Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial

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Summary

Background This trial assessed the efficacy and safety of the GLP-1 analogue once a week subcutaneous semaglutide 2·4 mg versus semaglutide 1·0 mg (the dose approved for diabetes treatment) and placebo for weight management in adults with overweight or obesity, and type 2 diabetes.

Methods This double-blind, double-dummy, phase 3, superiority study enrolled adults with a body-mass index of at least 27 kg/m² and glycated haemoglobin 7–10% (53–86 mmol/mol) who had been diagnosed with type 2 diabetes at least 180 days before screening. Patients were recruited from 149 outpatient clinics in 12 countries across Europe, North America, South America, the Middle East, South Africa, and Asia. Patients were randomly allocated (1:1:1) via an interactive web-response system and stratified by background glucose-lowering medication and glycated haemoglobin, to subcutaneous injection of semaglutide 2·4 mg, or semaglutide 1·0 mg, or visually matching placebo, once a week for 68 weeks, plus a lifestyle intervention. Patients, investigators, and those assessing outcomes were masked to group assignment. Coprimary endpoints were percentage change in bodyweight and achievement of weight reduction of at least 5% at 68 weeks for semaglutide 2·4 mg versus placebo, assessed by intention to treat. Safety was assessed in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, NCT03552757 and is closed to new participants.

Findings From June 4 to Nov 14, 2018, 1595 patients were screened, of whom 1210 were randomly assigned to semaglutide 2·4 mg (n=404), semaglutide 1·0 mg (n=403), or placebo (n=403) and included in the intention-to-treat analysis. Estimated change in mean bodyweight from baseline to week 68 was –9·6% (SE 0·4) with semaglutide 2·4 mg *vs* –3·4% (0·4) with placebo. Estimated treatment difference for semaglutide 2·4 mg versus placebo was –6·2 percentage points (95% CI –7·3 to –5·2; p<0·0001). At week 68, more patients on semaglutide 2·4 mg than on placebo achieved weight reductions of at least 5% (267 [68·8%] of 388 *vs* 107 [28·5%] of 376; odds ratio 4·88, 95% CI 3·58 to 6·64; p<0·0001). Adverse events were more frequent with semaglutide 2·4 mg (in 353 [87·6%] of 403 patients) and 1·0 mg (329 [81·8%] of 402) than with placebo (309 [76·9%] of 402). Gastrointestinal adverse events, which were mostly mild to moderate, were reported in 256 (63·5%) of 403 patients with semaglutide 2·4 mg, 231 (57·5%) of 402 with semaglutide 1·0 mg, and 138 (34·3%) of 402 with placebo.

Interpretation In adults with overweight or obesity, and type 2 diabetes, semaglutide 2·4 mg once a week achieved a superior and clinically meaningful decrease in bodyweight compared with placebo.

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Introduction

More than 90% of people with type 2 diabetes also have overweight or obesity,[1] and more than 20% of people with obesity also have type 2 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, because it improves glycaemic control and associated metabolic comorbidities.[4]

GLP-1 receptor agonists have shown efficacy in lowering glycated haemoglobin (HbA_{1c}) and decreasing weight in patients with type 2 diabetes, and are recommended as a second-line therapy after metformin, and as the first injectable treatment after failure of oral glucose-lowering agents.[5–7] Furthermore, the GLP-1 receptor agonist liraglutide is available for the treatment of overweight and obesity in people with or without type 2 diabetes.[8] Among GLP-1 receptor agonists currently available for the treatment of diabetes, semaglutide 1·0 mg has shown 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 for weight management. The aim of this study, part of the Semaglutide Treatment Effect in People With Obesity (STEP) programme,[12] was to evaluate the efficacy and safety of once a week subcutaneous semaglutide 2·4 mg versus semaglutide 1·0 mg (the

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See Online for appendix

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. GLP-1 receptor agonists have shown efficacy in lowering glycated haemoglobin (HbA_{1c}) and decreasing weight in patients with type 2 diabetes. Once a week 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 a day liraglutide 3·0 mg as an adjunct to lifestyle intervention in patients with overweight or obesity, and type 2 diabetes (n=846) reported a reduction in bodyweight of 5·4% from baseline. In a phase 2, dose-finding trial (n=957), once a day subcutaneous semaglutide 0·4 mg showed effective weight loss and an acceptable safety profile.

Added value of this study

In adults with overweight or obesity and type 2 diabetes, once a week semaglutide 2·4 mg achieved a superior decrease in mean bodyweight (–9·6% [SE 0·4]) compared with semaglutide 1·0 mg (–7·0% [SE 0·4]) and placebo (–3·4% [SE 0·4]), with clinically meaningful reductions (at least 5%) reported in more than 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 HbA_{1c} of 6·5% or lower. 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-1 receptor agonist.

Implications of all the available evidence

This is the first trial to show that in adults with overweight or obesity and type 2 diabetes, once a week subcutaneous semaglutide 2·4 mg produces clinically meaningful reductions in bodyweight. The magnitude of weight loss achieved with semaglutide 2·4 mg in STEP 2 was greater than that seen 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 or obesity and type 2 diabetes.

dose approved for diabetes treatment) and placebo for bodyweight management in adults with overweight or obesity, and type 2 diabetes.

Methods

Trial design and participants

This phase 3, randomised, double-blind, double-dummy, placebo-controlled, multicentre superiority study was done at 149 outpatient clinics in 12 countries across Europe, North America, South America, the Middle East, South Africa, and Asia, as described in a previous publication and listed in the appendix (p 2).[12] The trial complied with the International Conference on Harmonization Good Clinical Practice guidelines[13] 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 25–192).

Eligible participants were 18 years or older, reported at least one unsuccessful dietary effort to lose weight, had a body-mass index of at least 27 kg/m², HbA_{1c} of 7–10% (53–86 mmol/mol), and had been diagnosed with type 2 diabetes at least 180 days before screening. Participants were managed with diet and exercise alone, or treated with a stable dose of up to three oral glucose-lowering agents (metformin, sulfonylureas, SGLT2 inhibitors, or thiazolidinediones) for at least 90 days before screening.

Key exclusion criteria included self-reported changes in bodyweight of more than 5 kg within 90 days before screening, and previous or planned (ie, set to occur during the trial period) obesity treatment with surgery or a weight-loss device. Full eligibility criteria are in the appendix (pp 3–4). Participants gave written consent.

Randomisation and masking

Random allocation (1:1:1) to semaglutide 2·4 mg, semaglutide 1·0 mg, or placebo was done by the clinical research organisation (Parexel) using an interactive online response system that allocated dispensing unit numbers for each patient, with the trial product dispensed by the site investigator or study coordinator at the trial site visits. Randomisation was stratified according to background diabetes treatment: first, by patients who received diet plus physical exercise counselling or glucose background medication (metformin or SGLT2 inhibitors), or received a single oral glucose-lowering medication or a combination of up to three oral glucose-lowering medications; and second, by HbA_{1c} (above or below an HbA_{1c} of 8·5%). We used a double-blind, double-dummy design in which patients received the active drug or placebo subcutaneously (two injections once a week: active product plus placebo or placebo plus placebo). For both doses of semaglutide, the active products and corresponding placebo products were visually identical to maintain masking of patients and site staff. The people analysing the data were masked to group assignment until breaking the masking at database lock.

Procedures

Patients received semaglutide 2·4 mg or semaglutide 1·0 mg or placebo once a week for 68 weeks, plus a lifestyle intervention, followed by 7 weeks without treatment.

Semaglutide was started at 0·25 mg per week and escalated in a fixed-dose regimen every 4 weeks until the target dose was reached (ie, 2·4 mg or 1·0 mg in weeks 8–16; appendix p 15). The lifestyle intervention involved counselling on diet (500 kcal per day reduction relative to the estimated total daily energy expenditure calculated at time of random allocation) and physical activity (150 min per week—eg, walking or using the stairs). Counselling was provided by a dietitian or a similarly qualified health-care professional every fourth week, via in-person visit or telephone. Patients were instructed how to measure their physical activity and food intake, and were encouraged to keep a food and activity diary daily (using paper, an app, or another 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 amount 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 (ie, fasting plasma glucose >15 mmol/L). Patients remained in

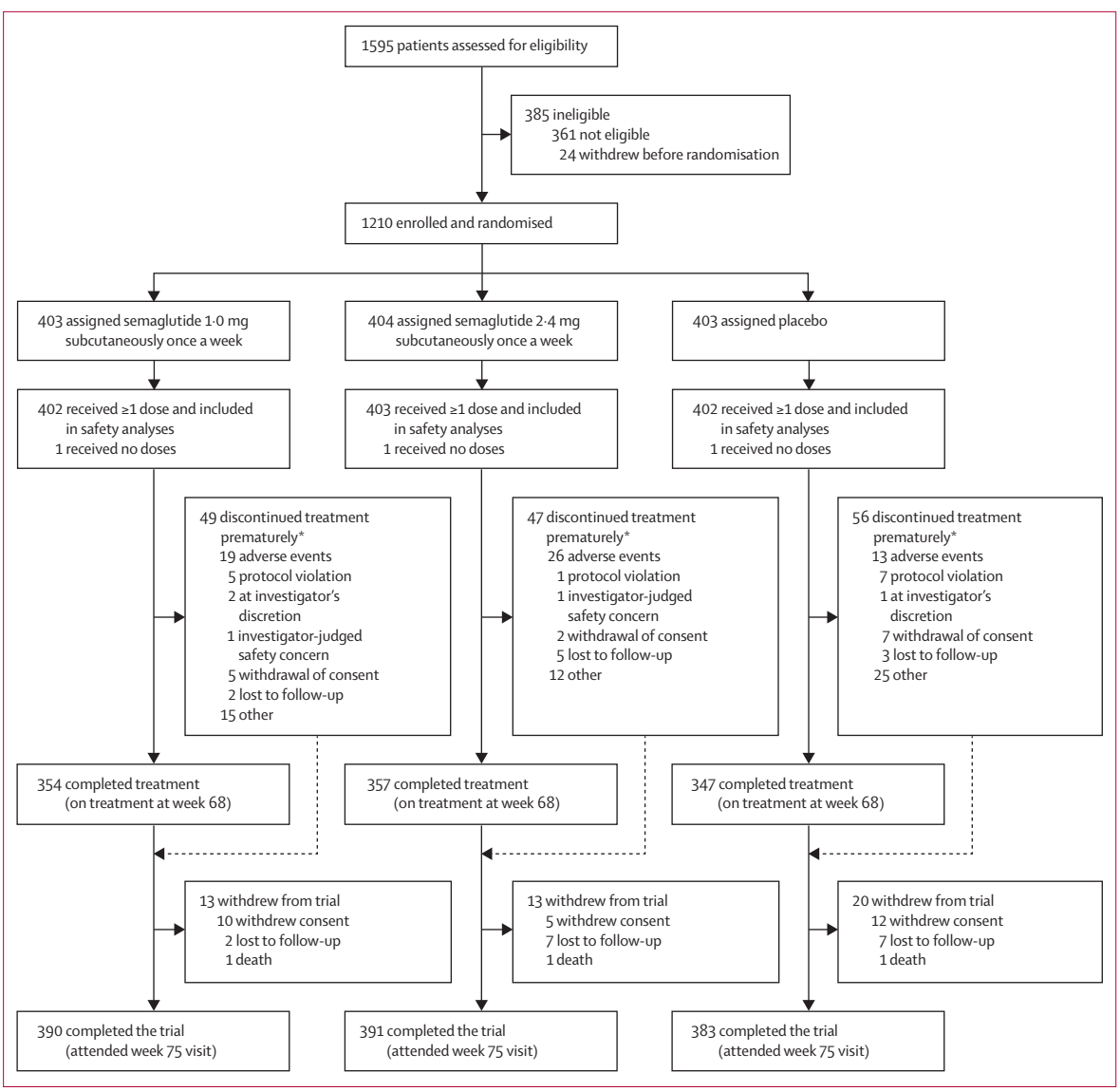


Figure 1: **Trial profile**
At the last treatment visit for the patients completing treatment, in the semaglutide 2·4 mg group 300 (84%) of 357 patients were on the full intended dose (2·4 mg), 17 (5%) were on 1·7 mg, and 37 (10%) were on less than 1·7 mg. In the semaglutide 1·0 mg group, 336 (95%) of 354 patients were on the full (1·0 mg) dose and 14 (4%) were on 0·5 mg or less. In the placebo group, 338 (97%) of 347 patients completed treatment with the intended dose, whereas only 6 (2%) completed treatment on a lower dose than intended. *Patients who discontinued treatment prematurely all completed the trial. In analyses of the treatment policy estimand, all the collected data were included, regardless of patient status for use of randomised treatment.

the trial regardless of whether they discontinued treatment using the study drug.

Height, bodyweight, waist circumference, and vital signs (systolic and diastolic blood pressure and pulse rate) were measured at baseline; except for height, these measurements were repeated at weeks 4, 8, 12, 16, 20, 28, 36, 44, 52, 60, and 68 (within 3 days either side of scheduled visit day). Bodyweight and vital signs were also measured at the end-of-trial visit at week 75 (within 5 days either side of scheduled visit day). HbA_{1c}, fasting plasma glucose, and fasting serum insulin were measured at weeks 0, 8, 20, 52, and 68; HbA_{1c} was additionally measured at weeks 28 and 44. Patients were also asked to self-measure fasting plasma glucose at weeks 4, 12, 16, 28, 36, 44, 60, and 68. Lipids and C-reactive protein were measured at weeks 0, 20, and 68. Physical examinations were done at baseline and week 68, and included assessments of general appearance, thyroid gland, breast (females), abdomen, respiratory, cardiovascular, and central and peripheral nervous systems. Eye examinations were done at baseline and at weeks 52 and 68. An electrocardiogram and urinalysis were done at baseline and at weeks 20 and 68. Haematology and biochemistry laboratory parameters were measured at baseline, weeks 20, 52, and 68. At baseline and at weeks 8, 16, 20, 36, 52, and 68, participants completed the Short Form 36v2 Health Survey acute version (SF-36v2) and the Impact of Weight on Quality of Life-Lite for Clinical Trials Version (IWQOL-Lite-CT) questionnaire. Adverse events, including hypoglycaemic episodes, were recorded at each visit. For all clinical and safety outcomes assessments, patients who discontinued study medication were encouraged to attend scheduled visits, particularly the visits at weeks 68 and 75.

	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	223 (55·2%)	203 (50·4%)	190 (47·1%)	616 (50·9%)
Race or ethnicity				
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%)
Hispanic or Latino	47 (11·6%)	59 (14·6%)	49 (12·2%)	155 (12·8%)
Other*	20 (5·0%)	6 (1·5%)	16 (4·0%)	42 (3·5%)
Bodyweight, kg	99·9 (22·5)	99·0 (21·1)	100·5 (20·9)	99·8 (21·5)
Body-mass index, kg/m²				
Mean	35·9 (6·4)	35·3 (5·9)	35·9 (6·5)	35·7 (6·3)
<30	68 (16·8%)	66 (16·4%)	77 (19·1%)	211 (17·4%)
30–<35	140 (34·7%)	163 (40·4%)	135 (33·5%)	438 (36·2%)
35–<40	103 (25·5%)	100 (24·8%)	97 (24·1%)	300 (24·8%)
≥40	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)
HbA_{1c}	8·1% (0·8)	8·1% (0·8)	8·1% (0·8)	8·1% (0·8)
HbA_{1c}, mmol/mol	65·3 (8·7)	65·4 (8·5)	65·3 (9·0)	65·3 (8·7)
Fasting plasma glucose, mmol/L	8·5 (2·3); n=396	8·6 (2·3); n=395	8·8 (2·3); n=400	8·6 (2·3); n=1191
Duration of diabetes, years	8·2 (6·2); n=404	7·7 (5·9); n=403	8·2 (6·2); n=402	8·0 (6·1); n=1209
Glucose-lowering drug class				
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%)
DPP-4 inhibitors†	2 (0·5%)	3 (0·7%)	1 (0·2%)	6 (0·5%)
α-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				
Diet and physical activity only	18 (4·5%)	17 (4·2%)	21 (5·2%)	56 (4·6%)
One	221 (54·7%)	229 (56·8%)	216 (53·6%)	666 (55·0%)
Two	133 (32·9%)	127 (31·5%)	138 (34·2%)	398 (32·9%)
Three	32 (7·9%)	29 (7·2%)	27 (6·7%)	88 (7·3%)
Four†	0	1 (0·2%)	1 (0·2%)	2 (0·2%)
Blood pressure, mm Hg				
Systolic	130 (13)	130 (14)	130 (13)	130 (14)
Diastolic	80 (9)	80 (9)	80 (9)	80 (9)
Lipids geometric mean (CV), mmol/L				
Total cholesterol	4·4 (23·0); n=402	4·5 (25·0); n=399	4·4 (23·3); n=402	4·4 (23·8); n=1203
LDL cholesterol	2·3 (37·3); n=402	2·3 (46·7); n=399	2·3 (37·8); n=402	2·3 (40·7); n=1203

(Table 1 continues on next page)

Outcomes

Co-primary outcomes were percentage change in bodyweight from baseline to week 68 and loss of at least 5% of baseline weight at week 68 (semaglutide 2·4 mg *vs* placebo).

Confirmatory secondary outcomes (semaglutide 2·4 mg *vs* placebo, unless stated otherwise) in hierarchical testing order were: proportions of patients achieving bodyweight reductions of at least 10% or 15% at week 68, change from baseline to week 68 in waist circumference, percentage change in bodyweight (semaglutide 2·4 *vs* 1·0 mg) at week 68, change from baseline to week 68 in HbA_{1c}, systolic blood pressure, SF-36v2 physical functioning score, and IWQOL-Lite-CT physical function score (appendix p 6). The semaglutide 1·0 mg group was included to enable comparison of bodyweight and safety outcomes with the semaglutide 2·4 mg group. Exploratory secondary outcomes compared semaglutide 2·4 mg versus placebo, and semaglutide 2·4 mg versus semaglutide 1·0 mg once a week, unless otherwise stated (for additional details and a full list of outcomes see appendix pp 6–7).

Safety assessments included the number of treatment-emergent adverse events and serious adverse events, and the 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 group) provided power of 94% for the coprimary and confirmatory secondary endpoints (see protocol, appendix pp 25–192), tested in a predefined hierarchical order (appendix p 8).

Efficacy outcomes were assessed using intention-to-treat analysis (ie, the full set of all randomly assigned patients). Safety outcomes were assessed using the safety analysis set of all randomly allocated patients exposed to at least one dose of randomised intervention. Observation periods included the in-trial period (ie, while in the 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% CIs 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 used to assess treatment efficacy, and accounted differently for intercurrent events and missing data, as described in a previous publication.[15]

The treatment policy estimand, which quantified average treatment effect among all randomly assigned 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 either placebo or 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 the results were combined using Rubin's rules.[16] Categorical endpoints were analysed by logistical regression using randomised treatment, stratification groups, and the interaction between stratification groups as factors, and the baseline endpoint value as a covariate. Analyses were done using SAS (version 9.4).

The trial product estimand modelled the average treatment effect in all randomly assigned patients, assuming that patients 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 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 mixed model for repeated measurements by logistic regression with treatment and

	Semaglutide 2·4 mg (n=404)	Semaglutide 1·0 mg (n=403)	Placebo (n=403)	Total (n=1210)
(Continued from previous page)				
HDL cholesterol	1·2 (23·3); n=402	1·1 (24·9); n=399	1·1 (24·2); n=402	1·1 (24·2); n=1203
VLDL cholesterol	0·8 (49·3); n=402	0·8 (48·4); n=399	0·8 (49·7); n=402	0·8 (49·3); n=1203
Free fatty acids	0·6 (54·7); n=390	0·6 (45·1); n=388	0·6 (55·4); n=393	0·6 (51·8); n=1171
Triglycerides	1·7 (53·4); n=402	1·9 (54·0); n=399	1·8 (52·9); n=402	1·8 (53·6); n=1203
Estimated glomerular filtration rate, mL/min per 1·73 m²				
Mean	94·25 (22·10)	93·43 (21·43)	92·32 (23·47)	93·33 (22·35)
Normal: ≥90	271 (67·1%)	265 (65·8%)	259 (64·3%)	795 (65·7%)
Mild impairment: ≥60–<90	114 (28·2%)	121 (30·0%)	120 (29·8%)	355 (29·3%)
Moderate impairment: ≥30–<60	18 (4·5%)	17 (4·2%)	24 (6·0%)	59 (4·9%)
Severe impairment: 15–<30	1 (0·2%)	0	0	1 (<0·1%)
Comorbidities at screening‡				
Coronary artery disease	26 (6·4%)	40 (9·9%)	33 (8·2%)	99 (8·2%)
Dyslipidaemia	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 apnoea	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 or chronic obstructive pulmonary disease	36 (8·9%)	47 (11·7%)	32 (7·9%)	115 (9·5%)
Number of comorbidities at screening‡				
Five or more	93 (23·0%)	86 (21·3%)	81 (20·1%)	260 (21·5%)
Four	89 (22·0%)	96 (23·8%)	105 (26·1%)	290 (24·0%)
Three	98 (24·3%)	107 (26·6%)	112 (27·8%)	317 (26·2%)
Two	77 (19·1%)	70 (17·4%)	72 (17·9%)	219 (18·1%)
One	47 (11·6%)	44 (10·9%)	33 (8·2%)	124 (10·2%)
SF-36v2 scores				
Physical functioning	49·2 (8·8); n=397	50·5 (7·7); n=396	49·6 (8·3); n=394	49·7 (8·3); n=1187
Physical component summary	49·8 (8·2); n=397	50·7 (7·3); n=396	49·9 (8·0); n=394	50·1 (7·9); n=1187
Mental component summary	55·6 (6·1); n=397	55·9 (6·0); n=396	56·2 (5·5); n=394	55·9 (5·9); n=1187
IWQOL-Lite-CT scores				
Physical function	67·1 (25·2); n=397	71·1 (22·5); n=395	69·2 (24·0); n=394	69·2 (24·0); n=1186
Total	71·9 (20·9); n=397	74·5 (18·6); n=395	74·2 (19·2); n=394	73·5 (19·6); n=1186

Data are n (%) or mean (SD) and include all patients in the full analysis set, unless indicated otherwise. There were no marked differences between treatment groups at baseline. CV=coefficient of variation percentage. HbA_{1c}=glycated haemoglobin. IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version. SF-36v2=Short Form 36v2 Health Survey, acute version. *Native American, Alaska Native, Native Hawaiian, other Pacific Islander, or Other. †Patients on DDP-4 inhibitors or GLP-1 receptor agonists were randomly assigned in error (because these patients received treatment with any medication indicated for the treatment of diabetes other than stated in the inclusion criteria, or had diabetes within the 90 days before screening); one patient began insulin on the day of random assignment but it was not known if this was before or after assignment. ‡Information collected at screening on comorbidities was based on medical history and included: type 2 diabetes, dyslipidaemia, hypertension, coronary artery disease, cerebrovascular disease, obstructive sleep apnoea, reproductive system disorders, liver disease, kidney disease, osteoarthritis, gout, and asthma or chronic obstructive pulmonary disease. §Percentage of female patients.

Table 1: **Baseline characteristics**

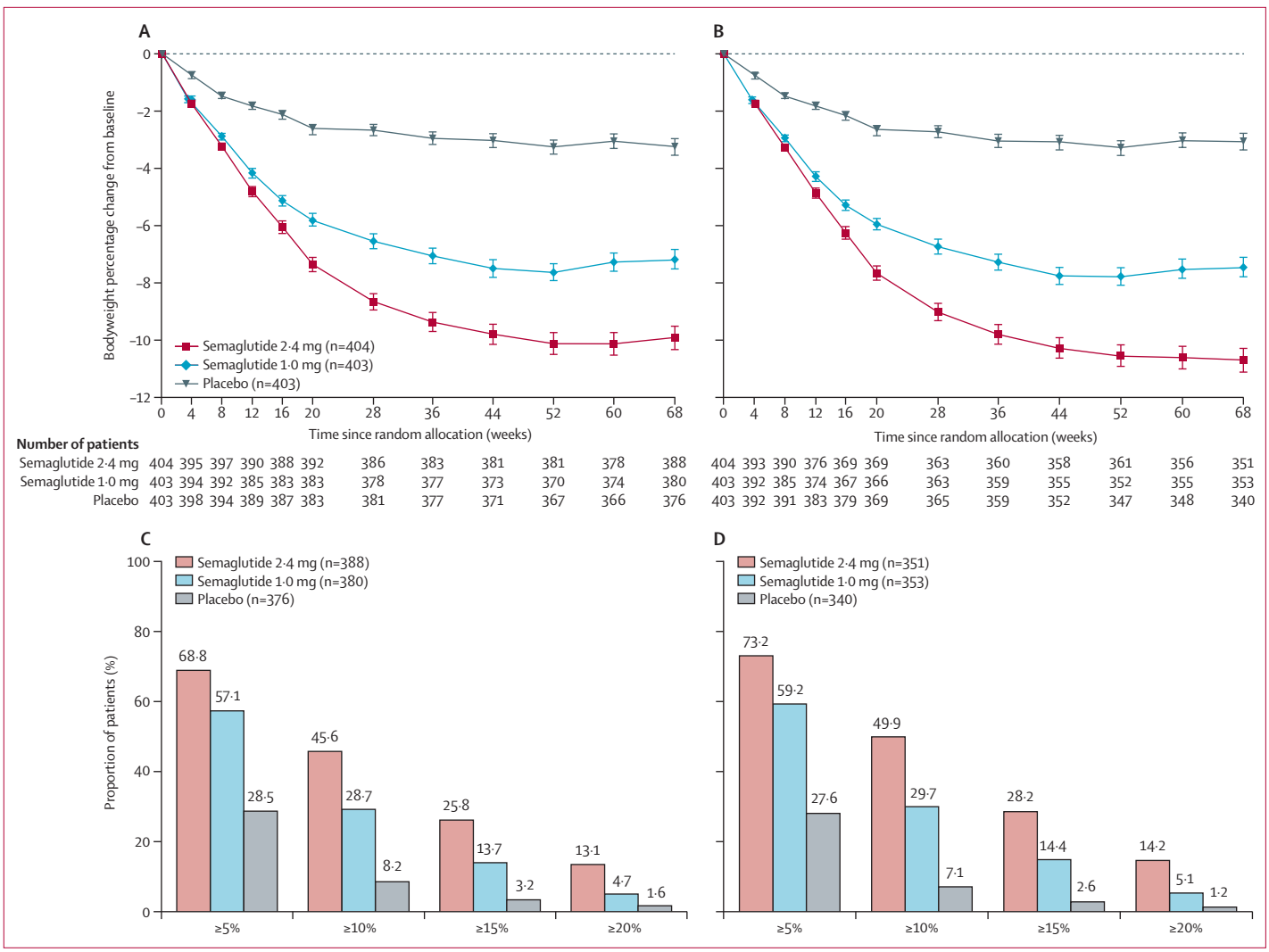


Figure 2: **Comparison of bodyweight parameters for semaglutide 2·4 mg versus semaglutide 1·0 mg versus placebo, given once a week**
Observed mean percentage change from baseline in bodyweight over time for patients in the full analysis set during the in-trial (A) and on treatment (B) observation period (error bars are SE of the mean; numbers below the panels are the number of patients contributing to the mean) and observed proportions of patients achieving bodyweight 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 (C) and on treatment observation period (D). A timepoint is considered as on treatment if any dose of trial product has been administered within the previous 14 days. Data are for the full analysis set.

stratification groups as factors and baseline endpoint as covariate. There was no data monitoring committee.

The trial is closed and completed. This study is registered with ClinicalTrials.gov, NCT03552757.

Role of the funding source

The funder designed the trial, oversaw its conduct, monitored trial sites, and collected and analysed the data; 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

Of 1595 patients screened from June 4 to Nov 14, 2018, 1210 were enrolled, randomly assigned to semaglutide 2·4 mg (n=404), semaglutide 1·0 mg (n=403), or placebo (n=403), and included in the intention-to-treat analysis (figure 1). There was high completion of treatment (1058 [87%] of 1210) and the trial (1164 [96%] of 1210; figure 1). 24 patients received obesity rescue medication (four in the semaglutide 2·4 mg group, seven with semaglutide 1·0 mg, and 13 with placebo). One patient in the placebo group received bariatric surgery.

Baseline characteristics were well balanced across groups (table 1). Means were bodyweight 99·8 kg (SD 21·5), body-mass index 35·7 kg/m² (6·3), and waist circumference 114·6 cm (14·1). Mean duration of diabetes was 8·0 years (6·1).

Mean bodyweight change over time is shown in figure 2A, B (for cumulative distribution function

plots, see appendix p 16). Using the treatment policy estimand, mean weight change at week 68 was –9·6% (SE 0·4) with semaglutide 2·4 mg versus –3·4% (0·4) with placebo (coprimary endpoint; estimated treatment difference –6·2 percentage points, 95% CI –7·3 to –5·2, p<0·0001) (figure 2A), and for semaglutide 1·0 mg –7·0% (SE 0·4). Estimated treatment difference for semaglutide 2·4 mg versus semaglutide 1·0 mg was –2·7 percentage points (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% (SE 0·4) for placebo (estimated treatment difference –7·6 percentage points, 95% CI –8·6 to –6·6; figure 2B), and –7·6% (SE 0·4) for semaglutide 1·0 mg (estimated treatment difference –3·1 percentage points for 2·4 mg *vs* 1·0 mg, 95% CI –4·1 to –2·1; figure 2B).

	Semaglutide 2·4 mg (n=404)	Semaglutide 1·0 mg (n=403)	Placebo (n=403)	Treatment comparison (95% CI); p value for confirmatory analyses		
				Semaglutide 2·4 mg *vs* placebo	Semaglutide 2·4 mg *vs* semaglutide 1·0 mg	Semaglutide 1·0 mg *vs* placebo
Primary endpoints						
Bodyweight change from baseline to week 68 (SE), %	–9·64% (0·4)	–6·99% (0·4)	–3·42% (0·4)	ETD –6·21 (–7·28 to –5·15); p<0·0001	ETD –2·65 (–3·66 to –1·64); p<0·0001	NA
≥5% bodyweight reduction to week 68	267/388 (68·8%)	217/380 (57·1%)	107/376 (28·5%)	OR 4·88 (3·58 to 6·64); p<0·0001	OR 1·62 (1·21 to 2·18)	NA
Confirmatory secondary endpoints						
≥10% bodyweight reduction to week 68	177/388 (45·6%)	109/380 (28·7%)	31/376 (8·2%)	OR 7·41 (4·89 to 11·24); p<0·0001	OR 2·07 (1·53 to 2·80)	NA
≥15% bodyweight reduction to week 68	100/388 (25·8%)	52/380 (13·7%)	12/376 (3·2%)	OR 7·65 (4·11 to 14·22); p<0·0001	OR 2·17 (1·50 to 3·15)	NA
Waist circumference, cm						
At week 68	104·4 (14·7); n=387	107·2 (14·6); n=380	111·0 (13·7); n=375	..	..	..
Change from baseline to week 68 (SE)	–9·4 (0·4)	–6·7 (0·4)	–4·5 (0·4)	ETD –4·9 (–6·0 to –3·8); p<0·0001	ETD –2·7 (–3·7 to –1·7)	NA
HbA_{1c}						
At week 68	6·4% (1·2); n=381	6·6% (1·1); n=376	7·8% (1·3); n=374	..	..	..
Change from baseline to week 68 (SE)	–1·6% (0·1)	–1·5% (0·1)	–0·4% (0·1)	ETD –1·2 (–1·4 to –1·0); p<0·0001	ETD –0·2 (–0·3 to 0·0)	ETD –1·1 (–1·3 to –0·9)
HbA_{1c}, mmol/mol						
At week 68	46·7 (12·9); n=381	48·4 (12·0); n=376	61·8 (14·4); n=374	..	..	..
Change from baseline to week 68 (SE)	–17·5 (0·7)	–15·9 (0·8)	–4·1 (0·8)	ETD –13·5 (–15·5 to –11·4); p<0·0001	ETD –1·7 (–3·7 to 0·4)	ETD –11·8 (–14·0 to –9·7)
Systolic blood pressure, mm Hg						
At week 68	126 (14); n=387	127 (15); n=379	130 (14); n=376	..	..	..
Change from baseline to week 68 (SE)	–3·9 (0·7)	–2·9 (0·9)	–0·5 (0·8)	ETD –3·4 (–5·6 to –1·3); p=0·0016	ETD –1·0 (–3·3 to 1·2)	NA
SF-36v2 physical functioning score						
At week 68	52·1 (7·9); n=381	52·6 (7·1); n=377	50·5 (9·0); n=374	..	..	..
Change from baseline to week 68 (SE)	2·5 (0·4)	2·4 (0·4)	1·0 (0·4)	ETD 1·5 (0·4 to 2·6); p=0·0061	ETD 0·1 (–1·0 to 1·2)	NA
IWQOL-Lite-CT physical function score						
At week 68	79·0 (23·3); n=381	79·6 (20·8); n=377	74·8 (24·6); n=374	..	..	..
Change from baseline to week 68 (SE)	10·1 (1·0)	8·7 (1·1)	5·3 (1·1)	ETD 4·8 (1·8 to 7·9); p=0·0018	ETD 1·4 (–1·5 to 4·3)	NA

(Table 2 continues on next page)

	Semaglutide 2·4 mg (n=404)	Semaglutide 1·0 mg (n=403)	Placebo (n=403)	Treatment comparison (95% CI); p value for confirmatory analyses		
				Semaglutide 2·4 mg *vs* placebo	Semaglutide 2·4 mg *vs* semaglutide 1·0 mg	Semaglutide 1·0 mg *vs* placebo
(Continued from previous page)						
Exploratory secondary endpoints						
Bodyweight, kg						
At week 68	89·6 (21·0); n=388	92·3 (20·7); n=380	96·8 (20·3); n=376	..	..	..
Change from baseline to week 68 (SE)	−9·7 (0·4)	−6·9 (0·4)	−3·5 (0·4)	ETD −6·1 (−7·2 to −5·0)	ETD −2·7 (−3·8 to −1·7)	NA
Body-mass index, kg/m²						
At week 68	32·3 (6·1); n=388	32·9 (5·9); n=380	34·6 (6·4); n=376	..	..	..
Change from baseline to week 68 (SE)	−3·5 (0·1)	−2·5 (0·1)	−1·3 (0·1)	ETD −2·3 (−2·6 to −1·9)	ETD −1·0 (−1·3 to −0·6)	NA
HbA_{1c}						
≤6·5% at week 68	257/381 (67·5%)	226/376 (60·1%)	58/374 (15·5%)	OR 10·91 (7·51 to 15·85)	OR 1·39 (1·03 to 1·88)	NA
<7·0% at week 68	299/381 (78·5%)	272/376 (72·3%)	99/374 (26·5%)	OR 9·77 (6·85 to 13·93)	OR 1·40 (1·01 to 1·96)	NA
Fasting plasma glucose, mmol/L						
At week 68	6·4 (2·0); n=381	6·7 (2·1); n=374	8·5 (2·7); n=373	..	..	..
Change from baseline to week 68 (SE)	−2·1 (0·1)	−1·8 (0·1)	−0·1 (0·1)	ETD −2·0 (−2·4 to −1·7)	ETD −0·3 (−0·7 to 0·0)	NA
Fasting serum insulin, pmol/L						
At week 68 geometric mean (CV)	84·5 (74·3); n=373	92·5 (75·1); n=364	92·7 (72·6); n=362	..	..	..
Ratio of week 68 to baseline†	0·88	0·93	0·94	ETR 0·94 (0·87 to 1·02)	ETR 0·95 (0·87 to 1·03)	NA
Diastolic blood pressure, mm Hg						
At week 68	78 (9); n=387	79 (9); n=379	79 (9); n=376	..	..	..
Change from baseline to week 68 (SE)	−1·6 (0·4)	−0·6 (0·5)	−0·9 (0·5)	ETD −0·7 (−2·0 to 0·6)	ETD −0·9 (−2·2 to 0·4)	NA
Lipids						
Total cholesterol, mmol/L						
Week 68 geometric mean (CV)	4·3 (23·7); n=382	4·3 (25·6); n=376	4·4 (24·4); n=374	..	..	..
Ratio of week 68 to baseline†	0·99	0·98	0·99	ETR 0·99 (0·96 to 1·02)	ETR 1·01 (0·98 to 1·04)	NA
HDL cholesterol, mmol/L						
Week 68 geometric mean (CV)	1·2 (23·6); n=377	1·2 (23·8); n=376	1·2 (23·1); n=370	..	..	..
Ratio of week 68 to baseline†	1·07	1·05	1·04	ETR 1·03 (1·00 to 1·05)	ETR 1·02 (1·00 to 1·04)	NA
LDL cholesterol, mmol/L						
Week 68 geometric mean (CV)	2·3 (39·2); n=382	2·3 (41·0); n=376	2·3 (39·3); n=374	..	..	..
Ratio of week 68 to baseline†	1·00	0·99	1·00	ETR 1·00 (0·96 to 1·05)	ETR 1·01 (0·97 to 1·06)	NA
VLDL cholesterol, mmol/L						
Week 68 geometric mean (CV)	0·6 (52·9); n=382	0·7 (54·3); n=376	0·7 (54·0); n=374	..	..	..
Ratio of week 68 to baseline†	0·79	0·83	0·90	ETR 0·88 (0·83 to 0·93)	ETR 0·95 (0·90 to 1·01)	NA

(Table 2 continues on next page)

Patients were more likely to achieve at least a 5% reduction in baseline bodyweight at week 68 (coprimary endpoint) with semaglutide 2·4 mg than with placebo (267 [68·8%] of 388 *vs* 107 [28·5%] of 376; odds ratio [OR] 4·88, 95% CI 3·58–6·64, p<0·0001, treatment policy estimand) or semaglutide 1·0 mg (267 [68·8%] of 388 *vs* 217 [57·1%] of 380; OR 1·62, 95% CI 1·21–2·18, p=0·0012, treatment policy estimand; figure 2C). Similarly, more patients achieved reductions of at least 10%, 15%, or 20% at week 68 with semaglutide 2·4 mg compared with either semaglutide 1·0 mg or placebo (≥20% threshold not part of statistical testing hierarchy; figure 2C, D).

	Semaglutide 2·4 mg (n=404)	Semaglutide 1·0 mg (n=403)	Placebo (n=403)	Treatment comparison (95% CI); p value for confirmatory analyses		
				Semaglutide 2·4 mg *vs* placebo	Semaglutide 2·4 mg *vs* semaglutide 1·0 mg	Semaglutide 1·0 mg *vs* placebo
(Continued from previous page)						
Free fatty acids, mmol/L						
Week 68 geometric mean (CV)	0·5 (61·6); n=373	0·5 (54·4); n=364	0·6 (56·0); n=362	..	..	..
Ratio of week 68 to baseline†	0·84	0·86	0·99	ETR 0·84 (0·78 to 0·91)	ETR 0·97 (0·90 to 1·05)	NA
Triglycerides, mmol/L						
Week 68 geometric mean (CV)	1·4 (53·1); n=382	1·5 (56·8); n=376	1·7 (58·7); n=374	..	..	..
Ratio of week 68 to baseline†	0·78	0·83	0·91	ETR 0·86 (0·81 to 0·92)	ETR 0·94 (0·89 to 1·00)	NA
C-reactive protein, mg/L						
Week 68 geometric mean (CV)	1·70 (224·6); n=382	1·93 (193·2); n=376	2·75 (176·1); n=374	..	..	..
Ratio of week 68 to baseline†	0·51	0·58	0·83	ETR 0·61 (0·54 to 0·70)	ETR 0·88 (0·77 to 1·01)	NA
Exploratory endpoint—concomitant glucose-lowering medication‡						
Decreased	106/371 (28·6%)	93/371 (25·1%)	26/364 (7·1%)	..	..	..
No change	247/371 (66·6%)	258/371 (69·5%)	249/364 (68·4%)	..	..	..
Increased	18/371 (4·9%)	19/371 (5·1%)	88/364 (24·2%)	..	..	..
Missing	0	1/371 (0·3%)	1/364 (0·3%)	..	..	..

Data are n (%), or mean (SD) unless stated otherwise. All patients in the full analysis set are included in the treatment comparisons (ie, intention-to-treat analysis). CV=coefficient of variation as a percentage. ETD=estimated treatment difference. ETR=estimated treatment ratio. HbA_{1c}=glycated haemoglobin. IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version. NA=statistical analysis not done. OR=odds ratio. SF-36v2=Short Form 36v2 Health Survey, acute version. *The treatment policy estimand assesses treatment effect regardless of treatment discontinuation or rescue intervention (see appendix pp 10–13 for corresponding data for the trial product estimand, which assesses treatment effect if all patients adhered to treatment and did not start any rescue intervention). †Data shown as ratio from baseline to week 68 (ratio to baseline and corresponding baseline were log-transformed before analysis). ‡Proportion of patients with change in glucose-lowering medication from baseline to week 68.

Table 2: **Co-primary, confirmatory secondary, and selected exploratory trial endpoints (treatment policy estimand*)**

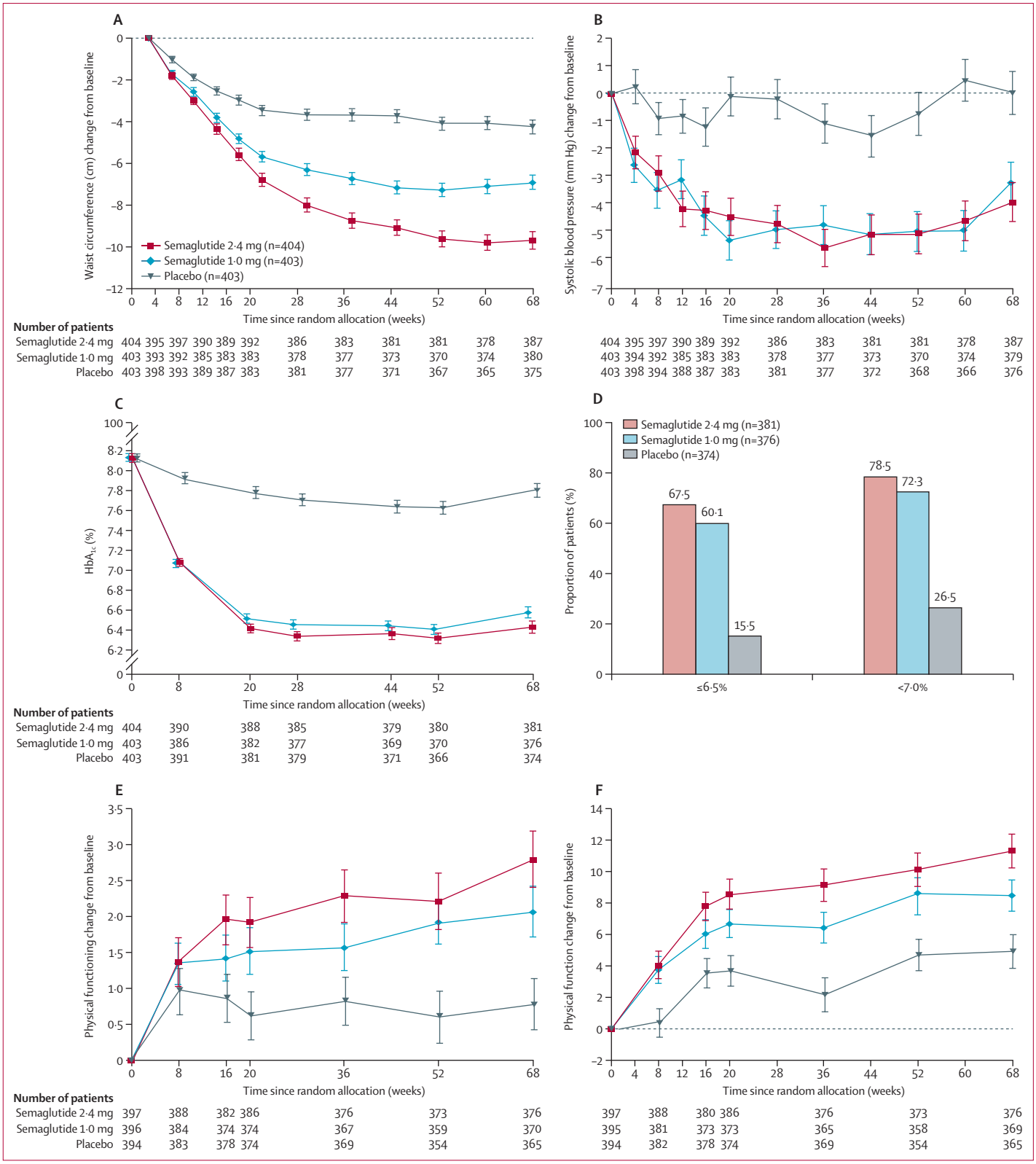
Benefits significantly favouring semaglutide 2·4 mg versus placebo were seen for changes in waist circumference and systolic blood pressure (table 2; figure 3A, B; appendix p 17). Improvements were also noted in lipid profile and inflammatory markers (table 2). Data for confirmatory secondary endpoints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

HbA_{1c} improved from baseline to week 68 in all three groups, by –1·6 percentage points (SE 0·1) with semaglutide 2·4 mg, –1·5 percentage points (0·1) with semaglutide 1·0 mg, and –0·4 percentage points (0·1) with placebo (table 2, figure 3C, appendix p 17). The proportion of patients in each group who achieved HbA_{1c} levels of 6·5% or lower, or of less than 7·0% at week 68 are shown in figure 2D and the appendix (p 17). Improvement in fasting plasma glucose was greater in both semaglutide groups compared with placebo (table 2). A decrease in use of concomitant glucose-lowering medication (reduction, change in product, or stopping the medication) was reported in 106 (28·6%) of 371 patients with semaglutide 2·4 mg, 93 (25·1%) of 381 with semaglutide 1·0 mg, and 26 (7·1%) of 364 with placebo.

Greater improvements in physical functioning scores for SF-36v2 and IWQOL-Lite-CT were seen with semaglutide 2·4 mg than with placebo (figure 3E, F; appendix pp 17–20).

The proportion of patients reporting adverse events was 353 (87·6%) of 403 with semaglutide 2·4 mg, 329 (81·8%) of 402 with semaglutide 1·0 mg, and 309 (76·9%) of 402 with placebo (table 3). Gastrointestinal disorders were the most frequently reported events. The most common gastrointestinal events were nausea, vomiting, diarrhoea, and constipation, which were mostly transient and mild to moderate in severity (appendix p 22), and the majority of patients continued the trial product and recovered. Serious adverse events were reported in 40 (9·9%) of 403 patients with semaglutide 2·4 mg, 31 (7·7%) of 402 with semaglutide 1·0 mg, and 37 (9·2%) of 402 with placebo. One death was reported in each of the three groups. More patients receiving semaglutide than placebo discontinued treatment because of adverse events, mainly because of gastrointestinal events (appendix p 23). The urine albumin-to-creatinine ratio decreased from baseline with semaglutide 2·4 mg and with semaglutide 1·0 mg, whereas it increased with placebo.

Alanine aminotransferase and aspartate aminotransferase decreased from baseline in the semaglutide 2·4 mg group and in the semaglutide 1·0 mg group; decreases were seen in the placebo group, but not to the same extent, with no clinically relevant findings in other biochemistry or haematology parameters (appendix p 14).


A
Waist circumference (cm) change from baseline
Semaglutide 2·4 mg (n=404)
Semaglutide 1·0 mg (n=403)
Placebo (n=403)
Time since random allocation (weeks)
Number of patients
Semaglutide 2·4 mg 404 395 397 390 389 392 386 383 381 381 378 387
Semaglutide 1·0 mg 403 393 392 385 383 383 378 377 373 370 374 380
Placebo 403 398 393 389 387 383 381 377 371 367 365 375
B
Systolic blood pressure (mm Hg) change from baseline
Time since random allocation (weeks)
404 395 397 390 389 392 386 383 381 381 378 387
403 394 392 385 383 383 378 377 373 370 374 379
403 398 394 388 387 383 381 377 372 368 366 376
C
HbA1c (%)
Time since random allocation (weeks)
Number of patients
Semaglutide 2·4 mg 404 390 388 385 379 380 381
Semaglutide 1·0 mg 403 386 382 377 369 370 376
Placebo 403 391 381 379 371 366 374
D
Semaglutide 2·4 mg (n=381)
Semaglutide 1·0 mg (n=376)
Placebo (n=374)
Proportion of patients (%)
67·5
60·1
15·5
78·5
72·3
26·5
≤6·5%
<7·0%
E
Physical functioning change from baseline
Time since random allocation (weeks)
Number of patients
Semaglutide 2·4 mg 397 388 382 386 376 373 376
Semaglutide 1·0 mg 396 384 374 374 367 359 370
Placebo 394 383 378 374 369 354 365
F
Physical function change from baseline
Time since random allocation (weeks)
397 388 380 386 376 373 376
395 381 373 373 365 358 369
394 382 378 374 369 354 365

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

Of events confirmed by the event adjudication committee, 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 in each of the three groups (table 3). No cases of medullary thyroid cancer or pancreatic cancer were reported.

Discussion

The STEP 2 study showed that in adults with overweight or obesity and type 2 diabetes, once a week subcutaneous semaglutide 2·4 mg as adjunct to lifestyle intervention was significantly more effective at reducing bodyweight than either semaglutide 1·0 mg or placebo, reducing it by 9·6% from baseline (6·2 percentage points more than placebo and 2·7 percentage points more than semaglutide 1·0 mg). Also, more than two-thirds of patients treated with semaglutide 2·4 mg achieved a target HbA_{1c} of 6·5% or less. Furthermore, at least 5% of baseline weight (a threshold cited as clinically meaningful weight loss[17]) was lost by 69% of patients on semaglutide 2·4 mg, compared with 57% on semaglutide 1·0 mg and 28% on placebo. All prespecified outcomes in the hierarchical stepwise testing were met, indicating that semaglutide 2·4 mg is not only effective at lowering bodyweight, 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 seen in other studies with a similar patient population. For example, in the SCALE Diabetes trial[8,18] of liraglutide 3·0 mg once a day as an adjunct to lifestyle intervention in patients with overweight or obesity and type 2 diabetes a 5·4% bodyweight reduction from baseline occurred (3·7 percentage points more than with placebo). Also, reductions in bodyweight of about 5% were reported in similar patient populations receiving orlistat 120 mg,[19] or the sustained-release combination of naltrexone 32 mg and bupropion 360 mg.[20] 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 than without type 2 diabetes. In the SCALE Obesity and Prediabetes trial[21] (patients with overweight or obesity but not type 2 diabetes), weight loss of 8·0% was achieved with liraglutide compared with 5·4% in patients with diabetes.[17] Furthermore, in the STEP 1 trial in people with overweight or obesity without type 2 diabetes, bodyweight reduction with semaglutide 2·4 mg as an adjunct to lifestyle intervention was 14·9% versus 2·4% with placebo.[22] The observed plateau of weight loss towards the end of the current 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 that accompany compensatory changes in appetite regulating hormones.[23–26]

Evidence suggests that overweight or obesity and type 2 diabetes considerably reduce health-related quality of life.[27] In this study, semaglutide 2·4 mg was associated with improvements in physical functioning, which can translate into benefits in daily living. Furthermore, there were improvements versus placebo on the SF-36v2 physical component summary score and the total score on the IWQOL-Lite-CT, an obesity-specific tool for measuring quality of life (appendix p 5).

The semaglutide 2·4 mg dose was selected on the basis of a phase 2 dose-finding trial in which semaglutide 0·4 mg once a day was effective in terms of weight loss, with an acceptable tolerability profile.[28] The higher dose of semaglutide increased the proportion of patients who lost at least 10% of baseline weight by week 68, from 28·7% with 1·0 mg to 45·6% with 2·4 mg, and nearly doubled the proportion who lost at least 15% bodyweight, from 13·7% with 1·0 mg to 25·8% with 2·4 mg. Semaglutide 1·0 mg once a week 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.[29] The effectiveness of semaglutide 1·0 mg on glycaemic control was shown in the present study in which HbA_{1c} 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 compared with patients receiving the 1·0 mg dose (29% *vs* 25%). The benefits of the higher dose of semaglutide can be clearly seen in the context of weight

Figure 3: **Comparison of selected confirmatory and exploratory secondary endpoints from baseline to week 68 for semaglutide 2·4 mg versus semaglutide 1·0 mg versus placebo, given once a week**

Line graphs show the observed mean change from baseline over time for patients in the full analysis set during the in-trial observation period in waist circumference (A), systolic blood pressure (B), glycated haemoglobin (C), Short Form 36v2 Health Survey, acute version physical functioning score (E), and Impact of Weight on Quality of Life-Lite Clinical Trials Version (F) (error bars are SE of the mean; numbers shown below the panel are patients contributing to the mean) and proportion of patients achieving HbA_{1c} targets of 6·5% or less, or less than 7·0% at week 68, for the in-trial period (D). Data are for the full analysis set.

	Semaglutide 2·4 mg (n=403)			Semaglutide 1·0 mg (n=402)			Placebo (n=402)		
	Patients	Events	Events per 100 patient- years	Patients	Events	Events per 100 patient- years	Patients	Events	Events per 100 patient- years
Any adverse events	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 leading to trial product discontinuation	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 at least 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§									
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

Data are n (%) of the safety analysis population (all randomly allocated patients exposed to at least one dose of randomised intervention) experiencing at least one event. Data are for on-treatment adverse events, occurring during treatment with any dose of trial intervention given within the previous 49 days (after excluding any temporary interruptions in taking trial intervention), unless indicated otherwise. MedDRA=Medical Dictionary for Regulatory Activities. *In-trial observation period. †Semaglutide 1·0 mg group: one death due to cardiorespiratory arrest in a patient with a medical history of coronary artery disease, triple vessel disease, and dilated cardiomyopathy with reduced left ventricular ejection fraction of 20%; semaglutide 2·4 mg group: one death due to myocardial infarction in a patient with a long-standing history of type 2 diabetes, hypertension, obesity, and previous smoking status (the patient also had a T-wave inversion detected on electrocardiogram for 4 years); placebo group: one 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. ‡Most common adverse events, by MedDRA preferred term, reported in at least 10% of patients in either treatment group. §Areas identified by searching MedDRA version 22.1; gastrointestinal disorders and psychiatric disorders defined by MedDRA version 22.1 system organ class; hepatobiliary defined by MedDRA system organ class and cholelithiasis defined by MedDRA preferred term. ¶Events confirmed by event adjudication committee. ‖Severe or blood glucose-confirmed hypoglycaemia.

Table 3: **Adverse events**

loss. In STEP 2, patients treated with semaglutide 2·4 mg achieved improvements in cardiometabolic risk factors—including waist circumference, HbA_{1c}, 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,[29] based on findings from the SUSTAIN 6 trial[29] in patients with type 2 diabetes at high cardiovascular risk. Treatments to reduce cardiovascular risk in people with type 2 diabetes and obesity are needed because of these patients' increased risk of morbidity and mortality from cardiovascular disease. For example, an analysis of data from over 820 000 people found that those with type 2 diabetes (versus those without) have a 2·3 times increased risk of mortality from vascular causes.[31] Also, a study of the US National Health and Nutrition Examination Survey Epidemiologic Follow-up Study population projected 10-year incidence rates of ischaemic heart disease, myocardial infarction, and congestive heart failure to be approximately 3% to 5% higher among people with obesity than without.[2] Although our findings suggest that semaglutide 2·4 mg might 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[32] in people with obesity without diabetes, is in progress. Although 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.[33,34] That increasing the dose of semaglutide reduced bodyweight more than it improved glycaemic control in STEP 2 is consistent with findings from the SCALE DIABETES trial[18] of liraglutide 1·8 mg and 3·0 mg, and findings from the Liraglutide Effect and Action in Diabetes programme[35] that investigated liraglutide at doses of 0·6 mg, 1·2 mg, and 1·8 mg—either alone or in combination with other oral glucose-lowering drugs—in patients with type 2 diabetes and a body-mass index less than 45 kg/m².

The safety profile of semaglutide 2·4 mg in patients with overweight or obesity and type 2 diabetes was typical of the GLP-1 receptor agonist class,[36,37] and consistent with the profile reported in the phase 2 study of once a day dosing in patients with obesity[28] and in the SUSTAIN trials[38] of once a week semaglutide in more than 8000 patients with type 2 diabetes. Transient, mild to moderate gastrointestinal disorders were the most frequently reported adverse events, and more patients discontinued treatment with semaglutide than with placebo. The rate of gastrointestinal adverse events was slightly higher with semaglutide 2·4 mg versus 1·0 mg, but discontinuations because of adverse events were low overall, and were similar in both semaglutide groups.

The strengths of this study include the large sample size (with a trial population different from others in the STEP trial programme[12]), double-dummy design, provision of lifestyle counselling, the high rate of treatment and trial completion, and the option of dose adjustment for glucose-lowering drugs. A notable limitation is the exclusion of patients on insulin. In the SUSTAIN 5 trial[39] in patients with type 2 diabetes, semaglutide 0·5 mg and 1·0 mg once a week as an add-on to basal insulin was associated with weight loss. Similar clinical benefits might be expected with semaglutide 2·4 mg in this patient population.

In conclusion, in adults with overweight (body-mass index ≥27 kg/m²) or obesity and type 2 diabetes, once a week semaglutide 2·4 mg as adjunct to lifestyle intervention led to a clinically meaningful bodyweight loss that was 6·2% greater than with placebo and 2·7% greater than with semaglutide 1·0 mg, with weight reductions of at least 5% achieved by 69% of patients with semaglutide 2·4 mg, 57% with semaglutide 1·0 mg, and 28% with placebo. The weight loss was accompanied by an HbA_{1c} reduction of 1·6% with semaglutide 2·4 mg, 1·5% with semaglutide 1·0 mg, and 0·4% with placebo. Also, patients treated with semaglutide 2·4 mg had greater improvements in cardiometabolic risk factors and physical functioning compared with patients treated with placebo.

Contributors

LF designed the trial. LF and OKJ did the data analysis. LF, OKJ, and AP interpreted the data. MD, LF, OKJ, SDP, LP, JR, IL, and AV did the trial. MD, LF, OKJ, SDP, LP, JR, and IL collected the data. 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

MD declares fees for consultancy, advisory board membership, and speaking from Novo Nordisk, Sanofi, Lilly, MSD, Boehringer Ingelheim, AstraZeneca, and Janssen; advisory board membership for Servier, Gilead Sciences, and Lexicon Pharmaceuticals; speaking fees from Napp Pharmaceuticals, Mitsubishi Tanabe Pharma, and Takeda; and research funding from Novo Nordisk, Sanofi, Lilly, Boehringer Ingelheim, AstraZeneca, and Janssen. LF is an employee of, and hold shares in, Novo Nordisk. OKJ is employee of, and hold shares in, Novo Nordisk. AP is an employee of Novo Nordisk. SDP declares personal fees for advisory board membership and speaking from Novo Nordisk, Janssen, Lilly, Merck, Bausch Health, AstraZeneca, Abbott, Boehringer Ingelheim, Sanofi, HLS Therapeutics, and Dexcom; consulting fees from Novo Nordisk, Janssen, AstraZeneca, Abbott, HLS therapeutics, and Dexcom; fees for clinical trials from Novo Nordisk, Lilly, AstraZeneca, Sanofi, Prometic, and Pfizer; grants from Lilly, AstraZeneca, Abbott, Boehringer Ingelheim, and Sanofi; and non-financial support for travel to meetings from Novo Nordisk, Janssen, Lilly, Bausch Health, AstraZeneca, Boehringer Ingelheim, and Sanofi. LP declares personal fees for consulting or speaking from Novo Nordisk, Sanofi, Boehringer Ingelheim, Lilly, AstraZeneca, Janssen, Merck, Medscape, and UpToDate. JR has served on scientific advisory boards for, and declares honoraria or consulting fees from, Applied Therapeutics, Lilly, Sanofi, Novo Nordisk, Janssen, Oramed, Boehringer Ingelheim, and Intarcia; and grants or research support from Applied Therapeutics, Merck, Novartis, Pfizer, Sanofi, Novo Nordisk, Lilly, GlaxoSmithKline, Genentech, Janssen, Lexicon, Boehringer Ingelheim, Oramed, and Intarcia. IS declares consulting or speaking fees from Astellas Pharma, Lilly, Kowa Company, Mitsubishi Tanabe Pharma, MSD, Boehringer Ingelheim, Novo Nordisk, Ono Pharmaceutical, Sanofi, Sanwa Kagaku Kenkyusho, and Takeda; research support from the Japan Agency for Medical Research and Development, Kowa Company, and Rohto Pharmaceutical; and scholarship grants from Astellas Pharma, AstraZeneca, Daiichi Sankyo, Japan Diabetes Foundation, Japan Foundation for Applied Enzymology, Kowa Company, Kowa Life Science Foundation, Kyowa Kirin, Novartis Pharma, Novo Nordisk, Midori Health Care Foundation, Mitsubishi Tanabe Pharma, MSD, MSD Life Science Foundation, Ono Pharmaceutical, Osaka Kaisei Hospital, Sanofi, Sumitomo Dainippon Pharma, Suzuken Memorial Foundation, Takeda, Teijin Pharma, Terumo Corporation, and The Japan Diabetes Society. AV has done research trials for, served as an advisor for, and received speaking fees from Amgen, AstraZeneca, Boehringer Ingelheim, Lilly, MannKind, Napp, Novartis, Novo Nordisk, Regeneron, Sanofi, Takeda, and Tosoh. TAW serves on advisory boards for Novo Nordisk and WW (formerly Weight Watchers) and declares grants, on behalf of the University of Pennsylvania, from Novo Nordisk. IL declares grants from Novo Nordisk, Sanofi, Merck, Mylan, and Pfizer; personal fees from Novo Nordisk, Sanofi, Lilly, AstraZeneca, Boehringer Ingelheim, Janssen, Intercept, Intarcia, TARGETPharma, Mannkind, Valeritas, Bayer, and Zealand Pharma; and non-financial support from Merck, Pfizer, Novo Nordisk, Sanofi, Lilly, AstraZeneca, Boehringer Ingelheim, Janssen.

Data sharing

Data will be shared with bona fide researchers who submit a research proposal approved by the independent review board. Individual patient data will be shared in data sets in a de-identified and anonymised format. Data will be made available after research completion and approval of the product and product use in the EU and the USA. Information about data access request proposals can be found at novonordisk-trials.com.

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