# Efficacy and safety of semaglutide 2·4 mg once weekly in adults with overweight or obesity and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 clinical trial

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# **Abstract**

**Background:** This trial assessed the efficacy and safety of the glucagon-like peptide-1 analogue once-weekly subcutaneous semaglutide 2·4 mg versus 1·0 mg (dose approved for diabetes treatment) and placebo for weight management in adults with overweight/obesity and type 2 diabetes.

**Methods:** This double-blind, double-dummy, phase 3 study, enrolled adults with body mass index ≥27 kg/m2 and glycated haemoglobin 7–10% (53–86 mmol/mol). Patients were randomised (1:1:1) via an interactive web-response system and stratified by background glucose-lowering medication and glycated haemoglobin, to once-weekly subcutaneous injection of semaglutide 2·4 mg, or 1·0 mg, or visually matching placebo for 68 weeks. Co-primary endpoints were percentage change in body weight and achievement of weight reduction ≥5% for semaglutide 2·4 mg versus placebo. Percentage change in body weight between semaglutide 2·4 mg and 1·0 mg was predefined in the hierarchical testing approach, all other comparisons between these groups are exploratory. Secondary endpoints included changes in waist circumference, HbA1c, blood pressure, and patient-reported physical functioning. Safety was assessed in all patients who received at least one dose of study drug.

**Findings:** From June to November 2018, 1595 patients were screened, of whom 1210 were randomised to semaglutide 2·4 mg (n=404) or 1·0 mg (n=403), or placebo (n=403) and included in the full analysis set. Estimated change in mean body weight from baseline to week 68 was –9·6% (SE 0.4), –7·0% (SE 0.4), and –3·4% (SE 0.4) with semaglutide 2·4 mg, 1·0 mg, and placebo, respectively. Estimated treatment difference (95% confidence interval) for semaglutide 2·4 mg versus placebo was −6·2 percentage-points (−7·3% to −5·2%; p<0·001), and for semaglutide 2·4 mg versus 1·0 mg was −2·7 percentage-points (−3·7% to −1·6%; p<0·001). At week 68, more patients on semaglutide 2·4 mg achieved weight reductions of ≥5% versus placebo (n=267/388 [68·8%] vs n=107/376 [28.5%]; odds ratio 4·88, 95% CI, 3·58 to 6·64; p<0·001). Semaglutide 2.4 mg improved glycaemic control (HbA1c levels; target HbA1c), cardiometabolic risk factors (waist circumference, blood pressure, lipids, C-reactive protein) and physical functioning compared with placebo. Adverse events were more frequent with semaglutide 2.4 mg (353/403; 87·6%), and 1.0 mg (329/402; 81·8%) than placebo (309/402; 76·9%). Gastrointestinal adverse events (mostly mild-to-moderate) were reported in 63·5% (256/403), 57·5% (231/402), and 34·3% (138/402) of patients treated with semaglutide 2·4 mg, 1·0 mg, and placebo, respectively.

**Interpretations:** In adults with overweight/obesity and type 2 diabetes, once-weekly semaglutide 2·4 mg achieved a superior and clinically meaningful decrease in body weight versus placebo and semaglutide 1·0 mg.

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**Keywords (3–10):** body weight; GLP-1 receptor agonist; IWQOL-Lite-CT; obesity; overweight; semaglutide; SF-36; type 2 diabetes; weight loss.

# Research in context

## Evidence before this study

Weight loss has been shown to improve glycaemic control and reverse disease progression in people with type 2 diabetes. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated efficacy in lowering glycated haemoglobin (HbA1c) and decreasing weight in patients with type 2 diabetes. Once-weekly semaglutide 2.4 mg is currently being investigated as an obesity pharmacotherapy.

We searched PubMed on Nov 24, 2020 for articles published in the past 5 years, with no language restrictions, using the search terms “glucagon-like peptide-1 receptor agonist”, “obesity”, and “overweight”. The SCALE Diabetes trial of once-daily liraglutide 3·0 mg as an adjunct to lifestyle intervention in patients with obesity/overweight and type 2 diabetes (N=846) reported a reduction in body weight of 5·4% from baseline. In a phase 2, dose-finding trial (N=957), once-daily subcutaneous semaglutide 0·4 mg demonstrated effective weight loss and an acceptable safety profile.

**Added value of this study**

In adults with overweight/obesity and type 2 diabetes, once-weekly semaglutide 2·4 mg achieved a superior decrease in mean body weight (–9.6% [SE 0.4]) compared with semaglutide 1·0 mg and placebo (–7·0% [SE 0.4] and –3·4% [SE 0.4], respectively), with clinically meaningful reductions (≥5%) reported in over two-thirds of patients on semaglutide 2·4 mg. Furthermore, more than two-thirds of patients treated with semaglutide 2·4 mg achieved a target HbA1c ≤6·5%. Semaglutide 2·4 mg also resulted in improvement in cardiometabolic risk factors compared with placebo. The safety profile of semaglutide 2·4 mg was typical of a GLP-1RA.

**Implications of all the available evidence**

This is the first trial to show that in adults with overweight/obesity and type 2 diabetes, once-weekly subcutaneous semaglutide 2·4 mg produces clinically meaningful reductions in body weight. The magnitude of weight loss achieved with semaglutide 2·4 mg in STEP 2 was greater than that observed with liraglutide and other approved anti-obesity medications in similar patient populations. Semaglutide 2.4 mg is a promising treatment option for weight management in patients with overweight/obesity and type 2 diabetes.

# **Introduction**

Over 90% of people with type 2 diabetes are also those with overweight/obesity1 and over 20% of people with obesity also have diabetes.2 Some medications used to treat type 2 diabetes are associated with weight gain,3 aggravating this common comorbidity. Weight loss is an important tool in the management of type 2 diabetes as it improves glycaemic control and associated metabolic comorbidities.4

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated efficacy in lowering glycated haemoglobin (HbA1c) and decreasing weight in patients with type 2 diabetes, and are recommended as a second-line therapy after metformin and as the first injectable after failure of oral glucose-lowering agents.5–7 Furthermore, the GLP-1RA liraglutide is available for the treatment of overweight and obesity in people with or without type 2 diabetes.8 Among currently available GLP-1 RAs for the treatment of diabetes, semaglutide 1·0 mg has demonstrated the greatest weight loss effect in patients with type 2 diabetes,9–11 and is currently being investigated at the higher dose of 2·4 mg as an obesity pharmacotherapy. The present study, part of the Semaglutide Treatment Effect for People with obesity (STEP) programme,12 evaluated the efficacy and safety of once-weekly subcutaneous semaglutide 2·4 mg versus 1·0 mg (dose approved diabetes treatment) and placebo for weight management in adults with overweight/obesity and type 2 diabetes.

# Methods

### **Trial design and oversight**

This phase 3, randomised, double-blind, double-dummy, placebo-controlled, multicentre study was conducted at 149 sites in 12 countries across Europe, North America, South America, Middle East, South Africa, and Asia, as described previously.12 The sponsor (Novo Nordisk) designed the trial and oversaw its conduct. The trial was conducted in compliance with the International Conference on Harmonization Good Clinical Practice guidelines13 and the Declaration of Helsinki. The protocol and amendments were approved by the relevant institutional review board or independent ethics committee at each study site. A redacted protocol is in the appendix (pp 25-191). Investigators were responsible for trial-related medical decisions and data collection, and the sponsor undertook site monitoring, data collation, and analysis.

All authors had access to study data, contributed to the manuscript writing (assisted by a sponsor-funded medical writer), approved the final version, agreed to submission for publication, and vouch for data accuracy and fidelity to the protocol.

### **Patients**

Eligible patients were ≥18-years-old, reported ≥1 unsuccessful dietary effort to lose weight, had body mass index (BMI) ≥27 kg/m2 and HbA1c 7–10% (53–86 mmol/mol), and had been diagnosed with type 2 diabetes ≥180 days prior to screening. Patients were managed with diet and exercise alone, or treated with a stable dose of up to three oral glucose-lowering agents (metformin, sulfonylureas, sodium–glucose co-transporter 2 inhibitors, or thiazolidinediones) for ≥90 days prior to screening.

Key exclusion criteria included: self-reported changes in body weight of >5 kg within 90 days before screening and previous/planned (during the trial period) obesity treatment with surgery or a weight-loss device. Full eligibility criteria are in the Supplementary Appendix (pp 3-4).

### **Randomisation and masking**

Patients were randomised 1:1:1 to semaglutide 2·4 or 1·0 mg or placebo once weekly for 68 weeks, plus lifestyle intervention, followed by 7 weeks without treatment. Semaglutide was initiated at 0·25 mg per week and escalated in a fixed-dose regimen every 4 weeks until target dose was reached (2·4 or 1·0mg, weeks 8–16; figure S1 in the Supplementary Appendix [p 15]). We used a double-blind, double-dummy design in which patients received active drug or placebo as an injection (two injections per week). For both doses of semaglutide, the active and corresponding placebo products were visually identical to maintain masking of patients and site staff. Randomisation was done centrally with an interactive web-response system that assigned subjects to the next available treatment, with trial product dispensed at the trial visits. Randomisation was stratified according to background diabetes treatment as follows: i) patients who received diet and physical activity counselling only or patients who received glucose-lowering background medication (metformin or sodium-glucose co-transporter 2 inhibitor); ii) patients who received a single oral glucose-lowering medication or patients who received a combination (up to three) of oral glucose-lowering medications. Subjects were further stratified by screening HbA1c (above/below 8.5%).

Lifestyle intervention involved counselling on diet (500 kcal/day reduction relative to the estimated total daily energy expenditure calculated at randomisation) and physical activity (150 min/week, eg walking or using the stairs). Counselling was provided by a dietician or a similarly qualified healthcare professional every fourth week via in-person visit or via telephone. Patients were instructed how to measure their physical activity and food intake, and were encouraged to keep a food and activity diary on a daily basis using paper, an app or other tool, which was reviewed during counselling sessions. The estimated total daily energy expenditure was calculated by multiplying the estimated basal metabolic rate with a physical activity level value of 1.3.14 To mitigate risk of hypoglycaemia, patients on sulfonylureas were to reduce the dose by approximately 50% at treatment start, at the investigator’s discretion. Patients could intensify glucose-lowering therapy as judged by the investigator according to local guidelines. Insulin was permitted only in cases of persistent hyperglycaemia (fasting plasma glucose >15 mmol/l). Patients remained in the trial regardless of whether they discontinued treatment with the study drug.

### **Endpoints**

Co-primary endpoints were percentage change in body weight from baseline to week 68 and loss of ≥5% of baseline weight at week 68 (semaglutide 2·4 mg *vs* placebo). Confirmatory secondary endpoints (semaglutide 2·4 mg *vs* placebo, unless stated otherwise) in hierarchical testing order were: proportions of patients achieving body weight reductions of at least 10% or 15% at week 68, change from baseline to week 68 in waist circumference, percentage change in body weight (semaglutide 2·4 *vs* 1·0 mg) at week 68, change from baseline to week 68 in HbA1c, systolic blood pressure, Short Form36v2® Health Survey, Acute Version (SF-36) physical functioning score, and Impact of Weight on Quality of Life-Lite for Clinical Trials Version (IWQOL-Lite-CT) physical function score (see Supplementary Appendix for additional details [p 6]). The semaglutide 1·0 mg arm was included to enable comparison of body weight and safety outcomes with the semaglutide 2·4 mg arm. Exploratory secondary endpoints compared semaglutide 2·4 mg versus placebo, and semaglutide 2·4 mg versus 1·0 mg once weekly, unless otherwise stated (see Supplementary Appendix for additional details and a full list of endpoints [pp 6-7]).

Safety assessments included number of treatment-emergent adverse events and serious adverse events, and number of severe or blood glucose-confirmed symptomatic hypoglycaemia episodes. An independent external event adjudication committee reviewed cardiovascular events, acute pancreatitis, and deaths.

### **Statistical analysis**

A sample size of 1200 patients (400 in each arm) provided power of 94% for the co-primary and confirmatory secondary endpoints (see protocol in the appendix [pp 25-191]), tested in a predefined hierarchical order (Table S1 in the Supplementary Appendix [p 8]). Efficacy endpoints were analysed using the full analysis set (all randomised patients according to the intention-to-treat principle); safety endpoints were analysed using the safety analysis set (all randomised patients exposed to at least one dose of randomised treatment). Observation periods included the in-trial period (while in trial, regardless of treatment discontinuation or obesity rescue intervention) and the on-treatment period (with trial product). All results from statistical analyses on confirmatory endpoints were accompanied by two-sided 95% confidence intervals (CI) and corresponding p values (superiority defined as p<0.05). Exploratory secondary endpoint analyses were not controlled for multiple comparisons and should not be used to infer definitive treatment effects.

Two estimands (the treatment policy estimand and the trial product estimand) were employed to assess treatment efficacy, and accounted differently for intercurrent events and missing data, as described previously.15

The treatment policy estimand, which quantified average treatment effect among all randomised patients, regardless of adherence to treatment or initiation of rescue intervention (patients in trial, ‘intention-to-treat’) was used to assess the superiority of semaglutide 2·4 mg versus placebo and versus semaglutide 1·0 mg for the primary and secondary confirmatory endpoints in a predefined hierarchical order. Continuous endpoints were analysed using an analysis of covariance model with randomised treatment, stratification groups, and the interaction between stratification groups as factors and baseline endpoint value as covariate. Missing data were imputed 1000 times from retrieved patients of the same randomised treatment and combined the results using Rubin’s rule. Categorical endpoints were analysed by logistic regression using randomised treatment, stratification groups, and the interaction between stratification groups as factors and baseline endpoint value as a covariate.

The trial product estimand modeled the average treatment effect in all randomised patients, assuming that they had remained on treatment for the duration of the trial, and without initiation of obesity rescue medication (patients on treatment). Continuous endpoints were analysed using a mixed model for repeated measurements (MMRM) with same factors and covariates as the treatment policy estimand all nested within visit, and categorical endpoints were analysed using the predicted values from the MMRM by logistic regression with treatment and stratification groups as factors and baseline endpoint as covariate.

### **Role of the funding source**

The funder designed the trial, monitored trial sites, and collected and analysed data. This manuscript was drafted under the guidance of the authors with medical writing and editorial support, which was paid for by the funder. All authors had full access to all the data in the study, actively contributed to all drafts of the manuscript, and made the decision to submit the manuscript for publication.

# Results

### **Patients**

Of 1595 patients screened from June to November 2018, 1210 were randomised to semaglutide 2·4 mg (404 patients) or 1·0 mg (403 patients), or placebo (403 patients), and included in the full analysis set (figure 1). Treatment and trial compliance were high (87% [1058/1210] and 96% [1164/1210], respectively; see figure 1). Twenty-four patients received obesity rescue medication (semaglutide 2·4 mg, n=4; semaglutide 1·0 mg, n=7; placebo, n=13). One patient in the placebo group received bariatric surgery.

Baseline characteristics were well balanced across groups (table 1). Mean (standard deviation [SD]) body weight, BMI, and waist circumference were 99·8 ± 21·5 kg, 35·7 ± 6·3 kg/m2 and 114·6 ± 14·1 cm, respectively. Mean duration of diabetes was 8·0 ± 6·1 years.

### **Body weight**

Mean body weight change over time is shown in figures 2A and B (see figure S2 in the Supplementary Appendix for cumulative distribution function plots [p 16]). Using the treatment policy estimand, percentage mean weight change at week 68 with semaglutide 2·4 mg was −9·6% (SE 0.4) versus −3·4% (SE 0.4) with placebo (co-primary endpoint; estimated treatment difference [ETD] –6·2 percentage-points, 95% CI –7·3 to –5·2; p<0·001) (figure 2A), and for semaglutide 1·0 mg was −7·0% (SE 0.4) (ETD for 2·4 mg vs 1·0 mg −2·7%, 95% CI −3·7 to −1·6; p<0·0001) (figure 2A). The change for the trial product estimand was −10·6% (SE 0.4) for semaglutide 2·4 mg versus −3·1% for placebo (ETD −7·6 percentage-points, 95% CI −8·6 to −6·6) (figure 2B), and −7·6% for semaglutide 1·0 mg (ETD for 2·4 mg vs 1·0 mg −3·1 percentage-points, 95% CI, −4·1 to −2·1) (figure 2B).

Patients were more likely to achieve ≥5% reduction in baseline body weight at week 68 (co-primary endpoint) with semaglutide 2·4 mg (68·8% [267/388]) versus placebo (28·5% [107/376]; odds ratio for semaglutide 2·4 mg *vs* placebo 4·88, 95% CI, 3·58 to 6·64; p<0·001; treatment policy estimand) or semaglutide 1·0 mg (57·1% [217/380]; odds ratio for semaglutide 2·4 mg *vs* 1·0 mg 1·62, 95% CI, 1·21 to 2·18; p=0.0012; treatment policy estimand) (figure 2C). Similarly, more patients achieved reductions of ≥10%, ≥15%, and ≥20% at week 68 with semaglutide 2·4 mg versus 1·0 mg or placebo (≥20% threshold not part of statistical testing hierarchy; figures 2C and 2D).

### **Cardiometabolic risk factors**

Benefits significantly favouring semaglutide 2·4 mg versus placebo were seen for changes in waist circumference and systolic blood pressure (table 2; figure 3A, B; figures S3A, B in the Supplementary Appendix [p 17]). Improvements were also noted in lipid profile and inflammatory markers (table 2). Data for confirmatory secondary endpoints and exploratory endpoints of interest are presented in table 2 (see also table S2 in the Supplementary Appendix [pp 9-13]).

### **Glycated haemoglobin**

HbA1c improved from baseline to week 68 by –1·6% (SE 0.1), –1·5% (SE 0.1), and –0·4% (SE 0.1) with semaglutide 2·4 mg, 1·0 mg, and placebo, respectively (table 2; figure 3C; figure S3C in the Supplementary Appendix [p 17]). The proportion of patients in each group who achieved HbA1c levels ≤6·5% and <7·0% at week 68 are shown in figure 2D (see also figure S3D in the Supplementary Appendix [p 17]). Improvement in fasting plasma glucose was observed for both semaglutide arms versus placebo (table 2). A decrease in use of concomitant glucose-lowering medication (reduction, change in product or stopping the medication) was reported in 28·6% (106/371), 25·1% (93/381), and (26/364) 7·1% of patients receiving semaglutide 2·4 mg, 1·0 mg, and placebo, respectively.

### **Physical functioning**

Improvements in SF-36 physical functioning score and IWQOL-Lite-CT physical function score were observed with semaglutide 2·4 mg relative to placebo (figures 3E, 3F; figures S3E, S3F, S4 in the Supplementary Appendix [pp 17-20]).

### **Safety and tolerability**

The proportion of patients reporting adverse events was 87·6% (353/403), 81·8% (329/402), and 76·9% (309/402) in the semaglutide 2·4 mg, 1·0 mg, and placebo groups, respectively (table 3). Gastrointestinal disorders were the most frequently reported events. The most common gastrointestinal events were nausea, vomiting, diarrhoea, and constipation, mostly mild–moderate in severity and transient (figure S5 in the Supplementary Appendix [p22]). The majority of patients continued the trial product and recovered. Serious adverse events were reported in 9·9% (40/403), 7·7% (31/402), and 9·2% (37/402) of patients in the semaglutide 2·4 mg, 1·0 mg, and placebo groups, respectively. One death was reported in each group. More patients receiving semaglutide discontinued treatment due to adverse events, mainly due to gastrointestinal events (figure S6 in the Supplementary Appendix [p 23]). A decrease from baseline in alanine aminotransferase, aspartate aminotransferase, and urine-to-albumin-creatinine ratio was observed with semaglutide 2·4 mg, with no clinically relevant findings in other biochemistry or haematology parameters (table S3 in the Supplementary Appendix [p14]).

Severe or blood glucose-confirmed symptomatic hypoglycaemic episodes were reported in 5·7% (23/403), 5·5% (22/402), and 3·0% (12/402) of patients treated with semaglutide 2·4 mg, 1·0 mg, and placebo, respectively. One severe hypoglycaemic episode was observed during dose escalation with semaglutide 2·4 mg. Diabetic retinopathy events were reported in 4·0% (16/403), 2·7% (11/402), and 2·7% (11/402) of patients receiving semaglutide 2·4 mg, 1·0 mg, and placebo, respectively.

Of event adjudication committee-confirmed events, acute pancreatitis was reported in one patient in each of the semaglutide 2·4 mg and placebo groups. Cardiovascular events were few and reported in similar proportions of patients (table 3).

No cases of medullary thyroid cancer or pancreatic cancer were reported.

# Discussion

STEP 2 demonstrated that in adults with overweight/obesity and type 2 diabetes, once-weekly subcutaneous semaglutide 2·4 mg as adjunct to lifestyle intervention significantly reduced body weight by 9·6% (6·2 and 2·7 percentage points more than placebo and semaglutide 1·0 mg, respectively). This degree of weight loss was achieved while more than two-thirds of patients treated with semaglutide 2·4 mg achieved a target HbA1c ≤6·5%. Furthermore, 69% of patients on semaglutide 2·4 mg lost ≥5% of baseline weight (compared with 57% with 1·0 mg and 29% with placebo), a threshold cited as clinically meaningful weight loss.16 All prespecified outcomes in the hierarchical stepwise testing were met, indicating that semaglutide 2·4 mg is not only effective at lowering weight, but also at improving cardiometabolic risk factors and glycaemic control in people with type 2 diabetes.

The magnitude of weight loss achieved with semaglutide 2·4 mg in STEP 2 was greater than that observed in other studies with a similar patient population. In the SCALE Diabetes trial of once-daily liraglutide 3·0 mg as an adjunct to lifestyle intervention in patients with obesity/overweight and type 2 diabetes, a 5·4% weight reduction from baseline occurred.8,17 Reductions in body weight of ~5% have also been reported in similar patient populations with orlistat, and with the combination of naltrexone 32 mg/bupropion 360 mg sustained-release.18,19 The challenges of achieving weight reduction in people with type 2 diabetes are well known, and smaller weight losses with the same drug would be predicted in treating patients with and without type 2 diabetes. In the SCALE Obesity and Prediabetes trial (with overweight or obesity but not type 2 diabetes), weight loss of 8·0% was achieved with liraglutide20 (compared with 5·4% in patients with diabetes16). Furthermore, in the STEP 1 trial in subjects with overweight/obesity without type 2 diabetes, body weight reduction with semaglutide 2.4 mg as adjunct to lifestyle intervention was 14·9% versus 2.4% with placebo.21 The observed plateau of weight loss towards the end of the study is consistent with metabolic adaptation and physiological response to the weight loss, and is typical of any weight loss intervention. These changes are a result of reductions in resting and non-resting energy expenditure which accompany compensatory changes in appetite regulating hormones.22–25

Evidence suggests that overweight/obesity and type 2 diabetes considerably reduce health-related quality of life.26 In this study, semaglutide 2·4 mg was associated with improvements in physical functioning, which may translate into benefits in daily living. Furthermore, there were improvements versus placebo on the SF-36 physical component summary as well as the total score on the IWQOL-Lite-CT, an obesity-specific tool for measuring quality of life (Supplementary Appendix Figure S4). Changes on the mental component summary of the SF-36 suggested a trend towards favouring semaglutide 2.4 mg.

The semaglutide 2·4 mg dose was selected based on a phase 2 dose-finding trial in which semaglutide 0·4 mg once daily was effective in terms of weight loss, with an acceptable tolerability profile.27 The higher dose of semaglutide increased the proportion of patients who lost ≥10% of baseline weight from 28·7% (with 1·0 mg) to 45·6% (with 2·4 mg) and nearly doubled the proportion who lost ≥15% body weight (from 13·7% with 1·0 mg to 25·8% with 2·4 mg). Semaglutide 1·0 mg once weekly was included in the STEP 2 trial to enable comparison of weight loss and safety with the higher 2·4 mg dose. Semaglutide 1.0 mg is an effective glucose lowering agent with an established safety and tolerability profile that clinicians will be familiar with for the management of patients with type 2 diabetes.28 The effectiveness of semaglutide 1.0 mg on glycaemic control was demonstrated in the present study in which HbA1c levels reached 6.6% by week 68. Semaglutide 2·4 mg was associated with only a small incremental improvement in glycaemic parameters versus 1·0 mg. Of note, use of up to three oral anti-diabetic medications was allowed and more patients treated with semaglutide 2·4 mg reduced their use of these concomitant medications after 68 weeks versus patients receiving the 1·0 mg dose (29 vs 25%). The benefits of treating with a higher dose of semaglutide can be clearly seen in the context of weight loss. In STEP 2, patients treated with semaglutide 2·4 mg achieved improvements in cardiometabolic risk factors including waist circumference, HbA1c, systolic blood pressure, lipids, urine albumin-to-creatinine ratio, C-reactive protein, and liver parameters. The semaglutide 1.0 mg dose is indicated in the USA to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular disease,28 based on findings from the SUSTAIN 6 trial in patients with type 2 diabetes at high cardiovascular risk.29 Treatments to reduce cardiovascular risk in people with type 2 diabetes and obesity are needed due to their increased risk of morbidity and mortality from cardiovascular disease. For example, an analysis of data from over 820,000 people found that people with type 2 diabetes (versus those without) have a 2.3-fold increased risk of mortality from vascular causes,30 and another study of the US NHANES population projected 10-year incidence rates of ischaemic heart disease, myocardial infarction, and CHF to be approximately 3-5% higher among people with obesity than without.2 While our findings suggest that semaglutide 2·4 mg may be associated with lowering cardiovascular risk in patients with type 2 diabetes, the patient population in the present study was at relatively low cardiovascular risk, as they were well controlled for existing comorbidities, and further studies are therefore needed. The SELECT trial (NCT03574597), in people with obesity without diabetes, is underway.31 While weight loss is associated with improvements in cardiovascular risk factors, studies have shown that weight loss in patients with type 2 diabetes is also associated with improvements in other factors, such as obstructive sleep apnoea and performance-based physical function.32,33 The observation that increasing the dose of semaglutide reduced body weight more than it improved glycaemic control in STEP 2 is consistent with findings from the SCALE DIABETES trial of liraglutide 1.8 mg and 3.0 mg,17 as well as those from the Liraglutide Effect and Action in Diabetes (LEAD) programme that investigated liraglutide at doses of 0.6 mg, 1.2 mg and 1.8 mg alone, or in combination with other oral glucose lowering drugs, in patients with type 2 diabetes and BMI <45 kg/m2.34,35

The safety profile of semaglutide 2·4 mg in patients with overweight/obesity and type 2 diabetes was typical of the GLP-1RA class,36,37 and consistent with that reported in the phase 2 study of once-daily dosing in patients with obesity27 and in the SUSTAIN trials of once-weekly semaglutide in over 8000 patients with type 2 diabetes.38 Transient, mild–moderate gastrointestinal disorders were the most frequently reported adverse events, and more patients discontinued treatment with semaglutide versus placebo. The rate of gastrointestinal adverse events was slightly higher with semaglutide 2·4 mg versus 1·0 mg, but discontinuations due to adverse events were low overall, and were comparable between semaglutide arms).

Strengths of the study include the large sample size (with a trial population different from others in the STEP trial programme12), double-dummy design, provision of lifestyle counselling, the high rate of treatment and trial completion, and the option for dose adjustment of glucose-lowering drugs. A notable limitation is the exclusion of patients on insulin. In the SUSTAIN 5 trial in patients with type 2 diabetes, semaglutide 0·5 and 1·0 mg once weekly as an add-on to basal insulin was associated with weight loss.39 Similar clinical benefits may be expected with semaglutide 2·4 mg in this patient population.

In conclusion, in adults with overweight (BMI ≥27 kg/m2)/obesity and type 2 diabetes, once-weekly semaglutide 2·4 mg as adjunct to lifestyle intervention led to a clinically meaningful body weight loss that was 6·2 and 2·7 percentage points greater than with placebo and semaglutide 1·0 mg, respectively, with weight reductions of ≥5% achieved by 69%, 57% and 29% of patients on semaglutide 2·4 mg, 1·0 mg or placebo, respectively. This was accompanied by a reduction in HbA1c of 1·6% (versus 0·4% and 1·5% with placebo and semaglutide 1·0 mg, respectively). Additionally, patients treated with semaglutide 2·4 mg experienced improvements in cardiometabolic risk factors as well as physical functioning versus those treated with placebo.

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### **Data sharing statement**

Data will be shared with bona fide researchers submitting a research proposal approved by the independent review board. Access request proposals can be found at novonordisk-trials.com. Data will be made available after research completion, and approval of the product and product use in the European Union and the USA. Individual patient data will be shared in data sets in a de-identified/anonymised format.

### **Author contributions**

Melanie Davies: contributed to the data interpretation and manuscript development.

Louise Færch: contributed to the design and conduct of the trial, data collection, analysis and interpretation, and manuscript development.

Ole Kleist Jeppesen: contributed to the conduct of the trial, data collection, analysis and interpretation, and manuscript development.

Arash Pakseresht: contributed to data interpretation and manuscript development.

Sue D. Pedersen: contributed to the conduct of the trial, data collection, data interpretation, and manuscript development.

Leigh Perreault: contributed to the conduct of the trial, data collection, data interpretation, and manuscript development.

Julio Rosenstock: contributed to the conduct of the trial, data collection, data interpretation, and manuscript development.

Iichiro Shimomura: contributed to data interpretation and manuscript development.

Adie Viljoen: contributed to the conduct of the trial, data interpretation, and manuscript development.

Thomas A. Wadden: contributed to the data interpretation and manuscript development.

Ildiko Lingvay: Contributed to the conduct of the trial, data collection, data interpretation, and manuscript development.

All authors had access to study data, approved the final version of the manuscript, agreed to submission for publication, and vouch for data accuracy and fidelity to the protocol.

### **Declaration of interests**

Dr. Davies: Consultant, advisory board member, and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Janssen; advisory board member for Servier, Gilead Sciences Ltd, and Lexicon; speaker for Napp, Mitsubishi Tanabe Pharma Corporation, and Takeda Pharmaceuticals International Inc.; research funding from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, AstraZeneca, and Janssen.

Dr. Færch is an employee of Novo Nordisk and holds shares in the company.

Mr. Kleist Jeppesen is an employee of Novo Nordisk and holds shares in the company.

Dr. Pakseresht is an employee of Novo Nordisk A/S.

Dr. Pedersen has received personal fees for advisory boards and speaker’s bureau from Novo Nordisk, Janssen, Eli Lilly, Merck, Bausch/Valeant, AstraZeneca, Abbott, Boehringer Ingelheim, Sanofi, HLS therapeutics, and Dexcom; personal fees for consulting from Novo Nordisk, Janssen, AstraZeneca, Abbott, HLS therapeutics, and Dexcom; personal fees for clinical trials from Novo Nordisk, Eli Lilly, AstraZeneca, Sanofi, Prometic, and Pfizer; grants from Eli Lilly, AstraZeneca, Abbott, Boehringer Ingelheim, and Sanofi; and non-financial support for travel to meetings from Novo Nordisk, Janssen, Eli Lilly, Bausch/Valeant, AstraZeneca, Boehringer Ingelheim, and Sanofi.

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Dr. Rosenstock has served on scientific advisory boards and received honoraria or consulting fees from Applied Therapeutics, Eli Lilly, Sanofi, Novo Nordisk, Janssen, Oramed, Boehringer Ingelheim, and Intarcia. He has also received grants/research support from Applied Therapeutics, Merck, Novartis, Pfizer, Sanofi, Novo Nordisk, Eli Lilly, GlaxoSmithKline, Genentech, Janssen, Lexicon, Boehringer Ingelheim, Oramed, and Intarcia.

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Dr. Viljoen has conducted research trials, served as an advisor, and received speakers’ bureau fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, MannKind, Napp, Novartis, Novo Nordisk, Regeneron, Sanofi, Takeda, and Tosoh.

Dr. Wadden serves on advisory boards for Novo Nordisk and WW (formerly Weight Watchers) and has received grant support, on behalf of the University of Pennsylvania, from Novo Nordisk.

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### **Disclosure of correspondence**

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# Tables and figures

### ***Table 1:*** Selected Baseline Demographic and Clinical Characteristics

| **Characteristic** | **Semaglutide 2·4 mg (N=404)** | **Semaglutide 1·0 mg (N=403)** | **Placebo (N=403)** | **Total (N=1210)** |
| --- | --- | --- | --- | --- |
| Age — years | 55 ± 11 | 56 ± 10 | 55 ± 11 | 55 ± 11 |
| Female sex — n (%) | 223 (55·2) | 203 (50·4) | 190 (47·1) | 616 (50·9) |
| Race or ethnic group — n (%) |  |  |  |  |
| Asian | 112 (27·7) | 97 (24·1) | 108 (26·8) | 317 (26·2) |
| Black or African American | 35 (8·7) | 28 (6·9) | 37 (9·2) | 100 (8·3) |
| White | 237 (58·7) | 272 (67·5) | 242 (60·0) | 751 (62·1) |
| Other\* | 20 (5·0) | 6 (1·5) | 16 (4·0) | 42 (3·5) |
| Hispanic or Latino ethnic group — n (%) | 47 (11·6) | 59 (14·6) | 49 (12·2) | 155 (12·8) |
| Body weight — kg | 99·9 ± 22·5 | 99·0 ± 21·1 | 100·5 ± 20·9 | 99·8 ± 21·5 |
| BMI |  |  |  |  |
| Mean — kg/m2 | 35·9 ± 6·4 | 35·3 ± 5·9 | 35·9 ± 6·5 | 35·7 ± 6·3 |
| <30 kg/m2 — n (%) | 68 (16·8) | 66 (16·4) | 77 (19·1) | 211 (17·4) |
| 30 – <35 kg/m2 — n (%) | 140 (34·7) | 163 (40·4) | 135 (33·5) | 438 (36·2) |
| 35 – <40 kg/m2 — n (%) | 103 (25·5) | 100 (24·8) | 97 (24·1) | 300 (24·8) |
| ≥40 kg/m2 — n (%) | 93 (23·0) | 74 (18·4) | 94 (23·3) | 261 (21·6) |
| Waist circumference — cm | 114·5 ± 14·3 | 113·9 ± 14·0 | 115·5 ± 13·9 | 114·6 ± 14·1 |
| HbA1c — % | 8·1 ± 0·8 | 8·1 ± 0·8 | 8·1 ± 0·8 | 8·1 ± 0·8 |
| Fasting plasma glucose — mmol/L | n=396  8·5 ± 2·3 | n=395  8·6 ± 2·3 | n=400  8·8 ± 2·3 | n=1191  8·6 ± 2·3 |
| Duration of diabetes —years | n=404  8·2 ± 6·2 | n=403  7·7 ± 5·9 | n=402  8·2 ± 6·2 | n=1209  8·0 ± 6·1 |
| Glucose-lowering drug class — n (%) |  |  |  |  |
| Biguanides | 370 (91·6) | 379 (94·0) | 362 (89·8) | 1111 (91·8) |
| Sulfonylureas | 110 (27·2) | 99 (24·6) | 99 (24·6) | 308 (25·5) |
| SGLT2 inhibitors | 99 (24·5) | 96 (23·8) | 105 (26·1) | 300 (24·8) |
| Thiazolidinediones | 19 (4·7) | 16 (4·0) | 19 (4·7) | 54 (4·5) |
| DPP4 inhibitors† | 2 (0·5) | 3 (0·7) | 1 (0·2) | 6 (0·5) |
| Alpha glucosidase inhibitors | 1 (0·2) | 1 (0·2) | 0 | 2 (0·2) |
| GLP-1 receptor agonists† | 0 | 1 (0·2) | 0 | 1 (<0·1) |
| Fast-acting insulins and insulin analogues for injection† | 0 | 0 | 1 (0·2) | 1 (<0·1) |
| Other blood glucose-lowering drugs | 1 (0·2) | 0 | 0 | 1 (<0·1) |
| Number of oral glucose-lowering drugs — n (%) |  |  |  |  |
| Diet and physical activity only | 18 (4·5) | 17 (4·2) | 21 (5·2) | 56 (4·6) |
| 1 | 221 (54·7) | 229 (56·8) | 216 (53·6) | 666 (55·0) |
| 2 | 133 (32·9) | 127 (31·5) | 138 (34·2) | 398 (32·9) |
| 3 | 32 (7·9) | 29 (7·2) | 27 (6·7) | 88 (7·3) |
| 4† | 0 | 1 (0·2) | 1 (0·2) | 2 (0·2) |
| Blood pressure — mmHg |  |  |  |  |
| Systolic | 130 ± 13 | 130 ± 14 | 130 ± 13 | 130 ± 14 |
| Diastolic | 80 ± 9 | 80 ± 9 | 80 ± 9 | 80 ± 9 |
| Lipids – geometric mean (CV) |  |  |  |  |
| Total cholesterol — mmol/L | n=402  4·4 (23·0) | n=399  4·5 (25·0) | n=402  4·4 (23·3) | n=1203  4·4 (23·8) |
| LDL cholesterol — mmol/L | n=402  2·3 (37·3) | n=399  2·3 (46·7) | n=402  2·3 (37·8) | n=1203  2·3 (40·7) |
| HDL cholesterol — mmol/L | n=402  1·2 (23·3) | n=399  1·1 (24·9) | n=402  1·1 (24·2) | n=1203  1·1 (24·2) |
| VLDL cholesterol — mmol/L | n=402  0·8 (49·3) | n=399  0·8 (48·4) | n=402  0·8 (49·7) | n=1203  0·8 (49·3) |
| Free fatty acids — mmol/L | n=390  0·6 (54·7) | n=388  0·6 (45·1) | n=393  0·6 (55·4) | n=1171  0·6 (51·8) |
| Triglycerides — mmol/L | n=402  1·7 (53·4) | n=399  1·9 (54·0) | n=402  1·8 (52·9) | n=1203  1·8 (53·6) |
| Estimated glomerular filtration rate |  |  |  |  |
| Mean — mL/min/1·73 m2 | 94·25 ± 22·10 | 93·43 ± 21·43 | 92·32 ± 23·47 | 93·33 ± 22·35 |
| Normal (≥90 mL/min/1·73 m2) — n (%) | 271 (67·1) | 265 (65·8) | 259 (64·3) | 795 (65·7) |
| Mild impairment (≥60 – <90 mL/min/1·73 m2) — n (%) | 114 (28·2) | 121 (30·0) | 120 (29·8) | 355 (29·3) |
| Moderate impairment (≥30 – <60 mL/min/1·73 m2) — n (%) | 18 (4·5) | 17 (4·2) | 24 (6·0) | 59 (4·9) |
| Severe impairment (15 – <30 mL/min/1·73 m2) — n (%) | 1 (0·2) | 0 | 0 | 1 (<0·1) |
| Comorbidities at screening — n (%)‡ |  |  |  |  |
| Coronary artery disease | 26 (6·4) | 40 (9·9) | 33 (8·2) | 99 (8·2) |
| Dyslipidemia | 265 (65·6) | 277 (68·7) | 284 (70·5) | 826 (68·3) |
| Hypertension | 276 (68·3) | 285 (70·7) | 287 (71·2) | 848 (70·1) |
| Knee osteoarthritis | 73 (18·1) | 56 (13·9) | 67 (16·6) | 196 (16·2) |
| Obstructive sleep apnea | 68 (16·8) | 54 (13·4) | 54 (13·4) | 176 (14·5) |
| Non-alcoholic fatty liver disease | 85 (21·0) | 82 (20·3) | 94 (23·3) | 261 (21·6) |
| Polycystic ovary syndrome | 7 (3·1) | 8 (3·9) | 10 (5·3) | 25 (4·1) |
| Asthma/chronic obstructive pulmonary disease | 36 (8·9) | 47 (11·7) | 32 (7·9) | 115 (9·5) |
| Number of comorbidities at screening — n (%)‡ |  |  |  |  |
| ≥5 | 93 (23·0) | 86 (21·3) | 81 (20·1) | 260 (21·5) |
| 4 | 89 (22·0) | 96 (23·8) | 105 (26·1) | 290 (24·0) |
| 3 | 98 (24·3) | 107 (26·6) | 112 (27·8) | 317 (26·2) |
| 2 | 77 (19·1) | 70 (17·4) | 72 (17·9) | 219 (18·1) |
| 1 | 47 (11·6) | 44 (10·9) | 33 (8·2) | 124 (10·2) |
| SF-36 |  |  |  |  |
| Physical functioning score | n=397  49·2 ± 8·8 | n=396  50·5 ± 7·7 | n=394  49·6 ± 8·3 | n=1187  49·7 ± 8·3 |
| Physical component summary score | n=397  49·8 ± 8·2 | n=396  50·7 ± 7·3 | n=394  49·9 ± 8·0 | n=1187  50·1 ± 7·9 |
| Mental component summary score | n=397  55·6 ± 6·1 | n=396  55·9 ± 6·0 | n=394  56·2 ± 5·5 | n=1187  55·9 ± 5·9 |
| IWQOL-Lite-CT |  |  |  |  |
| Physical function score | n=397  67·1 ± 25·2 | n=395  71·1 ± 22·5 | n=394  69·2 ± 24·0 | n=1186  69·2 ± 24·0 |
| Total score | n=397  71·9 ± 20·9 | n=395  74·5 ± 18·6 | n=394  74·2 ± 19·2 | n=1186  73·5 ± 19·6 |

All patients in the FAS contribute to the statistics, unless indicated otherwise. All data presented as means ± standard deviation, unless indicated otherwise. There were no marked differences between treatment groups at baseline.

\*Other refers to American Indian or Alaska Native, Native Hawaiian, other Pacific Islander, or Other.

†Patients on DDP4 inhibitors or GLP-1 receptor agonists were randomised in error; one patient initiated insulin on the day of randomisation but it was not known if this was initiated before or after the randomisation procedure.

‡Information on comorbidities was collected at screening based on medical history, and included: type 2 diabetes, dyslipidemia, hypertension, coronary artery disease, cerebrovascular disease, obstructive sleep apnea, reproductive system disorders, liver disease, kidney disease, osteoarthritis, gout, and asthma/chronic obstructive pulmonary disease.

BMI=body mass index; CV=coefficient of variation (in percent); DPP4=dipeptidyl peptidase-4. GLP-1=glucagon-like peptide-1. HbA1c=glycated haemoglobin. HDL=high-density lipoprotein. IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version. LDL=low-density lipoprotein. SF-36=Short Form36v2® Health Survey, Acute Version. SGLT2=sodium–glucose co-transporter 2. VLDL=very-low-density lipoprotein.

### ***Table 2:*** Co-primary, Confirmatory Secondary, and Selected Exploratory Trial Endpoints (Treatment Policy Estimand\*)

| **Endpoint** | **Semaglutide 2·4 mg (N=404)** | **Semaglutide 1·0 mg (N=403)** | **Placebo (N=403)** | **Treatment comparison (95% CI); p value provided only for confirmatory analyses** |
| --- | --- | --- | --- | --- |
| **Primary endpoints** | | | | |
| Body weight — % |  |  |  |  |
| Mean (SE) change from baseline to week 68 — % | −9·64 (0·4) | −6·99 (0·4) | −3·42 (0·4) | Semaglutide 2·4 mg – placebo (percentage points); ETD: −6·21 (−7·28 to −5·15); p<0·001 |
|  |  |  |  | Semaglutide 2·4 mg – semaglutide 1·0 mg (percentage points); ETD: −2·65 (−3·66 to −1·64); p<0·001 |
| Body weight reduction ≥5% |  |  |  |  |
| n | 388 | 380 | 376 |  |
| Proportion of patients at week 68 — n (%) | 267 (68·8) | 217 (57·1) | 107 (28·5) | Semaglutide 2·4 mg / placebo; OR: 4·88 (3·58 to 6·64); p<0·001 |
|  |  |  |  | Semaglutide 2·4 mg / semaglutide 1·0 mg; OR: 1·62 (1·21 to 2·18) |
| **Confirmatory secondary endpoints** | | | | |
| Body weight reduction ≥10% |  |  |  |  |
| n | 388 | 380 | 376 |  |
| Proportion of patients at week 68 — n (%) | 177 (45·6) | 109 (28·7) | 31 (8·2) | Semaglutide 2·4 mg / placebo; OR: 7·41 (4·89 to 11·24); p<0·001 |
|  |  |  |  | Semaglutide 2·4 mg / semaglutide 1·0 mg; OR: 2·07 (1·53 to 2·80) |
| Body weight reduction ≥15% |  |  |  |  |
| n | 388 | 380 | 376 |  |
| Proportion of patients at week 68 — n (%) | 100 (25·8) | 52 (13·7) | 12 (3·2) | Semaglutide 2·4 mg / placebo; OR: 7·65 (4·11 to 14·22); p<0·0001 |
|  |  |  |  | Semaglutide 2·4 mg / semaglutide 1·0 mg; OR: 2·17 (1·50 to 3·15) |
| Waist circumference — cm |  |  |  |  |
| n | 387 | 380 | 375 |  |
| Week 68 mean ± SD | 104·4 ± 14·7 | 107·2 ± 14·6 | 111·0 ±13·7 | Semaglutide 2·4 mg – placebo (cm); ETD: −4·9 (−6·0 to −3·8); p<0·001 |
| Change from baseline to week 68 — cm (SE) | −9·4 (0·4) | −6·7 (0·4) | −4·5 (0·4) | Semaglutide 2·4 mg – semaglutide 1·0 mg (cm); ETD: −2·7 (−3·7 to −1·7) |
| HbA1c — % |  |  |  |  |
| n | 381 | 376 | 374 |  |
| Week 68 mean ± SD | 6·4 ± 1·2 | 6·6 ± 1·1 | 7·8 ± 1·3 | Semaglutide 2·4 mg – placebo (percentage points); ETD: −1·2 (−1·4 to −1·1); p<0·001 |
| Change from baseline to week 68 — % points (SE) | −1·6 (0·1) | −1·5 (0·1) | −0·4 (0·1) | Semaglutide 2·4 mg – semaglutide 1·0 mg (percentage points); ETD: −0·2 (−0·3 to 0·0) |
|  |  |  |  | Semaglutide 1·0 mg – placebo (percentage points); ETD: −1·1 (−1·3 to −0·9) |
| HbA1c — mmol/mol |  |  |  |  |
| n | 381 | 376 | 374 |  |
| Week 68 mean ± SD | 46·7 ± 12·9 | 48·4 ± 12·0 | 61·8 ± 14·4 | Semaglutide 2·4 mg – placebo (mmol/mol); ETD: −13·5 (−15·5 to −11·4); p<0·001 |
| Change from baseline to week 68 — mmol/mol (SE) | −17·5 (0·7) | −15·9 (0·8) | −4·1 (0·8) | Semaglutide 2·4 mg – semaglutide 1·0 mg (mmol/mol); ETD: −1·7 (−3·7 to 0·4) |
|  |  |  |  | Semaglutide 1·0 mg – placebo (mmol/mol); ETD: −11·8 (−14·0 to −9·7) |
| Systolic blood pressure — mmHg |  |  |  |  |
| n | 387 | 379 | 376 |  |
| Week 68 mean ± SD | 126 ± 14 | 127 ± 15 | 130 ± 14 | Semaglutide 2·4 mg – placebo (mmHg); ETD: −3·4 (–5·6 to –1·3); p=0·0016 |
| Change from baseline to week 68 – mmHg (SE) | −3·9 (0·7) | −2·9 (0·9) | –0·5 (0·8) | Semaglutide 2·4 mg – semaglutide 1·0 mg (mmHg); ETD: −1·0 (−3·3 to 1·2) |
| SF-36 physical functioning score |  |  |  |  |
| n | 381 | 377 | 374 |  |
| Week 68 mean ± SD | 52·1 ± 7·9 | 52·6 ± 7·1 | 50·5 ± 9·0 | Semaglutide 2·4 mg – placebo; ETD: 1·5 (0·4 to 2·6); p=0·0061 |
| Change from baseline to week 68 (SE) | 2·5 (0·4) | 2·4 (0·4) | 1·0 (0·4) | Semaglutide 2·4 mg – semaglutide 1·0 mg; ETD: 0·1 (−1·0 to 1·2) |
| IWQOL-Lite-CT physical function score |  |  |  |  |
| n | 381 | 377 | 374 |  |
| Week 68 mean ± SD | 79·0 ± 23·3 | 79·6 ± 20·8 | 74·8 ± 24·6 | Semaglutide 2·4 mg – placebo; ETD: 4·8 (1·8 to 7·9); p=0·0018 |
| Change from baseline to week 68 (SE) | 10·1 (1·0) | 8·7 (1·1) | 5·3 (1·1) | Semaglutide 2·4 mg – semaglutide 1·0 mg; ETD: 1·4 (−1·5 to 4·3) |
| **Exploratory secondary endpoints** | | | | |
| Body weight — kg |  |  |  |  |
| n | 388 | 380 | 376 |  |
| Week 68 mean ± SD | 89·6 ± 21·0 | 92·3 ± 20·7 | 96·8 ± 20·3 | Semaglutide 2·4 mg – placebo (kg); ETD: −6·1 (−7·2 to −5·0) |
| Change from baseline to week 68 — kg (SE) | −9·7 (0·4) | −6·9 (0·4) | −3·5 (0·4) | Semaglutide 2·4 mg – semaglutide 1·0 mg (kg); ETD: −2·7 (−3·8 to −1·7) |
| BMI — kg/m2 |  |  |  |  |
| n | 388 | 380 | 376 |  |
| Week 68 mean ± SD) | 32·3 ± 6·1 | 32·9 ± 5·9 | 34·6 ± 6·4 | Semaglutide 2·4 mg – placebo (kg/m2); ETD: −2·3 (−2·6 to −1·9) |
| Change from baseline to week 68 — kg/m2 (SE) | −3·5 (0.1) | −2·5 (0.1) | −1·3 (0.1) | Semaglutide 2·4 mg – semaglutide 1·0 mg (kg/m2); ETD: −1·0 (−1·3 to −0·6) |
| HbA1c ≤6·5% |  |  |  |  |
| n | 381 | 376 | 374 |  |
| Proportion of patients — n (%) at week 68 | 257 (67·5) | 226 (60·1) | 58 (15·5) | Semaglutide 2·4 mg / placebo; OR: 10·91 (7·51 to 15·85) |
|  |  |  |  | Semaglutide 2·4 mg / semaglutide 1·0 mg; OR: 1·39 (1·03 to 1·88) |
| HbA1c <7·0% |  |  |  |  |
| n | 381 | 376 | 374 |  |
| Proportion of patients — n (%) at week 68 | 299 (78·5) | 272 (72·3) | 99 (26·5) | Semaglutide 2·4 mg / placebo; OR: 9·77 (6·85 to 13·93) |
|  |  |  |  | Semaglutide 2·4 mg / semaglutide 1·0 mg; OR: 1·40 (1·01 to 1·96) |
| Fasting plasma glucose — mmol/L |  |  |  |  |
| n | 381 | 374 | 373 |  |
| Week 68 mean ± SD | 6·4 ± 2·0 | 6·7 ± 2·1 | 8·5 ± 2·7 | Semaglutide 2·4 mg – placebo (mmol/L); ETD: −2·0 (−2·4 to −1·7) |
| Change from baseline to week 68 — mmol/L (SE) | −2·1 (0·1) | −1·8 (0·1) | −0·1 (0·1) | Semaglutide 2·4 mg – semaglutide 1·0 mg (mmol/L); ETD: −0·3 (−0·7 to 0·1) |
| Fasting serum insulin — pmol/L |  |  |  |  |
| n | 373 | 364 | 376 |  |
| Week 68 geometric mean (CV) | 84·5 (74·3) | 92·5 (75·1) | 92·7 (72·6) | Semaglutide 2·4 mg / placebo; ETR: 0·94 (0·87 to 1·02) |
| Ratio to baseline† | 0·88 | 0·93 | 0·94 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 0·95 (0·87 to 1·03) |
| Diastolic blood pressure — mmHg |  |  |  |  |
| n | 387 | 379 | 362 |  |
| Week 68 ± SD | 78 ± 9 | 79 ± 9 | 79 ± 9 | Semaglutide 2·4 mg – placebo (mmHg); ETD: −0·7 (−2·0 to 0·6) |
| Change from baseline to week 68 — mmHg (SE) | −1·6 (0·4) | −0·6 (0·5) | −0·9 (0·5) | Semaglutide 2·4 mg – semaglutide 1·0 mg (mmHg); ETD: −0·9 (−2·2 to 0·4) |
| Lipids |  |  |  |  |
| Total cholesterol — mmol/L |  |  |  |  |
| n | 382 | 376 | 374 |  |
| Week 68 geometric mean (CV) | 4·4 (23·7) | 4·3 (25·6) | 4·4 (24·4) | Semaglutide 2·4 mg / placebo; ETR: 0·99 (0·96 to 1·02) |
| Ratio to baseline† | 0·99 | 0·98 | 0·99 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 1·01 (0·98 to 1·04) |
| HDL cholesterol — mmol/L |  |  |  |  |
| n | 377 | 376 | 370 |  |
| Week 68 geometric mean (CV) | 1·2 (23·6) | 1·2 (23·8) | 1·2 (23·1) | Semaglutide 2·4 mg / placebo; ETR: 1·03 (1·00 to 1·05) |
| Ratio to baseline† | 1·07 | 1·05 | 1·04 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 1·02 (1·00 to 1·04) |
| LDL cholesterol — mmol/L |  |  |  |  |
| n | 382 | 376 | 374 |  |
| Week 68 geometric mean (CV) | 2·3 (39·2) | 2·3 (41·0) | 2·3 (39·3) | Semaglutide 2·4 mg / placebo; ETR: 1·00 (0·96 to 1·05) |
| Ratio to baseline† | 1·00 | 0·99 | 1·00 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 1·01 (0·97 to 1·06) |
| VLDL cholesterol — mmol/L |  |  |  |  |
| n | 382 | 376 | 374 |  |
| Week 68 geometric mean (CV) | 0·6 (52·9) | 0·7 (54·3) | 0·7 (54·0) | Semaglutide 2·4 mg / placebo; ETR: 0·88 (0·83 to 0·93) |
| Ratio to baseline† | 0·79 | 0·83 | 0·90 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 0·95 (0·90 to 1·01) |
| Free fatty acids — mmol/L |  |  |  |  |
| n | 373 | 364 | 362 |  |
| Week 68 geometric mean (CV) | 0·5 (61·6) | 0·5 (54·4) | 0·6 (56·0) | Semaglutide 2·4 mg / placebo; ETR: 0·84 (0·78 to 0·91) |
| Ratio to baseline† | 0·84 | 0·86 | 0·99 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 0·97 (0·90 to 1·05) |
| Triglycerides — mmol/L |  |  |  |  |
| n | 382 | 376 | 374 |  |
| Week 68 geometric mean (CV) | 1·4 (53·1) | 1·5 (56·8) | 1·7 (58·7) | Semaglutide 2·4 mg / placebo; ETR: 0·86 (0·81 to 0·92) |
| Ratio to baseline† | 0·78 | 0·83 | 0·91 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 0·94 (0·89 to 1·00) |
| C-reactive protein (mg/L) |  |  |  |  |
| n | 382 | 376 | 374 |  |
| Week 68 geometric mean (CV) | 1·70 (224·6) | 1·93 (193·2) | 2·75 (176·1) | Semaglutide 2·4 mg / placebo; ETR: 0·61 (0·54 to 0·70) |
| Ratio to baseline† | 0·51 | 0·58 | 0·83 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 0·88 (0·77 to 1·01) |
| **Exploratory endpoints** | | | | |
| Concomitant glucose-lowering medication — n (%)‡ |  |  |  |  |
| n | 371 | 371 | 364 |  |
| Decreased | 106 (28·6) | 93 (25·1) | 26 (7·1) |  |
| No change | 247 (66·6) | 258 (69·5) | 249 (68·4) |  |
| Increased | 18 (4·9) | 19 (5·1) | 88 (24·2) |  |
| Missing | 0 | 1 (0·3) | 1 (0·3) |  |

All patients in the full analysis set are included in the treatment comparisons. \*The treatment policy estimand assesses treatment effect regardless of treatment discontinuation or rescue intervention; see Table S2 in the Supplementary Appendix (pp 10-13) for corresponding data for the trial product estimand (assesses treatment effect if all patients adhered to treatment and did not start any rescue intervention).

†Data presented as ratio from baseline to week 68 (ratio to baseline and corresponding baseline were log-transformed prior to analysis).

‡Proportion of patients with change in glucose-lowering medication from baseline to week 68.

BMI=body mass index. CI=confidence interval. CV=coefficient of variation in percent. ETD=estimated treatment difference. ETR=estimated treatment ratio. HbA1c=glycated haemoglobin. HDL=high-density lipoprotein. LDL=low-density lipoprotein. OR=odds ratio. SD=standard deviation. VLDL=very low-density lipoprotein.

***Table 3:*** Adverse Events

|  | **Semaglutide 2·4 mg (N=403)** | | | **Semaglutide 1·0 mg (N=402)** | | | **Placebo (N=402)** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **n (%)** | **Events** | **Events per 100 patient years** | **n (%)** | **Events** | **Events per 100 patient years** | **n (%)** | **Events** | **Events per 100 patient years** |
| Any adverse event | 353 (87·6) | 2197 | 412·2 | 329 (81·8) | 1859 | 350·9 | 309 (76·9) | 1388 | 262·7 |
| Serious adverse events | 40 (9·9) | 71 | 13·3 | 31 (7·7) | 53 | 10·0 | 37 (9·2) | 53 | 10·0 |
| Adverse events leading to trial product discontinuation | 25 (6·2) | 34 | 6·4 | 20 (5·0) | 23 | 4·3 | 14 (3·5) | 18 | 3·4 |
| Gastrointestinal disorders | 17 (4·2) | 24 | 4·5 | 14 (3·5) | 16 | 3·0 | 4 (1·0) | 6 | 1·1 |
| Fatal events\*† | 1 (0·2) | 1 | 0·2 | 1 (0·2) | 1 | 0·2 | 1 (0·2) | 3 | 0·5 |
| **Adverse events reported in ≥10% of patients‡** | | | | | | | | | |
| Nausea | 136 (33·7) | 249 | 46·7 | 129 (32·1) | 198 | 37·4 | 37 (9·2) | 45 | 8·5 |
| Vomiting | 88 (21·8) | 188 | 35·3 | 54 (13·4) | 93 | 17·6 | 11 (2·7) | 12 | 2·3 |
| Diarrhoea | 86 (21·3) | 141 | 26·5 | 89 (22·1) | 158 | 29·8 | 48 (11·9) | 66 | 12·5 |
| Constipation | 70 (17·4) | 82 | 15·4 | 51 (12·7) | 70 | 13·2 | 22 (5·5) | 26 | 4·9 |
| Nasopharyngitis | 68 (16·9) | 115 | 21·6 | 47 (11·7) | 69 | 13·0 | 59 (14·7) | 92 | 17·4 |
| Upper respiratory tract infection | 42 (10·4) | 48 | 9·0 | 37 (9·2) | 54 | 10·2 | 38 (9·5) | 50 | 9·5 |
| **Safety areas of interest (MedDRA)§** | | | | | | | | | |
| Gastrointestinal disorders | 256 (63·5) | 924 | 173·3 | 231 (57·5) | 724 | 136·7 | 138 (34·3) | 262 | 49·6 |
| Gallbladder-related disorders | 1 (0·2) | 2 | 0·4 | 4 (1·0) | 4 | 0·8 | 3 (0·7) | 4 | 0·8 |
| Hepatobiliary | 1 (0·2) | 2 | 0·4 | 3 (0·7) | 3 | 0·6 | 3 (0·7) | 4 | 0·8 |
| Cholelithiasis | 1 (0·2) | 1 | 0·2 | 3 (0·7) | 3 | 0·6 | 3 (0·7) | 3 | 0·6 |
| Hepatic disorders | 10 (2·5) | 12 | 2·3 | 10 (2·5) | 11 | 2·1 | 14 (3·5) | 21 | 4·0 |
| Acute pancreatitis\*¶ | 1 (0·2) | 2 | 0·3 | 0 | 0 | 0 | 1 (0·2) | 1 | 0·2 |
| Cardiovascular events\*¶ | 6 (1·5) | 6 | 1·0 | 6 (1·5) | 7 | 1·2 | 5 (1·2) | 7 | 1·2 |
| Allergic reactions | 26 (6·5) | 29 | 5·4 | 22 (5·5) | 24 | 4·5 | 18 (4·5) | 21 | 4·0 |
| Injection site reactions | 12 (3·0) | 18 | 3·4 | 6 (1·5) | 7 | 1·3 | 10 (2·5) | 18 | 3·4 |
| Malignant neoplasms\* | 5 (1·2) | 6 | 1·0 | 7 (1·7) | 8 | 1·4 | 8 (2·0) | 9 | 1·6 |
| Psychiatric disorders | 24 (6·0) | 29 | 5·4 | 23 (5·7) | 28 | 5·3 | 15 (3·7) | 16 | 3·0 |
| Acute renal failure | 4 (1·0) | 5 | 0·9 | 2 (0·5) | 2 | 0·4 | 2 (0·5) | 2 | 0·4 |
| Hypoglycaemia# | 23 (5·7) | 51 | 9·6 | 22 (5·5) | 29 | 5·5 | 12 (3·0) | 18 | 3·4 |
| Retinal disorder events\* | 28 (6·9) | 36 | 6·3 | 25 (6·2) | 30 | 5·3 | 17 (4·2) | 19 | 3·4 |
| Diabetic retinopathy | 16 (4·0) | 17 | 3·0 | 11 (2·7) | 13 | 2·3 | 11 (2·7) | 12 | 2·1 |

Safety analysis set. All data are on-treatment (during treatment with trial product [any dose of trial medication administered within the previous 49 days (i.e. any period of temporary treatment interruption with trial product was excluded)]) adverse events, unless indicated otherwise.

n (%) is the number and percentage of patients experiencing at least one event.

\*In-trial observation period.

†Semaglutide 1·0 mg group: one case of death due to cardiorespiratory arrest in a patient with a medical history of coronary artery disease, triple vessel disease, dilated cardiomyopathy with reduced left ventricular ejection fraction of 20%; semaglutide 2·4 mg group: one case of death due to myocardial infarction in a patient with a long-standing history of type 2 diabetes mellitus, hypertension, obesity, and previous smoking status (the patient also had a ‘T-wave inversion’ detected on electrocardiogram for 2 years); placebo group: one case of death due to metastatic hepatocellular carcinoma, pulmonary embolism, and respiratory failure in a patient with a history of alcohol misuse, hepatic cirrhosis, hepatopathy, obesity, and type 2 diabetes mellitus.

‡Most common adverse events by preferred term reported in ≥10% of patients in either treatment group.

§Identified via MedDRA searches; gastrointestinal disorders and psychiatric disorders defined by MedDRA version 22.1 system organ class. Hepatobiliary ‘System Organ Class’ and Cholelithiasis ‘Preferred term’.

¶Event Adjudication Committee-confirmed events.

#Severe or blood glucose-confirmed hypoglycaemia. MedDRA denotes Medical Dictionary for Regulatory Activities.

***Figure 1:*** *Patient flow*

\*Patients who discontinued treatment prematurely all completed the trial. In analyses of the treatment policy estimand, all data collected were included, regardless of status of using randomised treatment.

Among treatment completers: in the semaglutide 2·4 mg group at the last treatment visit, 84% of patients were on the full intended dose (2·4 mg), 5% were on 1·7 mg, and 10% on <1·7 mg. In the semaglutide 1·0 mg group, 95% of patients were on the full dose (1·0 mg) and 5% were on ≤0.5 mg. In the placebo group, 97% completed treatment with the intended dose, while only 3% were on a lower dose than intended.

s.c.=subcutaneous.

***Figure 2:*** Semaglutide 2·4 mg once weekly compared with semaglutide 1·0 mg once weekly and placebo on body weight parameters

Panels A and B show the observed mean percentage change from baseline in body weight over time for patients in the full analysis set during the in-trial and on-treatment observation period, respectively. Error bars are ± standard error of the mean. Numbers shown in the lower panel are patients contributing to the mean.

Panels C and D show the observed proportions of patients achieving body weight reductions of at least 5%, 10%, 15%, and 20% from baseline at week 68 in the full analysis population during the in-trial observation period and on-treatment observation period, respectively.

On-treatment definition: a time point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days.

Data are for the full analysis set.

CI=confidence interval. MMRM=mixed model for repeated measurements.

***Figure 3:*** Semaglutide 2·4 mg once weekly compared with semaglutide 1·0 mg once weekly and placebo on selected confirmatory and exploratory secondary endpoints (baseline to week 68)

Line graphs show the observed mean change from baseline over time in waist circumference (A), systolic blood pressure (B), HbA1c (C), SF-36 physical functioning score (E), and IWQOL-Lite-CT physical function score (F) for patients in the full analysis set during the in-trial observation period. Error bars are ± standard error of the mean. Numbers shown in the lower panel are patients contributing to the mean.

Panel D shows proportion of patients achieving HbA1c targets of ≤6·5% or <7·0% at week 68 for the in-trial period.

Data are for the full analysis set.

CI=confidence interval. HbA1c=glycated haemoglobin.