Efficacy and safety of once-weekly semaglutide 2·4 mg versus placebo in people with obesity and prediabetes (STEP 10) : a randomised, double-blind, placebo-controlled, multicentre phase 3 trial

STEP 10 Study Group

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Efficacy and safety of once-weekly semaglutide 2·4 mg versus placebo in people with obesity and prediabetes (STEP 10): a randomised, double-blind, placebo-controlled, multicentre phase 3 trial

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Summary

Background There are currently limited data regarding the effect of semaglutide 2·4 mg in individuals with obesity and prediabetes in clinical trials. We aimed to assess the efficacy and safety of semaglutide 2·4 mg for weight management and glycaemic control in participants with obesity and prediabetes.

Methods STEP 10 was a randomised, double-blind, parallel-group, phase 3 trial done across 30 trial sites in Canada, Denmark, Finland, Spain, and the UK and included participants aged 18 years or older with a BMI of 30 kg/m² or higher and prediabetes according to UK National Institute for Health and Care Excellence criteria (defined as having at least one of the following at screening: HbA_{1c} of 6·0–6·4% [42–47 mmol/mol] or fasting plasma glucose [FPG] of 5·5–6·9 mmol/L). Participants were randomly assigned (2:1) to once-weekly subcutaneous semaglutide 2·4 mg or placebo with diet and physical activity counselling for 52 weeks, followed by a 28-week off-treatment period. Primary endpoints were percentage change in bodyweight and proportion of participants reverting to normoglycaemia (HbA_{1c} <6·0% [<42 mmol/mol] and FPG <5·5 mmol/L) at week 52 (assessed in all randomly assigned participants by intention to treat). Selective safety data were collected for participants who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT05040971, and is complete.

Findings Between Sept 16 and Dec 29, 2021, 138 participants were randomly assigned to semaglutide 2·4 mg and 69 to placebo. 147 (71%) were female and 60 (29%) were male; 183 (88%) were White. All randomly assigned participants received at least one dose of study drug. Baseline mean age was 53 years (SD 11), bodyweight 111·6 kg (22·2), BMI 40·1 kg/m² (6·9), waist circumference 120·1 cm (14·7), HbA_{1c} 5·9% (0·3; 41·3 mmol/mol [3·0]), and FPG 5·9 mmol/L (0·6). There was a significantly greater reduction in bodyweight with semaglutide 2·4 mg than with placebo at week 52 (–13·9% [SD 0·7] *vs* –2·7% [0·6]; estimated treatment difference –11·2% [95% CI –13·0 to –9·4]; p<0·0001). Greater proportions of participants reverted to normoglycaemia at week 52 with semaglutide 2·4 mg than with placebo (103 [81%] of 127 *vs* nine [14%] of 64; odds ratio 19·8 [95% CI 8·7 to 45·2]; p<0·0001). Serious adverse events occurred in 12 (9%) participants receiving semaglutide 2·4 mg versus six (9%) receiving placebo. Adverse events leading to treatment discontinuation occurred in eight (6%) participants in the semaglutide 2·4 mg group versus one (1%) participant in the placebo group. No new safety signals were reported.

Interpretation Semaglutide 2·4 mg provided superior reduction in bodyweight and reversion to normoglycaemia versus placebo in participants with obesity and prediabetes. The safety and tolerability profile was consistent with previous studies and with the GLP-1 receptor agonist class. These findings support the potential use of semaglutide 2·4 mg as a treatment option for individuals with obesity and prediabetes to achieve reversion to normoglycaemia.

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For the Spanish translation of the abstract see Online for appendix 1

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Introduction

Prediabetes (non-diabetic hyperglycaemia) is a global health concern, occurring in about 6–9% of adults.[1] It is characterised by blood glucose concentrations above normal but below the threshold for a diagnosis of type 2 diabetes, and is associated with an increased risk of developing type 2 diabetes.[1,2] Obesity, a prevalent chronic relapsing condition affecting 14% of the world's population in 2020 and an estimated 24% in 2035, is also associated with more than 220 comorbidities, including a pronounced risk of developing type 2 diabetes.[3,4] Prediabetes is also associated with obesity-related complications that lead to an increased risk of mortality, such as major cardiovascular adverse events; as such, individuals with prediabetes benefit from weight reduction.[5]

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See Online for appendix 2

Research in context

Evidence before this study

PubMed was searched for clinical trial results published between March 25, 2019, and March 25, 2024, with no language restrictions, using the search terms "glucagon-like peptide-1 receptor agonist", "GLP-1 receptor agonist", "semaglutide", "obesity", "overweight", and "prediabetes". The only randomised semaglutide data yielded from the search was a secondary analysis of STEP 1, STEP 3, and STEP 4 trials, which reported that semaglutide 2·4 mg was associated with a significant improvement in glycaemia versus placebo among participants with baseline prediabetes. So far, no other phase 3 trials have investigated the effect of semaglutide 2·4 mg in a population with obesity and prediabetes. The once-weekly GLP-1 receptor agonist semaglutide 2·4 mg, which is approved for weight management, is being investigated in several different populations as part of the STEP programme of clinical trials. The STEP 2 trial showed that semaglutide 2·4 mg is effective at reducing bodyweight and improving cardiometabolic risk factors and glycaemic control in participants with type 2 diabetes and obesity. However, there is a need to investigate the effect of semaglutide 2·4 mg specifically in individuals with obesity and prediabetes in a phase 3 trial. STEP 10 assessed the effect of semaglutide 2·4 mg in a population of participants with obesity and prediabetes.

Added value of this study

STEP 10 was the first phase 3 trial to investigate the efficacy of semaglutide in a trial population only consisting of participants with obesity and prediabetes, with a primary endpoint specifically evaluating reversion to normoglycaemia. Results of STEP 10 add to existing evidence on the benefits of obesity management with pharmacotherapy on the progression of prediabetes, a condition that as of yet has few treatment options.

Implications of all the available evidence

This trial showed superior bodyweight reductions and glycaemic control with once-weekly subcutaneous semaglutide 2·4 mg versus placebo in a population of participants with obesity and prediabetes. The findings of STEP 10 support semaglutide 2·4 mg as an efficacious and well tolerated treatment option for weight management and highlight the glycaemic benefit of semaglutide 2·4 mg treatment in participants with obesity and prediabetes. These findings suggest that semaglutide 2·4 mg should be considered for the treatment of individuals with obesity and prediabetes to achieve weight loss and potentially achieve reversion to normoglycaemia.

Obesity management should be focused towards improving patient-centred health outcomes including obesity-related complications;[6] beneficial effects on glycaemic status can be achieved with bodyweight loss in individuals with prediabetes.[5] A study investigating lifestyle intervention for weight management in participants with prediabetes found that lifestyle intervention can reduce the risk of progression of type 2 diabetes.[7] However, long-term weight loss through diet and exercise alone might be challenging because of metabolic and hormonal adaptations that resist weight loss and promote weight regain.[8] Hence, there is a need for efficacious pharmacotherapeutic agents to help individuals with overweight or obesity to achieve and sustain long-term weight loss and thereby help to improve obesity-related complications, including prediabetes.

Once-weekly subcutaneous semaglutide 2·4 mg, a GLP-1 receptor agonist, has been shown to reduce bodyweight[9] and is approved in the USA,[10] Europe,[11] and other countries for weight management in individuals with a BMI of 30 kg/m² or higher or 27 kg/m² or higher and at least one obesity-related comorbidity.

The STEP 2 trial showed that semaglutide 2·4 mg is effective at lowering bodyweight and improving glycaemic control and cardiometabolic risk factors in participants with type 2 diabetes and obesity.[10,11] Participants with obesity in the STEP 1 and STEP 4 trials reported similar results. However, some weight regain and loss of cardiometabolic and glycaemic benefit was observed after cessation of semaglutide 2·4 mg treatment in the STEP 1 extension and STEP 4 trials.[12,13] The weight regain observed in these trials highlights the chronicity and relapsing nature of obesity, which has also been observed with lifestyle intervention, other obesity pharmacotherapies, and bariatric surgery.[8,14] Therefore, there is a need to understand not only how semaglutide 2·4 mg can improve bodyweight, glycaemic parameters, and cardiovascular risk factors in people with prediabetes, but also whether any benefits persist or regress following cessation of semaglutide 2·4 mg.

We present the results of the STEP 10 trial, which aimed to evaluate the efficacy and safety of once-weekly subcutaneous semaglutide 2·4 mg versus placebo as an adjunct to lifestyle intervention on bodyweight and reversion to normoglycaemia in participants with obesity and prediabetes at baseline.

Methods

Study design and participants

STEP 10 was a two-arm, double-blind, parallel-group, randomised, phase 3 trial done across 30 sites in Canada, Denmark, Finland, Spain, and the UK (appendix 2 pp 4, 28). Eligible participants were aged 18 years or older with a BMI of 30 kg/m² or higher and prediabetes according to National Institute for Health and Care Excellence (NICE) criteria, defined as having at least one of the following: HbA_{1c} of 6·0–6·4% (42–47 mmol/mol) at screening or fasting plasma glucose (FPG) of

5·5–6·9 mmol/L at screening.[2] Participants were excluded if they had a history of diabetes or HbA_{1c} of 6·5% (48 mmol/mol) or higher or FPG of 7·0 mmol/L or higher at screening; or the following within 90 days of screening: treatment with glucose-lowering agents, a self-reported change in bodyweight of more than 5 kg, and treatment with any medication for obesity. Full eligibility criteria are available in appendix 2 (p 5).

The study was conducted in accordance with the International Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines.[15] The protocol (appendix 2) and amendments were approved by the relevant institutional review board or independent ethics committee at each study site. All participants provided written informed consent before any trial-related activities. This trial is registered with ClinicalTrials.gov, NCT05040971, and is complete.

Randomisation and masking

Participants were randomly assigned (2:1) to receive semaglutide 2·4 mg or placebo using an interactive web-response system. The site accessed the interactive web-response system before the start of trial drug administration for each participant. Treatment allocation remained masked to participants, investigators, and the trial sponsor during the entire trial until after database lock.

Procedures

During the main phase (from randomisation to week 52), participants were initiated at a once-weekly semaglutide or placebo dose of 0·25 mg, with dose increases every 4 weeks (to doses of 0·5 mg, 1·0 mg, 1·7 mg, and 2·4 mg per week), aiming to reach the maintenance dose of 2·4 mg by week 16. At every visit in the first 52-week phase (nine visits in total), participants were offered individual diet and physical activity counselling by a dietitian or a similar qualified health-care professional.

The last visit in the main phase (visit 12; week 52) was followed by the 28-week off-treatment period, in which participants were offered healthy lifestyle counselling according to standard clinical practice and country-specific guidelines. Two visits were planned, at weeks 66 and 80, for assessment of bodyweight and glycaemic and cardiometabolic parameters. The total trial duration (main phase and off-treatment period) was 80 weeks.

Trial visits by week of outcome measurements are shown in appendix 2 (p 16). Selected adverse events were assessed at all trial visits, with a specific safety visit at week 57. Participants were considered to have completed the trial if they had completed all phases of the trial, including the last visit (week 80).

Outcomes

The primary endpoints were percentage change in bodyweight from baseline to week 52 and the proportion of participants who reverted to normoglycaemia (HbA_{1c} <6·0% [<42 mmol/mol] and FPG <5·5 mmol/L) at week 52 with semaglutide 2·4 mg versus placebo.

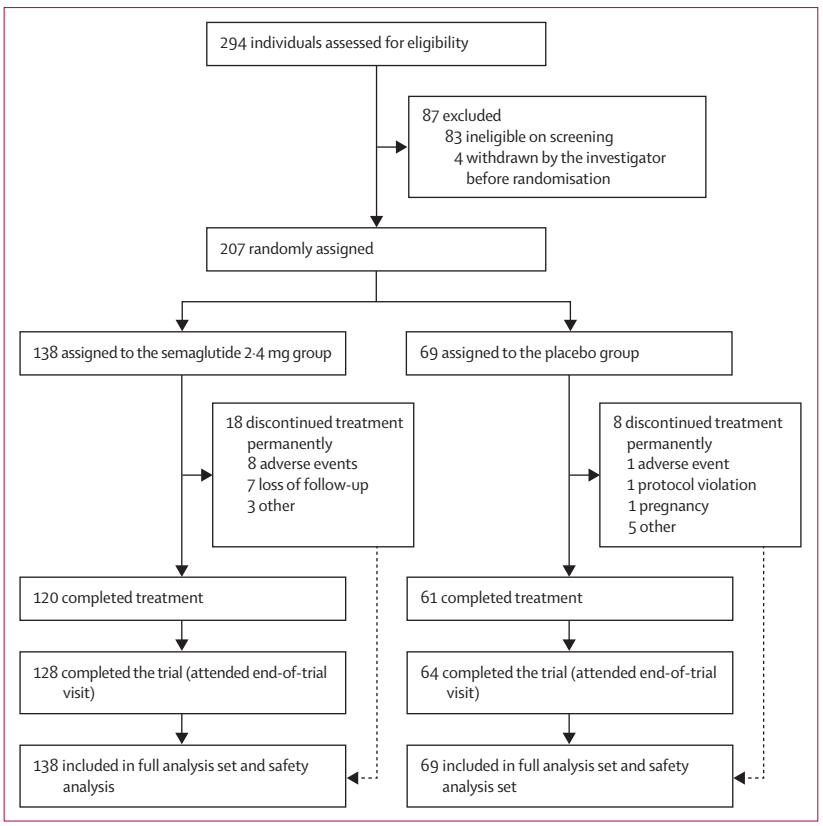

Figure 1: **Trial profile**
Of the 83 individuals who were ineligible on screening, 64 participants did not meet the inclusion criterion of having prediabetes (defined as at least one of the following: HbA_{1c} of 6·0–6·4% (42–47 mmol/mol) or FPG 5·5–6·9 mmol/L (99–125 mg/dL) as measured by central laboratory at screening); 30 participants met exclusion criteria, among which the major reasons included participants having FPG of 7·0 mmol/L (126 mg/dL) or higher, as measured by central laboratory at screening (17 [20%]) and participants with an HbA_{1c} of 6·5% (48 mmol/mol) or higher, as measured by central laboratory at screening (eight [10%]). FPG=fasting plasma glucose.

Supportive secondary endpoints (semaglutide 2·4 mg *vs* placebo) included change from baseline to week 52 in bodyweight (kg), HbA_{1c} (% and percentage points), FPG (mmol/L), waist circumference (cm), systolic blood pressure (mm Hg), pulse (beats per min [bpm]), lipids (triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, and VLDL cholesterol [%]), and proportion of participants at week 52 who had a weight loss of at least 5%, at least 10%, at least 15%, and at least 20%.

Prespecified exploratory endpoints included change from baseline to week 80 in bodyweight (%), HbA_{1c} (% and mmol/mol), FPG (mmol/L), waist circumference (cm), systolic blood pressure (mm Hg), and lipids (triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, and VLDL cholesterol [%]). Other prespecified exploratory endpoints included proportion of participants who reached normoglycaemia at week 80; proportion of participants progressing to type 2 diabetes at week 52; proportion of participants progressing to type 2 diabetes at week 80; change from baseline to week 52 in the

	Semaglutide 2·4 mg group (n=138)	Placebo group (n=69)	Total (n=207)
Age, years	53 (11)	53 (11)	53 (11)
Sex			
Female	100 (72%)	47 (68%)	147 (71%)
Male	38 (28%)	22 (32%)	60 (29%)
Country of residence			
Canada	47 (34%)	28 (41%)	75 (36%)
Spain	22 (16%)	10 (14%)	32 (15%)
UK	26 (19%)	19 (28%)	45 (22%)
Denmark	19 (14%)	4 (6%)	23 (11%)
Finland	24 (17%)	8 (12%)	32 (15%)
Race			
White	124 (90%)	59 (86%)	183 (88%)
Asian	4 (3%)	5 (7%)	9 (4%)
Black or African American	6 (4%)	3 (4%)	9 (4%)
American Indian or Alaska Native	0	1 (1%)	1 (<1%)
Other*	4 (3%)	1 (1%)	5 (2%)
Bodyweight, kg	111·9 (21·5)	111·0 (23·5)	111·6 (22·2)
BMI, kg/m²	39·9 (6·6)	40·4 (7·6)	40·1 (6·9)
Waist circumference, cm	120·1 (14·8)	119·9 (14·7)	120·1 (14·7)
HbA_{1c}, %	5·9% (0·3)	5·9% (0·3)	5·9% (0·3)
HbA_{1c}, mmol/mol	41·2 (3·1)	41·3 (2·8)	41·3 (3·0)
FPG, mg/dL	105·1 (9·8)	107·7 (12·4)	106·0 (10·7)
FPG, mmol/L	5·8 (0·5)	6·0 (0·7)	5·9 (0·6)
Systolic blood pressure, mm Hg	131 (15)	129 (15)	131 (15)
Geometric mean (coefficient of variation) in lipids, mmol/L			
Total cholesterol	4·8 (19·8)	4·7 (18·7)	4·7 (19·5)
VLDL cholesterol	0·7 (44·4)	0·7 (43·2)	0·7 (43·9)
Triglycerides	1·6 (46·4)	1·5 (44·5)	1·6 (45·8)
HDL cholesterol	1·2 (26·0)	1·2 (22·7)	1·2 (24·9)
LDL cholesterol	2·7 (31·6)	2·7 (32·1)	2·7 (31·7)
Comorbidities at screening			
Hypertension	64 (46%)	32 (46%)	96 (46%)
Dyslipidaemia	63 (46%)	22 (32%)	85 (41%)
Knee osteoarthritis	18 (13%)	8 (12%)	26 (13%)
Obstructive sleep apnoea	14 (10%)	8 (12%)	22 (11%)
Cardiovascular disease	14 (10%)	4 (6%)	18 (9%)

Data are mean (SD) or n (%) unless otherwise specified. Percentages might not sum to 100 as a result of rounding. FPG=fasting plasma glucose. *American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander.

Table 1: **Demographics and baseline characteristics of the full analysis set**

EQ-5D-3L index score and visual analogue scale, and Work Limitations Questionnaire 25-item (WLQ-25) Six-item Physical Demands scale and total score. A full list of objectives and endpoints (including exploratory endpoints) are included in appendix 2 (pp 7, 8).

STEP 10 used selective safety data collection. A full list of safety data recorded in this trial is included in appendix 2 (p 9).

Statistical analysis

A sample size of 207 participants provided more than 99% power for the primary endpoints (assumptions listed in appendix 2 pp 10, 17). Efficacy endpoints were analysed using the full analysis set (all randomly assigned participants by intention to treat). Safety endpoints were analysed using the safety analysis set (all randomly assigned participants who received at least one dose of randomly assigned treatment). All tests of superiority for primary endpoints were for semaglutide 2·4 mg versus placebo. There was no allowance for multiple comparisons for secondary outcomes.

Two observation periods were defined for this study: the in-trial period and on-treatment period (appendix 2 p 18). The treatment policy estimand is the traditional intention-to-treat analysis, with effects assessed regardless of treatment discontinuation or dose reduction of randomly assigned treatment or initiation of other glucose-lowering medication or weight management therapies (weight management drugs or bariatric surgery). The trial product estimand is the effects assessed if the trial product was taken as intended with effects until first treatment discontinuation or initiation of other glucose-lowering medication or weight management therapies. All reported results are for the treatment policy estimand, unless otherwise stated.

Results from statistical analyses are shown with two-sided 95% CIs and corresponding p values. Superiority was established for confirmatory statistical evaluations if p values were less than 0·05, with a point estimate favouring semaglutide 2·4 mg versus placebo.

Two estimands were used to assess treatment efficacy from different perspectives and accounted for intercurrent events and missing data differently; the treatment policy estimand (primary) and the trial product estimand (appendix 2 p 11).[16]

For the treatment policy estimand, the primary endpoints were analysed using linear regression (ANCOVA) for change in bodyweight and logistic regression for reversion to normoglycaemia. For the analysis of bodyweight, the model included randomly assigned treatment as a factor and baseline bodyweight as a covariate. For reversion to normoglycaemia, the model included randomly assigned treatment as a factor, and baseline HbA_{1c} and FPG as covariates. Results from statistical analyses are shown with two-sided 95% CIs and corresponding p values. Several prespecified sensitivity analyses (bodyweight endpoint: J2R-MI [jump to reference multiple imputation] and TP-MI [tipping point multiple imputation sensitivity analyses]; change to normoglycemia endpoint: non-responders, tipping point, and subset of participants with prediabetes at baseline sensitivity analyses) using different imputation methods were performed for the co-primary endpoints to assess the effect of missing data (appendix 2 p 12). The trial product estimand was assessed using

a mixed model for repeated measurements approach (appendix 2 p 13).

All statistical analyses were performed using SAS software (version 9.4). The database used for the study was Oracle (version 5.2). Data were transferred from the database to Study Data Tabulation Model as raw database and Analysis Data Model as analysis database, according to Clinical Data Interchange Standards Consortium standards (appendix 2 p 14).

Role of the funding source

Novo Nordisk was responsible for the trial design, preparing the trial protocol and statistical analysis plan, and performing the statistical analyses. The investigators were responsible for trial-related medical decisions and data collection. This article was drafted under the guidance of the authors, with medical writing and editorial support paid for by the funder.

Results

Between Sept 16 and Dec 29, 2021, 294 participants were screened and 207 (70%; 147 [71%] were female and 60 [29%] were male; 183 [88%] were White) were randomly assigned to receive semaglutide 2·4 mg (n=138) or placebo (n=69). All randomly assigned participants received at least one dose of study drug. 181 (87%) randomly assigned participants completed treatment (120 [87%] in the semaglutide 2·4 mg group and 61 [88%] in the placebo group), and 192 (93%) participants completed the trial (128 [93%] in the semaglutide 2·4 mg group and 64 [93%] in the placebo group; figure 1). Among participants who completed treatment, 101 (84%) were on the intended maximum dose of semaglutide 2·4 mg at week 20 and 106 (88%) at week 52.

Baseline characteristics are shown in table 1 and appendix 2 (p 19). Overall mean bodyweight was 111·6 kg (SD 22·2), BMI was 40·1 kg/m² (6·9), waist circumference was 120·1 cm (14·7), HbA_{1c} was 5·9% (0·3; 41·3 mmol/mol [3·0]), and FPG was 5·9 mmol/L (0·6).

Based on the treatment policy estimand, estimated mean percentage changes in bodyweight from baseline to week 52 were greater with semaglutide 2·4 mg (–13·9% [SD 0·7]) compared with placebo (–2·7% [0·6]; estimated treatment difference –11·2% [95% CI –13·0 to –9·4]; p<0·0001; figure 2A, B). Corresponding changes in bodyweight for the trial product estimand were similar (appendix 2 pp 29–30).

From baseline to week 80 (including 28 weeks off treatment), the observed mean change in bodyweight was –7·9% (SD 7·2) for semaglutide 2·4 mg and –1·3% (5·0) for placebo (figure 2A). Similar reductions were observed for bodyweight in kilograms (appendix 2 p 31). The reported changes in bodyweight from baseline to week 80 indicate partial bodyweight regain from week 52 to week 80; although bodyweight had not returned to baseline levels, the bodyweight trajectory continued upward at the end of the observation period (figure 2A). The cumulative distribution of change in bodyweight from baseline to week 52 is shown in appendix 2 (p 32).

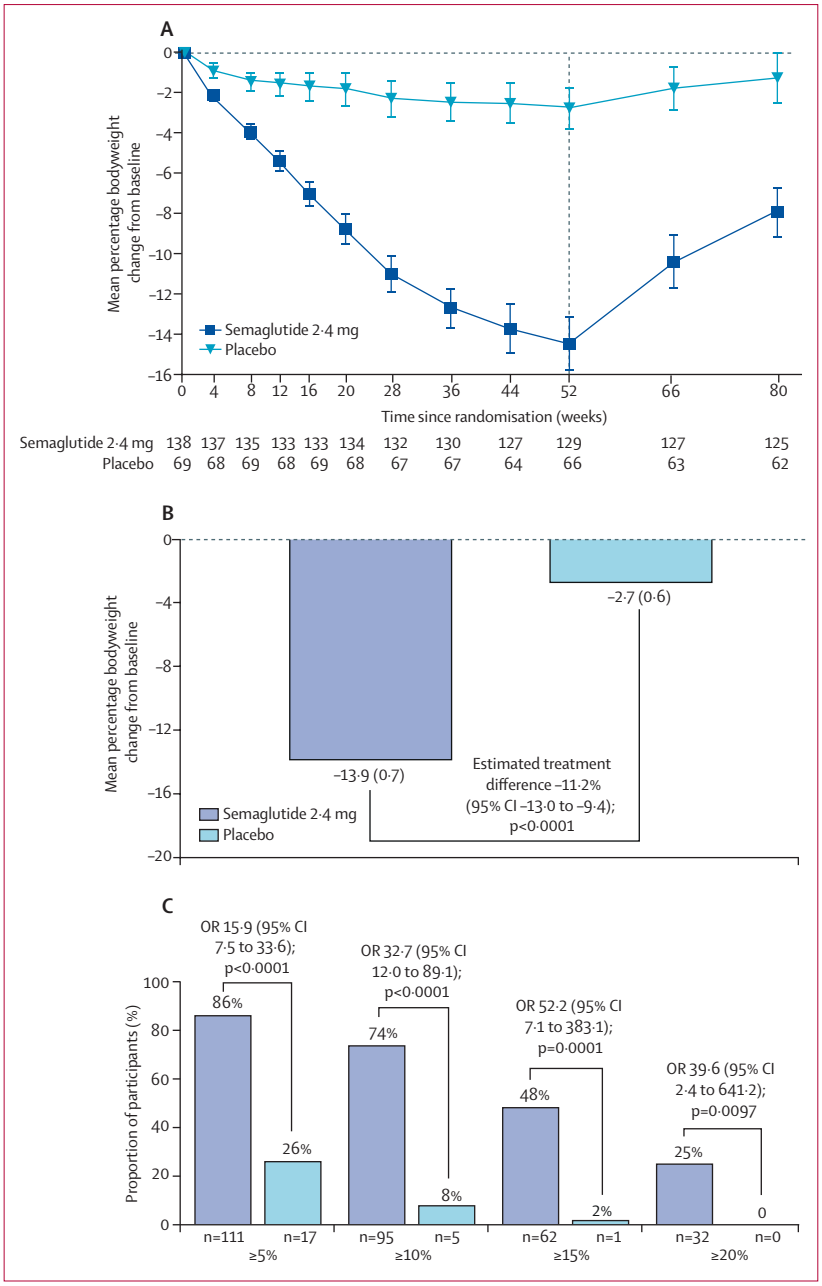

Figure 2: **Comparison of bodyweight parameters with semaglutide 2·4 mg versus placebo in the full analysis set during the in-trial observation period**

(A) Observed mean percentage change in bodyweight over time (error bars indicate 95% CIs; numbers below the panels are the number of participants contributing to the mean; dashed vertical line indicates end of treatment and the start of the off-treatment period). (B) Observed mean (SE) percentage change in bodyweight from baseline to week 52. The estimated treatment difference is for the treatment policy estimand. (C) Observed proportions of participants who had bodyweight reductions of at least 5%, 10%, 15%, and 20% at week 52. The ORs are for the treatment policy estimand. OR=odds ratio.

Participants in the semaglutide 2·4 mg group were more likely to have a bodyweight loss of at least 5% (odds ratio

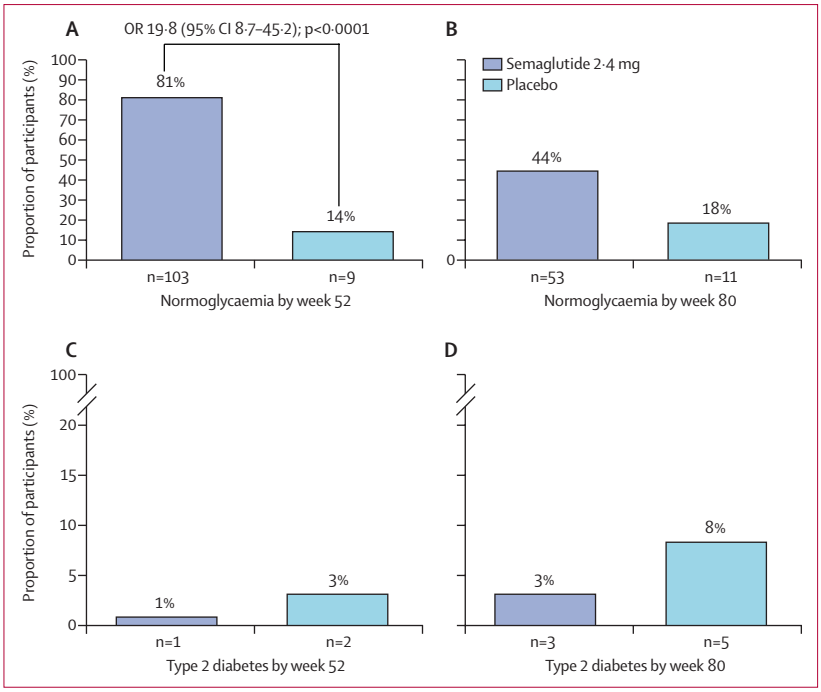

Figure 3: **Proportion of participants who reverted to normoglycaemia or progressed to type 2 diabetes with semaglutide 2·4 mg versus placebo in the full analysis set during the in-trial observation period**
Observed proportions of participants who reverted to normoglycaemia (HbA_{1c} <6·0% [<42 mmol/mol] and FPG <5·5 mmol/L) at week 52 (A; OR is for the treatment policy estimand) and week 80 (B). Observed proportions of who progressed to type 2 diabetes (HbA_{1c} ≥6·5% [≥48 mmol/mol] or FPG ≥7·0 mmol/L, verified with a repeated blood sample within 4 weeks from baseline) at week 52 (C) and week 80 (D). OR for panel A is for the treatment policy estimand. FPG=fasting plasma glucose. OR=odds ratio.

[OR] 15·9 [95% CI 7·5–33·6]; p<0·0001), at least 10% (32·7 [12·0–89·1]; p<0·0001), at least 15% (52·2 [7·1–383·1]; p=0·0001), and at least 20% (39·6 [2·4–641·2]; p=0·0097) than those in the placebo group at week 52 (figure 2C). Results for the trial product estimand were similar (appendix 2 p 33).

On the basis of the treatment policy estimand, a greater proportion of participants reverted to normoglycaemia at week 52 with semaglutide 2·4 mg than with placebo (103 [81%] of 127 *vs* nine [14%] of 64; OR 19·8 [95% CI 8·7–45·2]; p<0·0001; figure 3A). Corresponding changes for the trial product estimand were similar (appendix 2 p 34). At week 80, 53 (44%) of 120 participants in the semaglutide 2·4 mg group versus 11 (18%) of 60 participants in the placebo group reverted to normoglycaemia from baseline (figure 3B). Of the participants who reverted to normoglycaemia at week 52, and with available data at week 80, 44 (45%) of 97 in the semaglutide 2·4 mg group and four (57%) of nine in the placebo group regressed to prediabetes.

Across all bodyweight loss groups (≥5%, ≥10%, ≥15%, and ≥20%), most participants in the semaglutide 2·4 mg group reverted to normoglycaemia at week 52; a small proportion of participants still had prediabetes, and no participants who reached these bodyweight loss thresholds progressed to type 2 diabetes (appendix 2 p 35).

At week 52, one (1%) of 127 participants treated with semaglutide 2·4 mg had progressed to type 2 diabetes (this participant did not reach bodyweight loss ≥5%) compared with two (3%) of 64 participants receiving placebo (figure 3C). At week 80, three (3%) of 120 participants treated with semaglutide 2·4 mg had progressed to type 2 diabetes compared with five (8%) of 60 participants receiving placebo (figure 3D).

On the basis of the treatment policy estimand, semaglutide 2·4 mg was associated with significantly greater reductions from baseline to week 52 than placebo in HbA_{1c} (estimated treatment difference –0·5 [95% CI –0·5 to –0·4]; p<0·0001), FPG (–0·6 [–0·8 to –0·4]; p<0·0001), waist circumference (–8·3 [–10·4 to 6·2]; p<0·0001), and systolic blood pressure (–7·8 [–11·3 to –4·3]; p<0·0001; appendix 2 p 36). During the off-treatment period, HbA_{1c}, FPG, waist circumference, and systolic blood pressure increased in participants in the semaglutide 2·4 mg group but did not fully revert to baseline values (table 2; appendix 2 p 36).

At week 52, semaglutide 2·4 mg led to significant improvements in total cholesterol, VLDL cholesterol, and triglycerides (appendix 2 p 37). A similar trend was observed for LDL cholesterol, VLDL cholesterol, and triglycerides at week 80 as the previously mentioned cardiometabolic parameters. At week 80, total cholesterol and HDL cholesterol reverted to baseline values (table 2).

Change from baseline to week 52 in the EQ-5D-3L confirmed significant results favouring semaglutide 2·4 mg (0·1 score points) compared with placebo (0·02 score points; estimated treatment difference 0·1 [95% CI 0·0–0·1]; p=0·042). EQ-5D-3L visual analogue scale scores and WLQ-25 total score and physical scale did not show significant results (appendix 2 p 21).

Serious adverse events were reported by 12 (9%) of 138 participants in the semaglutide 2·4 mg group and six (9%) of 69 participants in the placebo group (table 3). Serious adverse events by system organ class and preferred term are shown in appendix 2 (pp 22–24). Gastrointestinal serious adverse events, such as diarrhoea, nausea, and vomiting, were only reported in participants treated with semaglutide 2·4 mg (three [2%] participants; table 3; appendix 2 pp 22–24).

The following serious adverse events of interest were only reported in the semaglutide 2·4 mg group; neoplasms (four [3%] of 138 participants), acute pancreatitis (two [1%]), malignant neoplasms (two [1%]), and acute gallbladder disease (one [1%]; table 3). Reports of COVID-19 were similar between the semaglutide 2·4 mg and placebo groups, and reports of cardiovascular disorders were more frequent in the placebo group (table 3). Additional descriptions of serious adverse events are included in appendix 2 (p 15).

Adverse events leading to permanent study drug discontinuation were reported by eight (6%) of

	Semaglutide 2·4 mg group (n=138)	Placebo group (n=69)	Treatment comparison (95% CI)	p value for confirmatory analysis
Primary endpoints				
Change in bodyweight from baseline to week 52, %	−13·9% (0·7)	−2·7% (0·6)	Estimated treatment difference −11·2 (−13·0 to −9·4)	<0·0001
Proportion of participants who reached normoglycaemia* at week 52	103/127 (81%)	9/64 (14%)	OR 19·8 (8·7 to 45·2)	<0·0001
Secondary endpoints				
Change from baseline to week 52 in bodyweight, kg	−15·2 (0·8)	−2·8 (0·6)	Estimated treatment difference −12·4 (−14·4 to −10·3)	<0·0001
Change from baseline to week 52 in HbA_{1c}, %	−0·4% (0·3)	0·1% (0·3)	Estimated treatment difference −0·5% (−0·5 to −0·4)	<0·0001
Change from baseline to week 52 in HbA_{1c}, mmol/mol	−4·2 (0·3)	−0·7 (0·4)	Estimated treatment difference −4·9 (−5·8 to −4·0)	<0·0001
Change from baseline to week 52 in FPG, mmol/L	−0·8 (0·1)	−0·2 (0·1)	Estimated treatment difference −0·6 (−0·8 to −0·4)	<0·0001
Change from baseline to week 52 in waist circumference, cm	−11·1 (0·8)	−2·8 (0·7)	Estimated treatment difference −8·3 (−10·4 to 6·2)	<0·0001
Change from baseline to week 52 in systolic blood pressure, mm Hg	−8·8 (1·1)	−1·0 (1·4)	Estimated treatment difference −7·8 (−11·3 to −4·3)	<0·0001
Change from baseline to week 52 in pulse, beats per min	2 (10)	0 (7)	..	..
Geometric mean (coefficient of variation) ratio to baseline at week 52 in lipids†				
Total cholesterol	0·9	1·0	Treatment ratio 0·9 (0·9 to 1·0)	0·017
VLDL cholesterol	0·8	1·0	Treatment ratio 0·9 (0·8 to 1·0)	0·0024
Triglycerides	0·8	1·0	Treatment ratio 0·9 (0·8 to 1·0)	0·0018
HDL cholesterol	1·0	1·0	Treatment ratio 1·0 (1·0 to 1·1)	0·14
LDL cholesterol	0·9	1·0	Treatment ratio 0·9 (0·9 to 1·01)	0·072
Proportion of participants with ≥5% bodyweight reduction at week 52	111/129 (86%)	17/66 (26%)	OR 15·9 (7·5 to 33·6)	<0·0001
Proportion of participants with ≥10% bodyweight reduction at week 52	95/129 (74%)	5/66 (8%)	OR 32·7 (12·0 to 89·1)	<0·0001
Proportion of participants with ≥15% bodyweight reduction at week 52	62/129 (48%)	1/66 (2%)	OR 52·2 (7·1 to 383·1)	0·0001
Proportion of participants with ≥20% bodyweight reduction at week 52	32/129 (25%)	0	OR 39·6 (2·4 to 641·2)	0·0097
Exploratory endpoints				
Change from baseline to week 80 in bodyweight, %	−7·9% (7·2)	−1·3% (5·0)	..	..
Change from baseline to week 80 in bodyweight, kg	−8·7 (8·4)	−1·2 (6·0)	..	..
Change from baseline to week 80 in HbA_{1c}, %	−0·1% (0·3)	0·0% (0·2)	..	..
Change from baseline to week 80 in HbA_{1c}, mmol/mol	−1·6 (3·2)	0·0 (2·7)		
Change from baseline to week 80 in FPG, mmol/L	−0·3 (0·7)	−0·1 (0·8)	..	..
Change from baseline to week 80 in waist circumference, cm	−6·6 (8·6)	−1·5 (6·5)	..	..
Change from baseline to week 80 in systolic blood pressure, mm Hg	−1 (14)	2 (11)	..	..
Geometric mean (coefficient of variation) ratio to baseline at week 80 in lipids†				
Total cholesterol	1·0 (15·7)	1·0 (14·6)	..	..
VLDL cholesterol	0·9 (32·1)	1·0 (26·4)	..	..
Triglycerides	0·9 (34·5)	1·0 (29·9)	..	..
HDL cholesterol	1·1 (14·4)	1·0 (13·6)	..	..
LDL cholesterol	1·0 (27·5)	1·0 (23·5)	..	..
Proportion of participants who reached normoglycaemia* at week 80	53/120 (44%)	11/60 (18%)	..	..
Proportion of participants progressing to type 2 diabetes‡ at week 52	1/127 (1%)	2/64 (3%)	..	..
Proportion of participants progressing to type 2 diabetes‡ at week 80	3/120 (3%)	5/60 (8%)	..	..

Data are mean (SD), n (%), or n/N (%) unless otherwise stated. All data are for the treatment policy estimand. Observed data are from the in-trial period. Exploratory endpoints and change from baseline in pulse are observed values. Bodyweight measurements were taken up to week 80. As such, estimated changes from baseline are not provided; observed values in kilograms are given. Treatment effect is regardless of study drug discontinuation or initiation of other obesity therapies. FPG=fasting plasma glucose. OR=odds ratio. *Normoglycaemia was defined as having an HbA_{1c} of less than 6·0% (<42 mmol/mol) and FPG of less than 5·5 mmol/L. †Ratio to baseline at week 80. ‡Type 2 diabetes was defined as having an HbA_{1c} of 6·5% or higher (≥48 mmol/mol) or FPG of 7·0 mmol/L or higher, verified with a repeated blood sample within 4 weeks.

Table 2: **Primary, supportive secondary, and selected exploratory trial endpoints (treatment policy estimand; full analysis set)**

138 participants in the semaglutide 2·4 mg group and one (1%) of 69 participants in the placebo group. Gastrointestinal disorders were the most frequently reported adverse events leading to permanent study drug discontinuation, with seven (5%) participants in the semaglutide 2·4 mg group and one (1%) participant in the placebo group (appendix 2 p 25).

Serious adverse events, adverse events of interest, and adverse events leading to permanent study drug discontinuation that were related to treatment during the on-treatment period are reported in appendix 2 (pp 26–27).

Two deaths were reported in the semaglutide 2·4 mg group, and both were considered by the trial sponsor to

	Semaglutide 2·4 mg group (n=138)			Placebo group (n=69)			Relative risk (95% CI)	Risk difference (95% CI)
	Participants (%)	Events	Events per 100 participant-years of exposure	Participants (%)	Events	Events per 100 participant-years of exposure		
Serious adverse events total	12 (9%)	25	17·9	6 (9%)	11	15·4	1·00 (0·41 to 2·50)	0·000 (–0·097 to 0·075)
Serious adverse events leading to study drug discontinuation	4 (3%)	4	2·9	0	0	0	..	0·029 (–0·027 to 0·072)
Serious adverse events with fatal outcome	2 (1%)	2	1·0	0	0	0	..	0·014 (–0·039 to 0·051)
Treatment-emergent serious adverse events reported in at least 5% of participants	0	0	0	0	0	0	..	..
Serious adverse events by system organ class								
Gastrointestinal disorders	3 (2%)	8	5·7	0	0	0	..	0·022 (–0·033 to 0·062)
Infections and infestations	3 (2%)	3	2·1	2 (3%)	2	2·8	0·75 (0·15 to 3·72)	–0·007 (–0·079 to 0·038)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	3 (2%)	3	2·1	0	0	0		0·022 (–0·033 to 0·062)
Cardiac disorders	2 (1%)	2	1·4	3 (4%)	5	7·0	0·33 (0·07 to 1·65)	–0·029 (–0·106 to 0·018)
Injury, poisoning, and procedural complications	2 (1%)	3	2·1	0	0	0	..	0·014 (–0·039 to 0·051)
Reproductive system and breast disorders	2 (1%)	3	2·1	0	0	0	..	0·014 (–0·039 to 0·051)
Eye disorders	1 (1%)	1	0·7	0	0	0	..	0·007 (–0·046 to 0·040)
General disorders and administration site conditions	1 (1%)	1	0·7	1 (1%)	1	1·4	0·50 (0·05 to 4·78)	–0·007 (–0·071 to 0·028)
Hepatobiliary disorders	1 (1%)	1	0·7	0	0	0	..	0·007 (–0·046 to 0·040)
Musculoskeletal and tissue disorders	0	0	0	1 (1%)	1	1·4	0·00 (0·00 to 1·92)	–0·014 (–0·078 to 0·015)
Product issues	0	0	0	1 (1%)	1	1·4	0·00 (0·00 to 1·92)	–0·014 (–0·078 to 0·015)
Vascular disorders	0	0	0	1 (1%)	1	1·4	0·00 (0·00 to 1·92)	–0·014 (–0·078 to 0·015)
Adverse events of special interest								
COVID-19 (on treatment)	49 (36%)	57	40·7	24 (35%)	25	35·0	1·02 (0·70 to 1·53)	0·007 (–0·132 to 0·138)
Cardiovascular disorders (in trial)*	4 (3%)	5	2·5	3 (4%)	7	6·7	0·67 (0·17 to 2·62)	–0·014 (–0·093 to 0·037)
Neoplasms (in trial)*	4 (3%)	6	3·0	0	0	0	..	0·029 (–0·027 to 0·072)
Gastrointestinal disorders (on treatment)*	3 (2%)	8	5·7	0	0	0	..	0·022 (–0·033 to 0·062)
Acute pancreatitis (on treatment)	2 (1%)	4	2·9	0	0	0	..	0·014 (–0·039 to 0·051)
Malignant neoplasms (in trial)*	2 (1%)	4	2·0	0	0	0	..	0·014 (–0·039 to 0·051)
Medication errors (on treatment)	2 (1%)	2	1·4	1 (1%)	3	4·2	1·00 (0·13 to 7·61)	0·007 (–0·046 to 0·040)
Acute gallbladder disease (on treatment)*	1 (1%)	1	0·7	0	0	0	..	0·000 (–0·064 to 0·039)
Misuse and abuse (on treatment)	0	0	0	0	0	0	..	..

Adverse events are sorted in descending order by preferred term, based on the percentage of participants in the semaglutide 2·4 mg group having at least one event. In addition to the above adverse events, adverse events of special interest were evaluated and are not shown because there were no occurrences. Adverse events are shown for the safety analysis set (all randomly assigned participants exposed to at least one dose of trial drug or placebo). Because all participants received at least one dose of drug or placebo, the safety population is the same as the full analysis set. Included are all adverse events that occurred during the on-treatment period (ie, the period during which any dose of semaglutide or placebo was administered within the previous 49 days, with any period of temporary interruption of a regimen excluded), unless indicated otherwise. Adverse events were classified by severity as mild (causing minimal discomfort and not interfering with everyday activities), moderate (causing sufficient discomfort to interfere with normal everyday activities), or severe (preventing normal everyday activities). STEP 10 used selective safety data collection; please see the Outcomes section in the Methods for further details. *Only serious adverse events were considered.

Table 3: **Selected adverse events in the safety analysis set**

be unrelated to study drug; one death was attributed to anaplastic thyroid cancer and one to pulmonary embolism in the off-treatment period (appendix 2 p 15).

Discussion

In STEP 10, semaglutide 2·4 mg provided superior reduction in bodyweight and reversion to normoglycaemia versus placebo in participants with obesity and prediabetes. Previous studies have highlighted the benefits of lifestyle intervention for weight loss to reduce the risk of progression to type 2 diabetes; however, weight loss can be difficult to maintain due to metabolic adaptations that resist this process.[8,17,18] STEP 10 is the first phase 3 trial to investigate the efficacy of semaglutide in a trial population consisting only of participants with obesity and prediabetes, with a primary endpoint specifically evaluating reversion to normoglycaemia. The results of STEP 10 add to existing evidence on the benefits of pharmacotherapy for obesity management and progression of prediabetes, a condition that, as of yet, has few treatment options.[19]

From baseline to week 52, semaglutide 2·4 mg, as an adjunct to lifestyle intervention in adults with obesity and prediabetes, resulted in a mean bodyweight loss of 13·9%, a difference of 11·2 percentage points versus placebo plus lifestyle intervention. This finding is similar to the mean placebo-corrected bodyweight losses reported in subgroup

analyses of participants with prediabetes at baseline who received semaglutide 2·4 mg plus lifestyle intervention versus placebo plus lifestyle intervention in STEP 1 (11·3 percentage points) and STEP 4 (11·3 percentage points).[20] There was a numerically larger difference in placebo-corrected bodyweight loss between STEP 10 and STEP 3 (9·1 percentage points), which might be due to STEP 3 being the only trial in which participants received intensive behavioural therapy in addition to semaglutide or placebo plus lifestyle intervention. Additionally, the guidelines for lifestyle interventions implemented in STEP 10 were less stringent than those in previous STEP trials. In STEP 10, participants received counselling during nine visits from a dietitian or similarly qualified health-care professional (who provided diet and physical activity strategies), whereas in STEP 3 counselling was provided during 30 visits from a registered dietitian (who provided diet, physical activity, and behavioural strategies).[21] The mean placebo-corrected bodyweight loss of 6·2 percentage points reported in STEP 2 in participants with type 2 diabetes who received semaglutide 2·4 mg plus lifestyle intervention was lower than that reported in STEP 10, which might be due to the challenges associated with bodyweight loss in participants with type 2 diabetes. The Look AHEAD trial and the Diabetes Prevention Program assessed the impact of lifestyle interventions on weight loss in participants with type 2 diabetes (Look AHEAD) and prediabetes (Diabetes Prevention Program). In these studies, participants lost 8·4% (Look AHEAD) and 7·5% (Diabetes Prevention Program) bodyweight, which is greater than the weight loss observed in the placebo group in STEP 10; however, this difference might be due to different trial populations and guidelines on lifestyle interventions.[14,22]

By the end of the on-treatment period, 86% of participants receiving semaglutide 2·4 mg had a bodyweight loss of 5% or more. The 5% threshold for bodyweight loss is a clinically meaningful response as it is associated with improvement of obesity-related complications, including type 2 diabetes, dyslipidaemia, and hypertension.[23] Additionally, participants treated with semaglutide 2·4 mg were more likely to have a bodyweight loss of 10% or more, 15% or more, and 20% or more than participants receiving placebo. Individuals who reach these thresholds have previously been shown to benefit from improvements in obesity-related complications, such as remission of type 2 diabetes.[24]

In STEP 10, a greater proportion of participants reverted to normoglycaemia with semaglutide 2·4 mg than with placebo. Although other STEP trials did not have trial populations solely consisting of participants with prediabetes, they did examine some outcomes in subpopulations of participants with this condition. The proportions of participants who reverted to normoglycaemia with semaglutide 2·4 mg versus placebo after 1 year in STEP 10 (81% *vs* 14%) were consistent with those reported in a subgroup analysis of participants with prediabetes at baseline in STEP 1 (n=856; 84·1% *vs* 47·8%), STEP 3 (n=304; 89·5% *vs* 55·0%), and STEP 4 (n=376; 89·8% *vs* 70·4%).[20] The proportions of participants in the placebo groups reverting to normoglycaemia in these trials differ to STEP 10, which might be due to STEP 10 having less strict guidance on lifestyle intervention than the previously mentioned STEP trials. Furthermore, the placebo group in STEP 4 had 20 weeks of semaglutide 2·4 mg before being randomly assigned to 48 weeks of placebo, which increased the proportion of participants having normoglycaemia at study end.[13] Additionally, the results from this study are consistent with proportions of participants who reverted to normoglycaemia with semaglutide 2·4 mg versus placebo in the 2-year STEP 5 (79·7% *vs* 37·0%) and STEP 6 (90·7% *vs* 32·0%) trials,[25,26] and versus liraglutide at week 68 in STEP 8 (89·5% *vs* 64·9%).[27] In the SCALE Obesity and Prediabetes trial, the proportion of participants reverting to normoglycaemia with liraglutide 3·0 mg versus placebo was 69·2% and 32·7% after 1 year, and 65·9% and 36·3% after 3 years, respectively.[22,28] Furthermore, the DIRECT trial found that more individuals (with <6 years' duration of type 2 diabetes, not receiving insulin, and BMI 27–45 kg/m²) assigned to an integrated structured weight-management programme had remission of diabetes than those on standard of care (35·6% *vs* 3·4%).[29]

In this study, a smaller proportion of participants progressed to type 2 diabetes at week 52 with semaglutide 2·4 mg than with placebo. This finding suggests that semaglutide 2·4 mg might potentially reduce or delay the progression of prediabetes to type 2 diabetes in participants with obesity; however, the study was not powered to evaluate this outcome. This hypothesis is supported by the results of the SELECT trial. SELECT used a different threshold for normoglycaemia (HbA_{1c} <5·7% [39 mmol/mol]) compared with STEP 10 (HbA_{1c} <6·0% [42 mmol/mol] and FPG <5·5 mmol/L) and found that 65·7% (n=3775) of participants receiving semaglutide with prediabetes at baseline had an HbA_{1c} of less than 5·7% at week 104 compared with 21·4% for placebo (n=1211) (estimated treatment difference 8·74 [95% CI 7·91–9·65]). Additionally, SELECT had a supportive secondary endpoint of time to an HbA_{1c} of 6·5% (48 mmol/mol) or more (indicating type 2 diabetes development), where 3·5% (n=306) of participants developed an HbA_{1c} of 6·5% or more with semaglutide 2·4 mg compared with 12·0% (n=1059) for placebo (hazard ratio 0·27 [95% CI 0·24–0·31]). Participants in SELECT had a mean exposure to semaglutide 2·4 mg of 34·2 months (SD 13·7), indicating such benefit occurs over the long term.[30] These findings suggest that semaglutide can reduce the risk of developing type 2 diabetes in participants with prediabetes. Furthermore, STEP 2 reported greater proportions of participants with obesity and type 2 diabetes reaching an HbA_{1c} of 6·5% or less with semaglutide 2·4 mg (n=257 [67·5%]) compared

with placebo (n=58 [15·5%]; OR 1·39 [95% CI 1·03–1·88]).[31] The SUSTAIN 1, SUSTAIN 5, and SUSTAIN 6 trials also reported similar findings with semaglutide 0·5 mg and 1·0 mg compared with placebo, suggesting that semaglutide might promote the remission from type 2 diabetes to prediabetes.[32–34]

We also found that participants treated with semaglutide 2·4 mg had improvements in cardiometabolic risk factors, including waist circumference, HbA_{1c}, FPG, systolic blood pressure, and lipids, compared with placebo. In line with this finding, SELECT, in which 66% of the entire population had prediabetes at baseline, showed a 20% reduction in cardiovascular events (hazard ratio 0·80 [95% CI 0·72–0·90]; p<0·001) with semaglutide versus placebo, both in addition to standard of care, in participants with obesity and established cardiovascular disease, but without diabetes.[30] In STEP 10, although bodyweight declined between week 28 and week 52, HbA_{1c} regressed towards baseline values by about 0·1% in the semaglutide 2·4 mg group; this decrease is probably not clinically significant in contrast to the steeper regression in HbA_{1c} observed in the off-treatment phase.

Changes in bodyweight, glycaemic status, and cardiometabolic parameters were assessed in the 28-week off-treatment period following the 52-week phase. During this period, increases in cardiometabolic risk factors and bodyweight, and decreases in the proportion of participants who remained normoglycaemic were observed in participants in the semaglutide 2·4 mg group. This finding suggests that there is a need to continue semaglutide 2·4 mg to maintain bodyweight loss, cardiometabolic benefits, and normoglycaemia in people with obesity and prediabetes, and that obesity is a chronic relapsing condition that requires long-term treatment, in line with the evidence-based principles of chronic disease management.[6] The results from STEP 10 are consistent with the STEP 1 extension and STEP 4 trials investigating semaglutide 2·4 mg cessation in participants with overweight or obesity, which reported regain in bodyweight and loss of benefit to cardiometabolic risk factors following treatment discontinuation.[12,13] Although bodyweight regain and loss of benefit to cardiometabolic risk factors was observed in the off-treatment phase, they remained lower than baseline values.[12,13]

The safety and tolerability profile of semaglutide 2·4 mg in participants with obesity and prediabetes was consistent with findings of other trials in the STEP programme, and with the GLP-1 receptor agonist class in general.[9] The most frequent serious adverse events were gastrointestinal disorders, with a higher frequency in the semaglutide 2·4 mg group than in the placebo group, which is consistent with the known safety profile of semaglutide 2·4 mg.[12,13] Two participants were diagnosed with malignant neoplasms during the trial: one was diagnosed with invasive lobular breast carcinoma at week 33 and one with anaplastic thyroid cancer at week 21. Both neoplasms were considered to be unrelated to semaglutide 2·4 mg by the study sponsor. Notably, SELECT, which had a much larger trial population (n=17 604) and longer duration (median follow-up 41·8 months [IQR 33·0–47·0]) compared with STEP 10 (n=207), did not report an increased risk of cancer with semaglutide 2·4 mg.[30] Additionally, the 2:1 randomisation in STEP 10 makes a chance finding of malignant neoplasms more likely in the semaglutide 2·4 mg group. A systematic review and meta-analysis of semaglutide and cancer reported that semaglutide use in randomised controlled trials and real-world studies was not associated with an increased risk of any types of cancer.[35]

Limitations of STEP 10 were that most participants were female and White, which could limit generalisability to a more heterogeneous population, and the overall trial population was relatively small. However, a post-hoc analysis of the STEP 1 and STEP 3 (pooled) and STEP 2 trials by race and ethnicity reported that there were no significant treatment differences in the treatment effect of semaglutide 2·4 mg on bodyweight by racial or ethnic subgroups.[36] Additionally, baseline values for FPG and HbA_{1c}, which were both used for the inclusion criteria, were at the lower end of the prediabetes range. A participant population with more severe prediabetes at baseline might have yielded a higher treatment effect than observed in this current trial; the Diabetes Prevention Program trial reported that participants with more severe prediabetes at baseline showed larger improvements in glycaemic outcomes than those with less severe prediabetes.[37] The 80-week study duration of STEP 10 does not provide insight into the long-term benefits of semaglutide 2·4 mg, such as the delay of progression to type 2 diabetes. The STEP 1 extension trial reported that 52 weeks after treatment withdrawal, 1·7% of participants had type 2 diabetes with semaglutide 2·4 mg versus 6·4% with placebo, although the trial was not powered for this analysis.[12] STEP 10 also did not use an active comparator such as high-intensity lifestyle intervention or metformin, potentially limiting comparisons to real-world practice on prediabetes management[38] However, although metformin is approved for prediabetes in some countries,[39] it is not approved for weight management, and high-intensity lifestyle intervention is difficult to enact in most clinical practices. Another limitation is that it was not possible to ascertain how much of the reduction in HbA_{1c} was caused by weight loss and how much was caused by the previously established direct glucose-lowering effect of semaglutide.[40] Strengths of STEP 10 include the off-treatment period and the high rates of treatment adherence and trial completion.

In conclusion, these findings support semaglutide 2·4 mg as an efficacious treatment option for weight management and highlight the glycaemic benefit of semaglutide 2·4 mg treatment in participants with obesity and prediabetes. The safety and tolerability profile of semaglutide 2·4 mg was consistent with previous studies and with the GLP-1 receptor agonist class. These

findings support the potential use of semaglutide 2·4 mg as a treatment option for individuals with obesity and prediabetes to achieve reversion to normoglycaemia.

Contributors

AV and HAKM designed the trial and performed the data analysis. All authors were involved in the conduct of the trial. AV, BMM, DCWL, HAKM, JMB, KHP, MC, and SDP contributed to data collection. HAKM, DCWL, and BMM verified all data in this publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors contributed to the data interpretation and manuscript writing (assisted by a medical writer paid for by the funder), approved the final version of the manuscript, and vouch for data accuracy and fidelity to the protocol.

Declaration of interests

AV, HAKM, and MQ are employees and shareholders of Novo Nordisk. BMM received a research grant from Novo Nordisk; received honoraria as a consultant or speaker for Eli Lilly, Amgen, Novo Nordisk, Pfizer, and Johnson & Johnson; and is a shareholder of Reset Health. DCWL received clinical trial funding from Amgen and Novo Nordisk, and honoraria as a consultant or speaker for Amgen, Bayer, Boehringer Ingelheim, CME at Sea, Canada Collaborative Research Network, Eli Lilly, Novartis, Novo Nordisk, Viatris, and Zealand Pharma. JMB is a member of speakers bureaus for Merck, Boehringer Ingelheim, and Novo Nordisk, and has received research grants from the Novo Nordisk Foundation. KHP received honoraria for attendance or talks at meetings from AstraZeneca, Boehringer Ingelheim, Eli Lilly, and Novo Nordisk, and research funding from the Novo Nordisk Foundation. MC received research grants and honoraria as a speaker for and member of advisory boards, and support to attend meetings from Novo Nordisk, Eli Lilly, and Boehringer Ingelheim. SDP received consulting fees from AstraZeneca, Bausch, Eli Lilly, Novo Nordisk, Janssen, Boehringer Ingelheim, Merck, Abbott, HLS Therapeutics, Sanofi, Dexcom, Bayer, and Pfizer; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events for AstraZeneca, Bausch, Eli Lilly, Novo Nordisk, GSK, Janssen, Boehringer Ingelheim, Sanofi, Merck, Abbott, Dexcom, HLS, Bayer, and Pfizer; support for attending meetings or travel from AstraZeneca, Bausch, Eli Lilly, Novo Nordisk, Janssen, Boehringer Ingelheim, Merck, Abbott, HLS Therapeutics, Sanofi, Dexcom, and Bayer; and participation on data safety monitoring boards or advisory boards for AstraZeneca, Bausch, Eli Lilly, Novo Nordisk, Janssen, Boehringer Ingelheim, Merck, Abbott, HLS Therapeutics, Sanofi, Dexcom, and Bayer.

Data sharing

Data will be shared with researchers who submit a research proposal approved by the independent review board. Individual participant data will be shared in datasets in a de-identified and anonymised format. Information about data access request proposals can be found online.

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