Population

From 8 August to 16 December 2022, 359 individuals were screened, of whom 245 were randomly assigned to receive semaglutide 2 mg ($n = 61$), 8 mg ($n = 62$), or 16 mg ($n = 62$) or matching placebo ($n = 60$) (Supplementary Fig. 2). Overall, 123 (50.2%) of the participants were recruited in the U.S., 54 (22.0%) in Greece, 35 (14.3%) in Hungary, and 33 (13.5%) in Poland. Four participants were withdrawn prior to receiving treatment. A total of 219 (89.4%) participants completed the trial, and treatment was completed by 181 (73.9%) participants. A higher proportion of participants completed treatment in the 2 mg group (85%), in comparison with the 8 mg (68%), 16 mg (69%), and placebo (73%) groups, and most treatment discontinuations occurred in the first half of the trial period (Supplementary Fig. 3). The most common reason for premature treatment discontinuation in the semaglutide groups was AEs, primarily gastrointestinal in nature. In the placebo group, 15 participants discontinued treatment, with 1 of them discontinuing due to AEs.

Among the treatment completers ($n = 181$), 153 of 181 (84.5%) completed treatment without rescue medication: 49 of 52 (94%), 35 of 42 (83%), and 42 of 43 (98%) in the 2, 8, and 16 mg semaglutide groups, respectively, with notably fewer (27 of 44 [61%]) in the placebo group. Among all participants ($n = 245$), rescue medication was initiated in 32 of 245

(13.1%). In all groups, the majority of participants who started rescue medication had a baseline HbA_{1c} >8.5%. Rescue medication included mainly sodium–glucose cotransporter 2 inhibitors and sulfonylureas (Supplementary Table 1).

Demographics and baseline characteristics were generally similar between treatment groups (Table 1). Overall, 125 (51.0%) were male and mean (SD) age was 52.8 (8.3) years, duration of diabetes 6.9 (5.7) years, HbA_{1c} 8.3% (1.0%) (67.5 [10.8] mmol/mol), and body weight 109.7 (23.6) kg. Higher body weight (113.9 [27.8] kg) and larger waist circumference (123.2 [20.3] cm) were noted in the 16 mg group in comparison with the other groups (Table 1). Furthermore, there were slightly larger proportions of males in the semaglutide groups compared with the placebo group. Relevant comorbidities and medication use at baseline were generally evenly distributed across the groups (Supplementary Table 2). The most prevalent comorbidities were metabolic disorders, while the most frequently prescribed medications were lipid-lowering agents and antihypertensive medications. In general, participants discontinuing treatment were overall similar to those continuing treatment; however, a larger proportion had BMI ≥ 35 kg/m² at baseline among those completing treatment (Supplementary Tables 3 and 4).

Efficacy

HbA_{1c} levels decreased steadily in the semaglutide groups until approximately week 20 (Fig. 1A and C). Estimated mean changes from baseline were -1.8 , -1.8 , -2.1 , and -1.0 %-points for the 2 mg, 8 mg, 16 mg, and placebo groups, respectively, for the treatment policy (primary) estimand (i.e., based on in-study observation period; Fig. 1B), and -1.9 , -2.2 , -2.4 , and 0.1 %-points for the hypothetical estimand (based on the on-treatment-without-rescue-medication observation period; Fig. 1D). The differences between the two estimands in mean change for the placebo group are mainly due to the substantial placebo effect estimated with the treatment policy estimand where rescue medication influence the HbA_{1c} levels. The estimated treatment difference between 16 mg and 2 mg was -0.3 %-points (95% CI -0.7 to 0.2 ; $P = 0.245$). For the hypothetical estimand, the treatment differences indicated an additional glucose-lowering effect, -0.5 %-points (-1.0 to -0.1 ; $P = 0.015$),

Table 1—Participant demographics and baseline characteristics

| | Semaglutide 2 mg (n = 61) | Semaglutide 8 mg (n = 62) | Semaglutide 16 mg (n = 62) | Placebo (n = 60) |
|---|------------------------------|------------------------------|-------------------------------|---------------------------|
| Age (years) | 52.3 (7.6) | 53.7 (7.5) | 52.9 (8.6) | 52.1 (9.5) |
| Sex, n (%) | | | | |
| Female | 27 (44) | 33 (53) | 25 (40) | 35 (58) |
| Male | 34 (56) | 29 (47) | 37 (60) | 25 (42) |
| Duration of diabetes (years) | 6.1 (4.7) | 7.7 (7.7) [†] | 7.6 (5.5)* | 6.4 (4.3) [†] |
| Hispanic or Latino ethnicity, n (%) | 9 (15) | 8 (13) | 9 (15) | 13 (22) |
| Race, n (%) | | | | |
| Asian | 1 (2) | 1 (2) | 0 | 1 (2) |
| Black or African American | 6 (10) | 11 (18) | 4 (6) | 4 (7) |
| White | 54 (89) | 49 (79) | 56 (90) | 55 (92) |
| Other§ | 0 | 1 (2) | 2 (3) | 0 |
| Body weight (kg) | 109.6 (21.6) | 109.8 (20.6) | 113.9 (27.8) | 105.2 (23.4) |
| BMI (kg/m ²) | 37.0 (5.8) | 37.6 (6.4) | 38.6 (7.8) | 37.4 (6.9) |
| BMI ≥35 kg/m ² , n (%) | 40 (66) | 41 (66) | 37 (60) | 33 (55) |
| Waist circumference (cm) | 119.2 (19.4)* | 119.1 (14.4)* | 123.2 (20.3)* | 115.0 (18.4)* |
| Systolic blood pressure (mmHg) | 130 (15) | 129 (14) | 133 (11) | 130 (13) |
| Diastolic blood pressure (mmHg) | 80 (8) | 82 (8) | 82 (8) | 82 (11) |
| Fasting plasma glucose (mmol/L) | 9.9 (2.9) | 9.5 (3.2) [†] | 9.8 (2.9)* | 9.5 (2.7) [‡] |
| HbA _{1c} (%) | 8.4 (1.0) | 8.3 (1.0) | 8.3 (0.9) | 8.4 (1.0) |
| HbA _{1c} (mmol/mol) | 67.9 (11.0) | 67.2 (10.7) | 67.0 (10.2) | 68.0 (11.4) |
| HbA _{1c} ≥8.5% (≥69 mmol/mol), n (%) | 24 (39) | 26 (42) | 24 (39) | 24 (40) |
| hs-CRP (mg/L) | 3.50 (151.2) | 4.65 (150.8)* | 4.72 (124.9)* | 5.00 (148.0) [†] |
| Free fatty acids (mmol/L) | 0.52 (51.6)* | 0.56 (58.6)* | 0.55 (44.9) | 0.60 (39.3) [†] |
| HDL cholesterol (mmol/L) | 1.09 (22.3) | 1.09 (24.7)* | 1.06 (20.9)* | 1.12 (27.3) [†] |
| LDL cholesterol (mmol/L) | 2.24 (43.3) | 2.57 (33.0)* | 2.48 (42.0) [†] | 2.46 (34.5) [†] |
| Total cholesterol (mmol/L) | 4.35 (25.0) | 4.67 (23.6)* | 4.57 (25.9)* | 4.57 (21.5) [†] |
| Triglycerides (mmol/L) | 1.91 (56.3) | 1.95 (64.1)* | 1.91 (60.2)* | 1.87 (52.8) [†] |
| VLDL cholesterol (mmol/L) | 0.84 (51.3) | 0.85 (53.0) | 0.83 (52.8) | 0.83 (48.0) |

Data are means (SD) unless otherwise indicated. Percentages may not add up to 100 due to rounding. Data are shown for the full analysis set, including all randomized participants. *Data are missing for one participant. [†]Data are missing for two participants. [‡]Data are missing for three participants. §“Other” included two participants in the 16 mg group reported to be of multiple races and one participant in the 8 mg group for whom information on race was not available. ||Data are geometric means (coefficient of variation).

of 16 mg in comparison with 2 mg semaglutide.

Body weight decreased steadily up to week 40 in all semaglutide groups (Fig. 2A and C). With semaglutide 16 mg, statistically significant additional body weight loss was seen of 3.4 kg (95% CI 0.8 to 6.0; $P = 0.011$) and 4.5 kg (1.4 to 7.6; $P = 0.004$), in comparison with 2 mg, for the treatment policy estimand and the hypothetical estimand, respectively, and of 2.5 kg (not statistically significant) and 4.2 kg in comparison with 8 mg (Fig. 2B and D). Estimated mean percent change in body weight from baseline was -7.3% , -8.3% , -10.8% , and -2.0% for the 2 mg, 8 mg, 16 mg, and placebo groups for

the treatment policy estimand (Supplementary Fig. 4A) and -8.3% , -9.0% , -12.9% , and -2.8% for the hypothetical estimand (Supplementary Fig. 4B). With semaglutide 16 mg, statistically significant additional body weight change was seen of -3.5% -points (-6.0 to -1.1 ; $P = 0.005$) and -4.6% -points (-7.4 to -1.7 ; $P = 0.002$), in comparison with 2 mg, for the treatment policy estimand and the hypothetical estimand and of -2.5% -points (-4.9 to 0 ; $P = 0.047$) and -3.9% -points (-7.0 to -0.8 ; $P = 0.013$) in comparison with 8 mg (Supplementary Fig. 4A–B).

The dose-response modeling for HbA_{1c} suggests that doses >2 mg provide modest incremental effect (Supplementary Fig. 5A).

For body weight, the dose-response modeling suggests additional weight loss with higher doses of semaglutide (Supplementary Fig. 5B). These patterns were seen for both estimands. Estimated odds ratios for reaching glycemic targets of $<6.5\%$ (48 mmol/mol) and $<5.7\%$ (39 mmol/mol) and weight loss targets of at least 5% and 10% weight loss, between groups, supported a dose-response relationship with higher odds of reaching targets with higher doses of semaglutide (Supplementary Figs. 6–9).

In general, neither statistically significant differences between the semaglutide groups nor clear dose-response patterns were seen for the post hoc analyses of

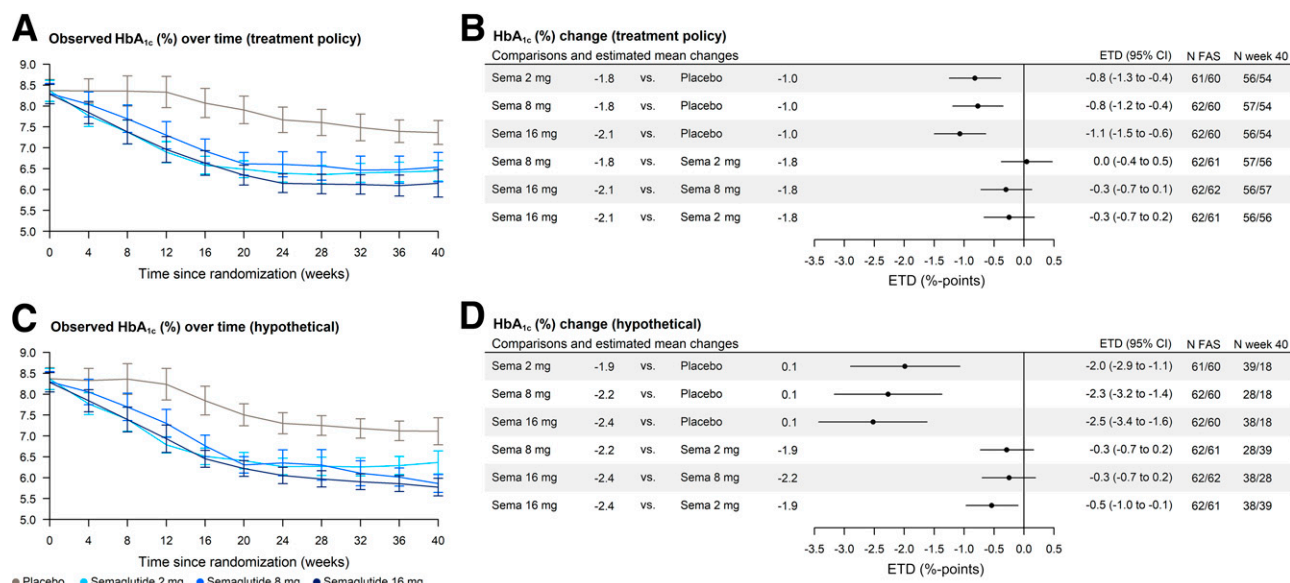


Figure 1—HbA_{1c} over time and estimated treatment differences at week 40. The treatment policy estimand was the primary estimand. In A and C, dots indicate group means and error bars represent SEM. In B and D, dots indicate estimated treatment differences and error bars represent 95% CIs. Estimated mean changes from baseline are reported for both groups in each comparison. N FAS, the no. of participants in the full analysis set, where the no. on the left corresponds with the group in the leftmost column and the no. on the right with the group in the column fourth from the left; N week 40, the no. of participants contributing to the analysis and with measurement at week 40, where the no. on the left corresponds with the group in the leftmost column and the no. on the right with the group in the column fourth from the left. Missing data were imputed using multiple imputation. An ANCOVA model was applied for each data set with treatment, stratification factor, and sex as fixed effects and baseline value as a covariate (sex was not included as fixed effect for the hypothetical estimand), and estimates were pooled with use of Rubin rules. ETD, estimated treatment difference; sema, semaglutide.

free fatty acids; triglycerides; HDL, LDL, or VLDL cholesterol; hs-CRP; diastolic or systolic blood pressure; or waist circumference (Supplementary Fig. 10A–I).

Safety

The AEs and treatment discontinuations due to AEs were more frequent in the semaglutide 8 mg and 16 mg groups than

in the 2 mg group (Table 2). Treatment discontinuations were mainly reported as due to gastrointestinal disorders. Overall, the most frequent AEs were nausea,

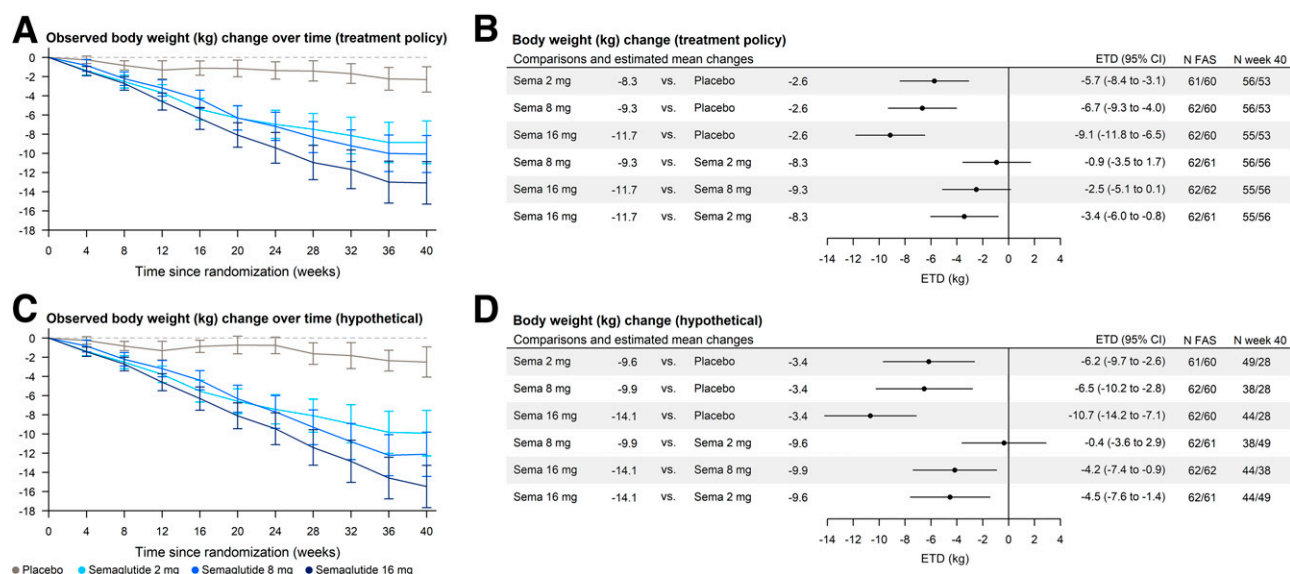


Figure 2—Body weight change from baseline over time and estimated treatment differences at week 40. The treatment policy estimand was the primary estimand. In A and C, dots indicate group means and error bars represent SEM. In B and D, dots indicate estimated treatment differences and error bars represent 95% CIs. Estimated mean changes from baseline are reported for both groups in each comparison. N FAS, the no. of participants in the full analysis set, where the no. on the left corresponds with the group in the leftmost column and the no. on the right with the group in the column fourth from the left; N week 40, the no. of participants contributing to the analysis and with measurement at week 40, where the no. on the left corresponds with the group in the leftmost column and the no. on the right with the group in the column fourth from the left. Missing data were imputed using multiple imputation. An ANCOVA model was applied to each data set with treatment, stratification factor, and sex as fixed effects and baseline value as a covariate (sex was not included as fixed effect for the hypothetical estimand), and estimates were pooled with use of Rubin rules. ETD, estimated treatment difference; sema, semaglutide.

Table 2—AEs

| | Semaglutide 2 mg (n = 60) | | | | Semaglutide 8 mg (n = 60) | | | | Semaglutide 16 mg (n = 62) | | | | Placebo (n = 59) | | | |
|--|------------------------------|----|-----|-------|------------------------------|----|------|-------|-------------------------------|----|-----|-------|---------------------|----|-----|-------|
| | n | % | E | R | n | % | E | R | n | % | E | R | n | % | E | R |
| All AEs | 43 | 72 | 179 | 340.8 | 54 | 90 | 260 | 547.4 | 55 | 89 | 255 | 529.1 | 37 | 63 | 234 | 490.7 |
| AEs resulting in treatment discontinuation | 4 | 7 | 4 | 7.6 | 14 | 23 | 14 | 29.5 | 11 | 18 | 11 | 22.8 | 1 | 2 | 1 | 2.1 |
| Serious AEs | 4 | 7 | 4 | 7.6 | 2 | 3 | 2 | 4.2 | 1 | 2 | 1 | 2.1 | 2 | 3 | 2 | 4.2 |
| Fatal events | 0 | | | | 0 | | | | 0 | | | | 0 | | | |
| Severity | | | | | | | | | | | | | | | | |
| Mild | 38 | 63 | 124 | 236.1 | 47 | 78 | 177 | 372.7 | 46 | 74 | 190 | 394.2 | 33 | 56 | 201 | 421.5 |
| Moderate | 16 | 27 | 48 | 91.4 | 25 | 42 | 67 | 141.1 | 26 | 42 | 62 | 128.6 | 14 | 24 | 32 | 67.1 |
| Severe | 4 | 7 | 7 | 13.3 | 5 | 8 | 16 | 33.7 | 3 | 5 | 3 | 6.2 | 1 | 2 | 1 | 2.1 |
| Severe hypoglycemic episodes | 0 | | | | 0 | | | | 0 | | | | 0 | | | |
| Safety focus area† | | | | | | | | | | | | | | | | |
| Gastrointestinal disorders | 28 | 47 | 96 | 182.8 | 41 | 68 | 152* | 320.0 | 44 | 71 | 138 | 286.3 | 20 | 34 | 99* | 207.6 |
| Acute kidney injury | 0 | | | | 0 | | | | 0 | | | | 1 | 2 | 1 | 2.1 |
| Hepatic events‡ | 1 | 2 | 1 | 1.9 | 2 | 3 | 3 | 6.3 | 2 | 3 | 2 | 4.1 | 0 | | | |
| Gallbladder-related disorders | 2 | 3 | 2 | 3.8 | 1 | 2 | 1 | 2.1 | 3 | 5 | 3* | 6.2 | 0 | | | |
| Acute pancreatitis | 0 | | | | 1 | 2 | 1 | 2.1 | 0 | | | | 1 | 2 | 1* | 2.1 |
| Neoplasms | 1 | 2 | 1* | 1.9 | 0 | | | | 2 | 3 | 2 | 4.1 | 1 | 2 | 1 | 2.1 |
| Diabetic retinopathy complications | 0 | | | | 0 | | | | 1 | 2 | 1 | 2.1 | 0 | | | |
| Hypersensitivity | 2 | 3 | 2 | 3.8 | 0 | | | | 2 | 3 | 2 | 4.1 | 4 | 7 | 5 | 10.5 |
| Hypoglycemia general | 0 | | | | 1 | 2 | 1 | 2.1 | 0 | | | | 0 | | | |

*One of the AEs of the safety focus areas was a serious AE. †Predefined safety focus areas for this trial. ‡Hepatic events included hepatomegaly, increased blood bilirubin, increased ALT, and increased hepatic enzyme. %, percentage of participants; E, no. of events; n, no. of participants; R, event rate per 100 patient-years at risk.

vomiting, and diarrhea (Supplementary Fig. 11).

The rate of gastrointestinal disorders was highest in the 8 mg and 16 mg groups and lowest in the 2 mg and placebo groups. The majority of the gastrointestinal disorders were assessed to be mild, and two were serious AEs (one each in the 8 mg and placebo groups). In the 2 mg, 8 mg, 16 mg, and placebo groups, 4, 11, 6, and 0 of the gastrointestinal disorders led to treatment discontinuation (Supplementary Table 5). Common gastrointestinal disorders included nausea, vomiting, diarrhea, constipation, dyspepsia, eructation, abdominal pain, and abdominal distension. For the remaining safety focus areas, the distribution appeared similar between groups (Table 2).

More participants reported dysesthesia in the 8 mg (8%) and 16 mg (18%) groups than in the 2 mg (0%) and placebo (2%) groups (Supplementary Table 6). A total of 19 cases of dysesthesia were reported, in 17 participants. Of these, 8 were of moderate severity and 11 were of mild severity. In two cases, the treatment was withdrawn (a case of sensitive skin in the 8 mg group and a case of paresthesia in the 16 mg

group, both of moderate severity with recovery after treatment discontinuation). In four cases, the participants did not recover within the follow-up period (sensitive skin, paresthesia, and hyperesthesia in the 16 mg group and hypoesthesia in the placebo group). Nine serious AEs were reported. Individuals recovered from all serious AEs, except for a case of invasive ductal breast carcinoma in the semaglutide 2 mg group. Serious AEs possibly related to the trial product included acute cholecystitis in the semaglutide 16 mg group and acute pancreatitis in the placebo group. Clinically significant (level 2) hypoglycemic episodes were reported in two participants (one each in the 2 mg and placebo groups). No severe (level 3) hypoglycemic episodes or deaths were reported.

There were no differences in pulse change from baseline to week 40 between any of the semaglutide groups. There were no clinically relevant findings observed for any other measured biochemistry parameters, hematology parameters, antibodies, physical examination, or electrocardiogram.

Comparison of participants on treatment with rescue medication with those

on treatment not using rescue medication showed that a higher proportion of participants in the placebo group who received rescue medication experienced mild-to-moderate AEs in comparison with those who did not receive rescue medication (Supplementary Tables 7 and 8).

CONCLUSIONS

In this dose-exploring randomized phase 2 trial, higher doses of semaglutide (namely, 16 mg) provided a modest incremental glucose-lowering effect (−0.5%-points; $P = 0.015$), with additional weight loss (4.5 kg; $P = 0.004$), in comparison with the approved dose (2 mg), in participants with type 2 diabetes and overweight or obesity, when the treatment was taken as intended and without rescue medication (hypothetical estimand). With inclusion of all in-study observations (treatment policy estimand, primary estimand), substantial glucose lowering was seen in the placebo group (likely due to the use of rescue medication) and the additional glucose-lowering effect from higher semaglutide dose in comparison with 2 mg was modest (−0.3%-points; $P = 0.245$).

The dose-response analyses demonstrated that the additional glycemic benefits of increasing dosing to >2 mg were modest, but a clear dose-response relationship was demonstrated for weight loss. The safety profile was similar across semaglutide groups. However, the rate of AEs and treatment discontinuations due to (mainly gastrointestinal) AEs were higher in the 8 mg and 16 mg groups than in the 2 mg group, and dysesthesia was mainly reported in the 8 mg and 16 mg groups. Furthermore, it was noted that a high number of participants received rescue medication—mainly in the placebo group, but also in the 8 mg group.

The number of treatment discontinuations (including treatment discontinuations due to AEs) was higher in the 8 mg and 16 mg groups ($\sim 30\%$) than in the 2 mg group ($\sim 15\%$) and also higher than in previous phase 3 trials. In the SUSTAIN FORTE trial, with investigation of 2 vs. 1 mg semaglutide for 40 weeks for type 2 diabetes, 92% completed treatment in the 2 mg group (18). In the STEP 2 trial, with investigation of 1.0 and 2.4 mg semaglutide vs. placebo for 68 weeks for overweight or obesity and type 2 diabetes, 88% completed treatment in the 2.4 mg group (21). In this trial, 85% completed treatment in the 2 mg group. The lower proportion of treatment completers likely stems from the forced monthly dose escalation, without any flexibility to delay titration, modify dose, or maintain a lower drug dose if AEs occurred. This appears to play a substantially larger role for the higher doses, particularly for those with BMI <35 kg/m².

Modest additional glucose-lowering effects were seen in the 8 and 16 mg groups in comparison with the 2 mg group, with statistically significant effect demonstrated with the hypothetical estimand for 16 mg vs. 2 mg. This could be due to a number of factors, including the impact of more treatment discontinuations in the high-dose groups, and potential lower limit of achievable HbA_{1c} changes, given the starting HbA_{1c} levels (i.e., HbA_{1c} floor). At baseline, overall mean HbA_{1c} was 8.3% (68.0 mmol/mol) and 60% had HbA_{1c} $<8.5\%$ (<69 mmol/mol). After 40 weeks, HbA_{1c} had decreased substantially to an observed mean of 6.4% in the 2 mg group, leaving little room for further improvement. The HbA_{1c} levels at end of treatment in the 2 mg group were

similar to the levels observed in the SUSTAIN FORTE trial (18) and the STEP 2 trial (21).

The additional weight loss from 8 mg and 16 mg in comparison with 2 mg ranged between 0.4 and 4.5 kg, and absolute weight loss between 9.3 and 14.1 kg, depending on dose and estimand. This well exceeds what has been observed in the SUSTAIN FORTE and STEP 2 trials (18,21). A weight loss of at least 5%–10% is generally considered clinically relevant, with greater weight losses producing greater health benefits (22,23). In this trial, the mean weight loss was $>5\%$ in all semaglutide groups and $>10\%$ in the 16 mg group. Participants in the 16 mg group had two to three times higher odds of achieving a weight loss of at least 5% or 10% in comparison with those in the 2 mg group (statistically significant for the hypothetical estimand only). These results, together with the dose-response modeling reported here, clearly show that while the glucose-lowering effect of semaglutide is present already at a low dose, additional weight loss can be induced by increasing doses further. There may be several explanations for this, but one interpretation could be that the biological systems expressing glucagon-like peptide 1 receptors that regulate body weight are less readily accessed than those that control glucose metabolism. The higher exposure that results from increasing semaglutide dose would most likely result in higher receptor engagement in these body weight-regulating pathways and, as a result, greater weight loss.

The additional benefits of high doses of semaglutide need to be balanced with the tolerability. An extensive clinical trial program as well as real-world evidence has shown semaglutide to be safe in the treatment of type 2 diabetes with additional benefits such as protection from cardiovascular and renal events (13,24–27). In general, the occurrence of gastrointestinal AEs is the main determinant of semaglutide tolerability. Here we found the number of gastrointestinal AEs to be substantially higher in the high-dose semaglutide groups. A new finding, not commonly reported in the subcutaneous semaglutide clinical trial program, was dysesthesia. Dysesthesia was reported in a high-dose oral semaglutide trial (OASIS 1) (28), but it is the first time dysesthesia has been demonstrated with subcutaneous semaglutide, indicating that route of administration is not determining this. The exact mechanism of action is still

unknown, but it is likely a class effect, as a similar reporting has been made in the phase 2 trial with glucagon-like peptide 1/glucose-dependent insulinotropic polypeptide/glucagon triagonist, retatrutide, in individuals with obesity (29).

From a clinical perspective, the modest improvements in glycemia and the statistically significant small additional weight loss (3.4 kg) with the highest dosages in comparison with 2 mg semaglutide do not justify the increased rates of AEs in this population. A phase 3 study with evaluation of a 7.2-mg dose of semaglutide for weight management in adults with type 2 diabetes and higher BMI (>30 kg/m²) is underway (clinical trial reg. no. NCT05649137, ClinicalTrials.gov) and may shed further light on the efficacy and tolerability of high-dose semaglutide with dosing flexibility that closer models clinical practice. The trial consists of three arms, 7.2 mg s.c. semaglutide, 2.4 mg s.c. semaglutide, and placebo, in addition to lifestyle counseling. The dose escalation is similar to that in the present study, but dose modifications are allowed if needed, and the study is longer, with a treatment duration of 72 weeks.

This trial had several limitations. The sample size was relatively small, powered to detect differences in HbA_{1c} of $\sim 0.5\%$. Combined with the increase in rescue medication use in placebo, dropout rates in the higher-dose groups, baseline HbA_{1c}, and HbA_{1c} floor, this did not provide much opportunity to detect differences in HbA_{1c} between doses. For weight loss, possibly a longer treatment duration would have shown further weight loss and larger differences between groups. Furthermore, imbalances in randomization may have impacted the findings. In addition, the forced and intensive dose escalation with large increments may have impacted potential risk-benefit effects. Smaller and more increments over a longer period, or a more patient-centered dose escalation, allowing dosing flexibility, could potentially have improved tolerability and treatment completion rates in the high-dose groups. However, given the constraints of this phase 2 dose-finding study, this would have jeopardized the chance of getting participants to the intended maintenance doses within the trial duration. Finally, this trial was not powered for investigation of subgroup effects to explore who had the most benefit at higher doses. A

person-centered trial design including individuals with inadequate metabolic response to subcutaneous semaglutide 2 mg once weekly, but who tolerate the dose well, could be used to more precisely assess whether higher doses are beneficial for such a subpopulation.

In conclusion, this trial showed that higher semaglutide doses (8 and 16 mg weekly) provide modest additional glucose-lowering effect, with additional weight loss, in comparison with 2 mg, in individuals with type 2 diabetes and overweight or obesity. The dose-response relationship was weak for glycemic control but more evident for weight loss. The overall safety profile was similar across semaglutide groups, but the rates of gastrointestinal AEs and treatment discontinuations due to AEs (mainly gastrointestinal) were higher in the 8 and 16 mg groups. A current phase 3 study with evaluation of semaglutide at a dose of 7.2 mg for weight management in type 2 diabetes and obesity is currently underway.

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References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 10th ed. Brussels, Belgium, 2021

2. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 2023;402:203–234
3. World Obesity Federation. *World Obesity Atlas* 2024. London, World Obesity Federation, 2024. Available from <https://data.worldobesity.org/publications/?cat=22>
4. Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. *Lancet* 2022;399:394–405
5. Henry RR, Wallace P, Olefsky JM. Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. *Diabetes* 1986;35:990–998
6. Adler AI, Coleman RL, Leal J, Whiteley WN, Clarke P, Holman RR. Post-trial monitoring of a randomised controlled trial of intensive glycaemic control in type 2 diabetes extended from 10 years to 24 years (UKPDS 91). *Lancet* 2024;404:145–155
7. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care* 2018;41:258–266
8. Pratley RE, Aroda VR, Lingvay I, et al.; SUSTAIN 7 investigators. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol* 2018;6:275–286
9. Lingvay I, Catarig A-M, Frias JP, et al. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. *Lancet Diabetes Endocrinol* 2019;7:834–844
10. Capehorn MS, Catarig A-M, Furberg JK, et al. Efficacy and safety of once-weekly semaglutide 1 mg vs once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes Metab* 2019;46:100–109
11. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naïve patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol* 2017;5:355–366
12. Kellner M, Kaltoft MS, Lawson J, et al. Effect of once-weekly semaglutide versus thrice-daily insulin aspart, both as add-on to metformin and optimized insulin glargine treatment in participants with type 2 diabetes (SUSTAIN 11): a randomized, open-label, multinational, phase 3b trial. *Diabetes Obes Metab* 2022;24:1788–1799
13. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–1844
14. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al.; SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 2023;389:2221–2232
15. Nauck MA, Petrie JR, Sesti G, et al.; Study 1821 Investigators. A phase 2, randomized, dose-finding study of the novel once-weekly human

- GLP-1 analog, semaglutide, compared with placebo and open-label liraglutide in patients with type 2 diabetes. *Diabetes Care* 2016;39:231–241
16. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet* 2018;392:637–649
17. Petri KCC, Ingwersen SH, Flint A, Zacho J, Overgaard RV. Exposure-response analysis for evaluation of semaglutide dose levels in type 2 diabetes. *Diabetes Obes Metab* 2018;20:2238–2245
18. Friás JP, Auerbach P, Bajaj HS, et al. Efficacy and safety of once-weekly semaglutide 2.0 mg versus 1.0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial. *Lancet Diabetes Endocrinol* 2021;9:563–574
19. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;36:1384–1395
20. Little RJA, Rubin DB. *Statistical Analysis With Missing Data*. New York, Wiley, 1987
21. Davies M, Færch L, Jeppesen OK, et al.; STEP 2 Study Group. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 2021;397:971–984
22. American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Obesity Expert Panel, 2013. Executive summary: guidelines (2013) for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society published by the Obesity Society and American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Based on a systematic review from the The Obesity Expert Panel, 2013. *Obesity (Silver Spring)* 2014;22(Suppl. 2):S5–S39
23. Williamson DA, Bray GA, Ryan DH. Is 5% weight loss a satisfactory criterion to define clinically significant weight loss? *Obesity (Silver Spring)* 2015;23:2319–2320
24. Yale J-F, Major-Pedersen A, Catarig A-M, Jain R, Menzen M, Holmes P. Real-world safety profile of once-weekly semaglutide in people with type 2 diabetes: analysis of pooled data from the Semaglutide Real-world Evidence (SURE) programme. *Diabetes Obes Metab* 2024;26:4429–4440
25. Rajamand Ekberg N, Bodholdt U, Catarig A-M, et al. Real-world use of once-weekly semaglutide in patients with type 2 diabetes: results from the SURE Denmark/Sweden multicentre, prospective, observational study. *Prim Care Diabetes* 2021;15:871–878
26. Sorli C, Harashima S-I, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol* 2017;5:251–260
27. Perkovic V, Tuttle KR, Rossing P, et al.; FLOW Trial Committees and Investigators. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med* 2024;391:109–121
28. Knop FK, Aroda VR, do Vale RD, et al.; OASIS 1 Investigators. Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2023;402:705–719
29. Jastreboff AM, Kaplan LM, Friás JP, et al.; Retatrutide Phase 2 Obesity Trial Investigators. Triple-hormone-receptor agonist retatrutide for obesity - a phase 2 trial. *N Engl J Med* 2023;389:514–526