Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background We assessed the efficacy and safety of the oral glucagon-like peptide-1 analogue, semaglutide 50 mg, taken once per day versus placebo for the treatment of overweight or obesity in adults without type 2 diabetes.

Methods This randomised, double-blind, placebo-controlled, phase 3, superiority trial enrolled adults with a BMI of at least 30 kg/m², or at least 27 kg/m² with bodyweight-related complications and comorbidities, without type 2 diabetes. The trial was done at 50 outpatient clinics in nine countries across Asia, Europe, and North America. Participants were randomly allocated (1:1) via an interactive web-response system to oral semaglutide escalated to 50 mg, or visually matching placebo, once per day for 68 weeks, plus lifestyle intervention. Group assignment was masked for participants, investigators, and those assessing outcomes. Coprimary endpoints were the percentage change in bodyweight and whether participants reached a bodyweight reduction of at least 5% at week 68 for oral semaglutide 50 mg versus placebo, assessed regardless of treatment discontinuation or use of other bodyweight-lowering therapies (an intention-to-treat analysis). Safety was assessed in participants who received at least one dose of trial drug. This trial, registered with ClinicalTrials.gov (NCT05035095), is now complete.

Findings From Sept 13 to Nov 22, 2021, 709 participants were screened, of whom 667 were randomly assigned to oral semaglutide 50 mg (n=334) or placebo (n=333). The estimated mean bodyweight change from baseline to week 68 was −15·1% (SE 0·5) with oral semaglutide 50 mg versus −2·4% (0·5) with placebo (estimated treatment difference −12·7 percentage points, 95% CI −14·2 to −11·3; p<0·0001). More participants reached bodyweight reductions of at least 5% (269 [85%] of 317 *vs* 76 [26%] of 295; odds ratio [OR] 12·6, 95% CI 8·5 to 18·7; p<0·0001), 10% (220 [69%] *vs* 35 [12%]; OR 14·7, 9·6 to 22·6), 15% (170 [54%] *vs* 17 [6%]; OR 17·9, 10·4 to 30·7), and 20% (107 [34%] *vs* 8 [3%]; OR 18·5, 8·8 to 38·9) at week 68 with oral semaglutide 50 mg versus placebo. Adverse events were more frequent with oral semaglutide 50 mg (307 [92%] of 334) than with placebo (285 [86%] of 333). Gastrointestinal adverse events (mostly mild to moderate) were reported in 268 (80%) participants with oral semaglutide 50 mg and 154 (46%) with placebo.

Interpretation In adults with overweight or obesity without type 2 diabetes, oral semaglutide 50 mg once per day led to a superior and clinically meaningful decrease in bodyweight compared with placebo.

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*A complete list of OASIS 1 Investigators is provided in the appendix (p 2)

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See Online for appendix

Introduction

The goal of obesity treatment is not only the reduction of bodyweight, but curtailment of the pathogenic processes exacerbated by obesity that lead to additional complications and comorbidities, such as dyslipidaemia, type 2 diabetes, non-alcoholic steatohepatitis, obstructive sleep apnoea, and hypertension.[1,2] Indeed, treatment for obesity is a crucial aspect in the prevention of type 2 diabetes[3,4] and reduction of cardiovascular disease risk.[5]

People with overweight or obesity can struggle to manage their bodyweight long term using diet and physical activity alone.[6] The pathophysiological processes integral to the disease produce and sustain increased adiposity, which, together with metabolic maladaptation following bodyweight reduction, act to drive bodyweight regain.[6,7] For such individuals, anti-obesity medications can be used as adjunctive pharmacotherapy.[1,2] Subcutaneous semaglutide 2·4 mg taken once per week is a glucagon-like peptide-1 (GLP-1) analogue approved for the treatment of obesity on the basis of the findings of the global phase 3 STEP programme, which demonstrated bodyweight reductions of 14·9–17·4% on average in people with overweight or obesity, without type 2 diabetes, with accompanying reductions in cardiometabolic risk factors. A lower bodyweight reduction of 9·6% was reported in people with type 2 diabetes and overweight or obesity.[8] Exposure–response analyses of the oral (14 mg once per day) and subcutaneous (1 mg once per week) formulations in people with type 2 diabetes indicate there

Research in context

Evidence before this study

In people with overweight or obesity, reducing bodyweight is known to reduce the risk of bodyweight-related complications and comorbidities such as type 2 diabetes, sleep apnoea, hypertension, and dyslipidaemia. Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue available as subcutaneous and oral formulations. Subcutaneous semaglutide 2·4 mg once per week has been approved for the chronic treatment of overweight and obesity, and substantially reduces bodyweight and improves cardiometabolic risk factors in people with overweight or obesity with or without type 2 diabetes. Oral semaglutide 7 mg and 14 mg once per day has been approved for the treatment of type 2 diabetes and improves glycaemic control with accompanying bodyweight reductions. A higher dose of oral semaglutide 50 mg once per day is currently being investigated for the treatment of obesity in people with overweight or obesity, and for glycaemic control in people with type 2 diabetes. We searched PubMed on May 5, 2023, for articles published in the past 5 years, with no language restrictions, using the search terms "glucagon-like peptide-1 receptor agonist", "oral", "obesity", and "overweight". No publications reporting the results of trials investigating oral GLP-1 receptor agonists for the treatment of overweight or obesity in humans were identified.

Added value of this study

In adults with overweight or obesity without type 2 diabetes, oral semaglutide 50 mg once per day achieved a superior decrease in mean bodyweight (–15·1%, SE 0·5) compared with placebo (–2·4%, 0·5; p<0·0001), with clinically meaningful reductions of at least 5% reported for 85% of participants receiving oral semaglutide 50 mg compared with 26% with placebo. Among the participants who received oral semaglutide 50 mg, more than two-thirds had bodyweight reductions of at least 10%, more than half had reductions of at least 15%, and one-third had reductions of at least 20%, all more than with placebo. These findings were accompanied by substantial improvements in physical functioning scores and cardiometabolic risk factors compared with placebo. Oral semaglutide 50 mg had a safety profile that was consistent with previous data for subcutaneous semaglutide in obesity and with the GLP-1 receptor agonist class.

Implications of all the available evidence

To our knowledge, this was the first trial to assess the bodyweight-lowering effect of an oral GLP-1 analogue (semaglutide 50 mg taken once per day) in adults with overweight or obesity, without type 2 diabetes. The study showed that, in this population, oral semaglutide 50 mg induced clinically meaningful reductions in bodyweight, with accompanying improvements in cardiometabolic risk factors. These results were notably consistent with those previously reported for subcutaneous semaglutide 2·4 mg taken once per week in a similar population. Oral semaglutide 50 mg therefore might represent an effective option for the treatment of obesity.

is a near-identical relationship between plasma semaglutide concentration and effect on glycated haemoglobin (HbA_{1c}) and bodyweight regardless of administration route.[9] Despite their availability, prescribing rates for all anti-obesity medications remain low; analyses of prescribing rates between 2009 and 2019 suggest only 1–3% of people eligible for anti-obesity medications actually receive treatment, for several reasons, including access and cost.[10,11] Availability of an oral GLP-1 analogue with demonstrated bodyweight-lowering efficacy could give people requiring treatment for obesity, and their physicians, an additional treatment to address obesity and associated comorbidities. Patients would be able to choose a GLP-1 analogue that can be administered either subcutaneously or orally according to their preferences, and physicians might find an oral medication easy and convenient to provide in a primary care setting.

Oral semaglutide is coformulated in a tablet with the absorption enhancer sodium N-(8-[2-hydroxylbenzoyl] amino) caprylate.[12] In a phase 2 dose-finding trial, oral semaglutide 40 mg taken once per day resulted in bodyweight reductions of 5·7 kg over 26 weeks in people with type 2 diabetes, with or without overweight or obesity, with a safety profile consistent with other GLP-1 receptor agonists.[12] The dose was increased to 50 mg because modelling indicated that this increase would improve bodyweight reductions while obtaining a safety profile similar to that of the 40 mg dose (unpublished data). A dose of oral semaglutide 50 mg was therefore chosen for obesity treatment trials. Compared with the 2·4 mg dose taken once per week, used for the subcutaneous formulation, this dose is greater because of differences in bioavailability between the formulations (unpublished data).

The aim of the Oral Semaglutide Treatment Effect in People with Obesity (OASIS) 1 trial was to evaluate the efficacy and safety of oral semaglutide 50 mg taken once per day plus lifestyle intervention in people with overweight or obesity.

Methods

Study design

This randomised, double-blind, placebo-controlled, phase 3, superiority trial (appendix p 24) was done at 50 outpatient centres in nine countries across east Asia, Europe, and North America (appendix p 2). The trial was carried out in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines.[13] The protocol and amendments (appendix pp 33–121) were approved by each trial site's institutional review board or independent

ethics committee. Deviations from the protocol are listed in the appendix (p 6); these deviations did not affect the conclusions of the trial.

Participants

Male or female participants who were aged 18 years or older (aged 20 years or older in Japan per Japanese regulatory requirements), with a BMI of at least 30 kg/m², or at least 27 kg/m² with one or more bodyweight-related complications or comorbidities (hypertension, dyslipidaemia, obstructive sleep apnoea, or cardiovascular disease), and with at least one self-reported dietary bodyweight loss effort were eligible. Sex was self-reported with options for male or female. Key exclusion criteria included self-reported bodyweight changes of more than 5 kg in the 90 days before screening, previous or planned surgery for bodyweight loss, an HbA_{1c} of 6·5% (48 mmol/mol) or more at screening, and a history of either type 1 or 2 diabetes. The absence of type 2 diabetes was confirmed at screening by the investigators on the basis of available information, including medical records, concomitant medication, and blood glucose variables (eg, HbA_{1c}). Full eligibility criteria are provided in the appendix (pp 3–4). All participants provided written informed consent.

Randomisation and masking

Participants were randomly allocated 1:1 to oral semaglutide 50 mg or placebo by trial staff using an interactive web-based response system, which allocated a treatment code to each participant in block sizes of four. Trial product was dispensed by trial staff at each site. Oral semaglutide and placebo were visually identical to maintain masking for trial staff and participants, and those conducting data analysis were masked to treatment assignment until final database lock.

Procedures

Participants received oral semaglutide 50 mg or placebo once per day for 68 weeks as an adjunct to lifestyle intervention, followed by 7 weeks of off-treatment follow-up.

Oral semaglutide was initiated at 3 mg and escalated every 4 weeks (or longer, if needed, to improve tolerability) to 7 mg, 14 mg, 25 mg, and up to 50 mg (the maintenance dose) by week 16. If a participant could not tolerate the 50 mg maintenance dose, a lower dose could be used at the investigator's discretion, with at least one attempt to re-escalate to 50 mg recommended. However, participants could remain on a lower dose if they would otherwise have prematurely discontinued trial product. In the event of premature treatment discontinuation, participants were requested to remain in the trial; trial product could be reintroduced if the participant agreed. Per the prescribing information for oral semaglutide in type 2 diabetes,[14,15] participants were instructed to swallow their assigned trial product whole each morning with no more than half a glass of water (approximately 120 mL) and at least 30 min before intake of food, any other liquids, or any other oral medication. Two excipients (microcrystalline cellulose [filler] and povidone K 90 [binder]) included in the formulation currently available for the treatment of type 2 diabetes[14,15] were omitted from the oral semaglutide formulation used for the 25 mg and 50 mg doses, for enhanced bioavailability.

All participants received counselling on diet (500 kcal deficit per day, relative to total energy expenditure at randomisation, estimated using the calculation in the protocol [appendix pp 59–60]) and physical activity (150 min per week—eg, walking) from a dietitian or other similarly qualified health-care professional every

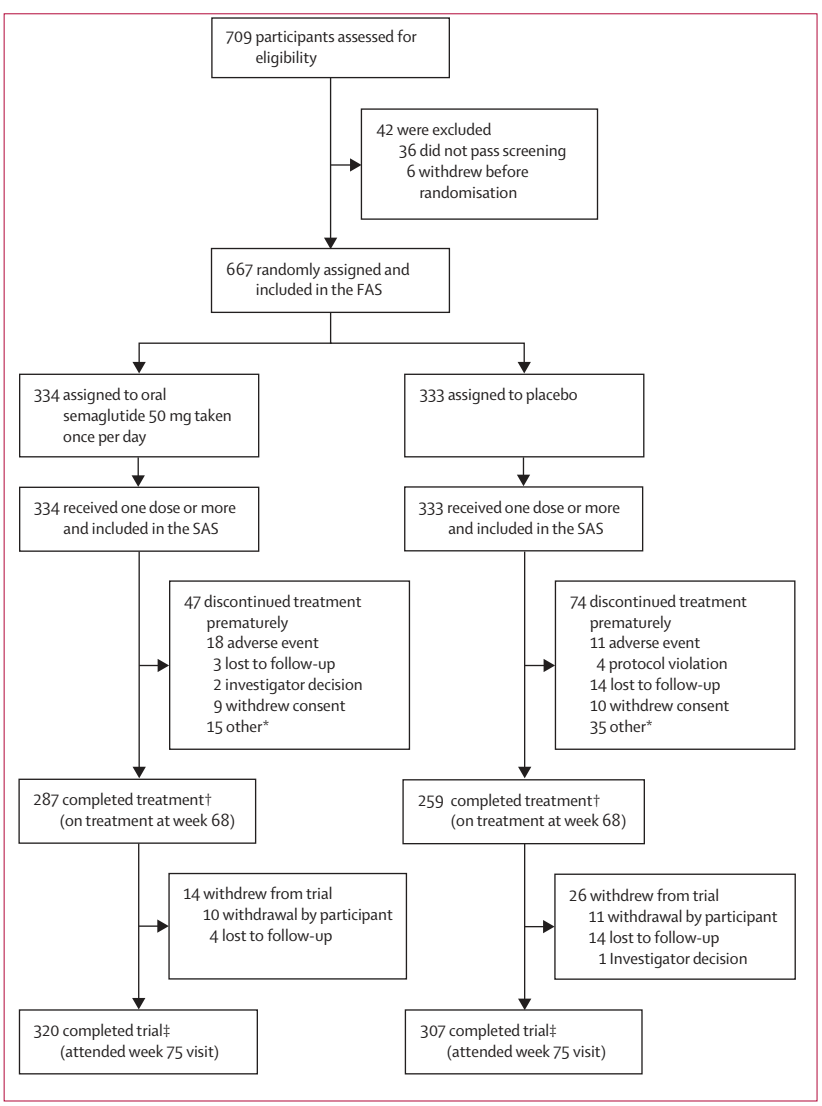

Figure 1: **Trial profile**

FAS=full-analysis set. SAS=safety-analysis set. *Other reasons for premature treatment discontinuation are listed in the appendix (p 8). †Participants were considered to have completed treatment if they were on treatment at week 68. ‡Participants were considered to have completed the trial if they attended the end-of-trial visit at week 75, regardless of whether they completed treatment.

	Oral semaglutide 50 mg (n=334)	Placebo (n=333)	Total (n=667)
Age, years	49 (13)	50 (12)	50 (13)
Sex			
Female	247/334 (74%)	238/333 (71%)	485/667 (73%)
Male	87/334 (26%)	95/333 (29%)	182/667 (27%)
Race			
Asian	36/334 (11%)	36/333 (11%)	72/667 (11%)
Black or African American	21/334 (6%)	22/333 (7%)	43/667 (6%)
White	246/334 (74%)	248/333 (74%)	494/667 (74%)
Other*	31/334 (9%)	27/333 (8%)	58/667 (9%)
Ethnicity			
Hispanic or Latino	14/334 (4%)	13/333 (4%)	27/667 (4%)
Not Hispanic or Latino	288/334 (86%)	296/333 (89%)	584/667 (88%)
Not reported	32/334 (10%)	24/333 (7%)	56/667 (8%)
Bodyweight, kg	104·5 (22·0)	106·2 (22·3)	105·4 (22·2)
BMI, kg/m^2			
Mean	37·3 (6·3)	37·7 (6·8)	37·5 (6·5)
Distribution			
Less than 30	24/334 (7%)	30/333 (9%)	54/667 (8%)
30 to less than 35	108/334 (32%)	106/333 (32%)	214/667 (32%)
35 to less than 40	110/334 (33%)	101/333 (30%)	211/667 (32%)
40 or more	92/334 (28%)	96/333 (29%)	188/667 (28%)
Waist circumference, cm	112·6 (13·6)	114·5 (15·4)	113·6 (14·6)
HbA_{1c}, %	5·6 (0·3)	5·6 (0·3)	5·6 (0·3)
HbA_{1c}, mmol/mol	37·5 (3·6)	37·9 (3·7)	37·7 (3·7)
Fasting plasma glucose, mmol/L	5·4 (0·7); n=333	5·5 (0·5); n=331	5·5 (0·6); n=664
Fasting serum insulin, geometric mean (CV), pmol/L	93·7 (60·4); n=296	92·7 (57·6); n=299	93·2 (59·0); n=595
Prediabetes†	132/334 (40%)	130/333 (39%)	262/667 (39%)
Blood pressure, mm Hg			
Systolic	129 (16)	130 (15)	129 (15)
Diastolic	82 (11)	83 (11)	82 (11)
Pulse, bpm	71 (10)	72 (10)	72 (10)
Lipids, geometric mean (CV), mmol/L			
Total cholesterol	5·0 (20·7); n=332	4·9 (20·1); n=328	5·0 (20·4); n=660
HDL cholesterol	1·3 (24·7); n=331	1·3 (23·3); n=326	1·3 (24·0); n=657
LDL cholesterol	3·0 (31·1); n=331	2·8 (34·0); n=326	2·9 (32·7); n=657
VLDL cholesterol	0·6 (44·3); n=332	0·6 (50·9); n=328	0·6 (47·6); n=660
Free fatty acids	0·4 (63·1); n=296	0·4 (60·6); n=299	0·4 (62·0); n=595
Triglycerides	1·4 (44·8); n=332	1·4 (52·2); n=328	1·4 (48·5); n=660
High-sensitivity C-reactive protein, geometric mean (CV), mg/dL	3·4 (138·0); n=333	3·4 (143·3); n=328	3·4 (140·4); n=661
eGFR, geometric mean (CV), mL/min per 1·73 m^2	96·1 (17·0)	93·3 (20·5)	94·7 (18·9)
IWQOL-Lite-CT scores			
Physical Function	63·6 (22·4); n=322	61·3 (22·9); n=328	62·4 (22·7); n=650
Total	62·0 (20·9); n=322	60·4 (19·9); n=328	61·2 (20·4); n=650
SF-36v2 scores			
Physical Functioning	51·4 (7·0); n=327	51·0 (7·0); n=331	51·2 (7·0); n=658
Physical Component Summary	51·4 (7·4); n=327	51·0 (7·4); n=331	51·2 (7·4); n=658
Mental Component Summary	54·8 (6·1); n=327	55·4 (5·6); n=331	55·1 (5·9); n=658

(Table 1 continues on next page)

4 weeks throughout the trial. Participants were encouraged to record their food intake and physical activity every day via an app or similar tool.

Outcomes

The coprimary endpoints were the percentage change in bodyweight from baseline to week 68 and whether participants reached at least 5% bodyweight reduction from baseline at week 68 for oral semaglutide 50 mg versus placebo. Confirmatory (ie, those included in the statistical testing hierarchy) secondary endpoints in hierarchical testing order were whether participants reached at least 10%, 15%, and 20% bodyweight reduction from baseline at week 68, and change from baseline to week 68 in the participant-reported physical function outcomes, consisting of the Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT) Physical Function score, and the Short Form-36v2 Health Survey acute version (SF-36v2) Physical Functioning score. Supportive (ie, those not included in the statistical testing hierarchy) secondary endpoints included changes in absolute bodyweight (in kg), BMI, waist circumference, blood pressure, glucose homoeostasis (HbA_{1c}, fasting plasma glucose, and fasting serum insulin), glycaemic status (HbA_{1c} less than 5·7% [indicative of normoglycaemia], from 5·7% to less than 6·5% [indicative of prediabetes], and at least 6·5% [indicative of type 2 diabetes]), fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, free fatty acids, and triglycerides), and high-sensitivity C-reactive protein; and whether participants reached clinically meaningful changes in IWQOL-Lite-CT Physical Function and SF-36v2 Physical Functioning scores, and a BMI of less than 30 kg/m² in participants whose baseline BMI was 30 kg/m² or more; a full list of these and the exploratory endpoints is provided in the appendix (pp 4–5). Prespecified exploratory analyses were done to assess treatment-by-subgroup interactions for the percentage change in bodyweight by sex, baseline bodyweight, and baseline BMI.

Safety assessments included the number of treatment-emergent adverse events and serious adverse events assessed up to week 75. Adverse events were assessed over two observation periods; the on-treatment period and the in-trial period. For the majority of adverse events, data are reported for the on-treatment period, whereas fatal events and those related to cardiovascular disease, neoplasms, and hypoglycaemia are reported for the in-trial period. Clinical laboratory assessments were done by a central laboratory. Physical examinations, vital sign assessments, and electrocardiograms were done as outlined in the protocol (appendix p 73), but did not routinely involve any further complementary assessments such as imaging.

The timing of key assessments done throughout the trial is provided in the appendix (p 10).

Statistical analysis

As outlined in the protocol (appendix pp 81–82), a sample size of 660 participants (330 per group) was required to provide more than 99% power to confirm superiority of oral semaglutide 50 mg to placebo for the two coprimary endpoints, and power of 66% to confirm superiority for the coprimary and confirmatory secondary endpoints, tested in a prespecified hierarchical order (appendix p 11).

Efficacy outcomes were assessed in all randomly assigned participants (per the intention-to-treat principle, termed the full-analysis set) and safety outcomes were assessed in all randomly assigned participants who received at least one dose of trial product (per the treatment actually received, termed the safety-analysis set). There were two observation periods: the in-trial period, which was the time from randomisation to last contact with a trial site, regardless of trial product discontinuation or use of other bodyweight-lowering therapies (ie, anti-obesity medications or bariatric surgery); and the on-treatment period, which was the time from the first dose of trial product to 3 days after the last dose for efficacy analyses, or to 49 days after the last dose for safety analyses, excluding any temporary interruptions. Statistical analyses were done using SAS software, version 9·4. Results from statistical analyses of the coprimary and confirmatory secondary endpoints were accompanied by two-sided 95% CIs and corresponding p values (superiority was $p<0·05$). For the coprimary endpoints, superiority had to be demonstrated for both endpoints independently at a significance level of 0·05 before oral semaglutide 50 mg could be claimed superior to placebo. The bodyweight-related coprimary and confirmatory secondary endpoints were correlated, but the degree of correlation was not estimated, nor included in the design considerations. p values are not reported for the supportive secondary or exploratory endpoints as their analyses were not controlled for multiplicity; results for these endpoints should therefore not be used to infer definitive treatment effects.

Two coprimary estimands assessed the treatment effect in the full-analysis set regardless of adherence or use of other bodyweight-lowering therapies (per intention-to-treat), using the data from the in-trial observation period, for each of the coprimary endpoints. This strategy for handling intercurrent events is referred to as the treatment policy strategy, and aims to reflect clinical practice as closely as possible by assessing the treatment effect on the basis of exactly how the treatments were taken in the trial.[16] Secondary estimands, which addressed each of the confirmatory and supportive secondary endpoints, were similar to the coprimary estimands except for the endpoint attribute. For the coprimary and secondary estimands, missing data were imputed 1000 times by sampling from available measurements at week 68 from retrieved participants (ie, participants who discontinued treatment but attended the end-of-treatment visit) using a multiple imputation approach similar to that described by McEvoy.[17] The 1000 complete datasets were analysed, resulting in 1000 estimates that were then combined using Rubin's rules.[18] Continuous endpoints were assessed using an analysis of covariance model, with randomised treatment as a factor and baseline value of the outcome as a covariate. Binary endpoints were assessed using a logistic regression model, with the same factor and covariate. In line with previous semaglutide trials, the coprimary and secondary estimands will be referred to as the treatment policy estimand.

Additional estimands addressed each of the coprimary, and confirmatory and supportive secondary endpoints, and assessed the effect in the full analysis set assuming all participants remained on treatment throughout the trial and did not use other bodyweight-lowering therapies, using the data from the on-treatment observation period until first discontinuation or initiation of another weight-lowering therapy, referred to as the trial product strategy.

	Oral semaglutide 50 mg (n=334)	Placebo (n=333)	Total (n=667)
(Continued from previous page)			
Comorbidities at screening‡			
Hypertension	144/334 (43%)	161/333 (48%)	305/667 (46%)
Dyslipidaemia	128/334 (38%)	139/333 (42%)	267/667 (40%)
Obstructive sleep apnoea	45/334 (13%)	48/333 (14%)	93/667 (14%)
Knee or hip osteoarthritis	34/334 (10%)	42/333 (13%)	76/667 (11%)
Asthma or chronic obstructive pulmonary disease	41/334 (12%)	29/333 (9%)	70/667 (10%)
Thyroid disorder	33/334 (10%)	33/333 (10%)	66/667 (10%)
Glucose metabolism disorder	29/334 (9%)	24/333 (7%)	53/667 (8%)
Liver disease	20/334 (6%)	20/333 (6%)	40/667 (6%)
Gout	12/334 (4%)	15/333 (5%)	27/667 (4%)
Reproductive system disorders	8/334 (2%)	5/333 (2%)	13/667 (2%)
Coronary artery disease	6/334 (2%)	3/333 (1%)	9/667 (1%)
Kidney disease	4/334 (1%)	3/333 (1%)	7/667 (1%)
Cerebrovascular disease	1/334 (0%)	3/333 (1%)	4/667 (1%)
Number of comorbidities at screening‡			
Five or more	12/334 (4%)	6/333 (2%)	18/667 (3%)
Four	12/334 (4%)	17/333 (5%)	29/667 (4%)
Three	40/334 (12%)	50/333 (15%)	90/667 (13%)
Two	90/334 (27%)	87/333 (26%)	177/667 (27%)
One	96/334 (29%)	100/333 (30%)	196/667 (29%)
None	84/334 (25%)	73/333 (22%)	157/667 (24%)

Data are n (%) or mean (SD) and include all participants in the full-analysis set, unless stated otherwise. Numbers of participants analysed (where different from the number in the full-analysis set) are denoted by n for each parameter. Proportions may not total 100 because of rounding. CV=coefficient of variation in percentage. bpm=beats per minute. eGFR=estimated glomerular filtration rate. 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, Other, or not reported. †Based on an HbA_{1c} concentration of 5·7% or more to less than 6·5%. No participants had an HbA_{1c} of 6·5% or more at screening. However, five participants (n=2, oral semaglutide 50 mg; n=3, placebo) developed an HbA_{1c} of 6·5% or more between screening and baseline; these participants are not shown in the table. ‡Information collected at screening on comorbidities was based on medical history and included glucose metabolism disorder, 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.

Table 1: **Baseline characteristics**

The trial product strategy assessed the treatment effect if the treatments were taken as intended. For these additional estimands, the continuous and binary endpoints were assessed using a mixed model for repeated measurements with the same factor and covariate as for the coprimary and secondary estimands, all nested within visit. An unstructured covariance matrix for measurements within the same participant was used, assuming that measurements for different participants were independent. Using predicted values from the mixed model for repeated measurements for participants with missing week 68 data, the binary endpoints were then

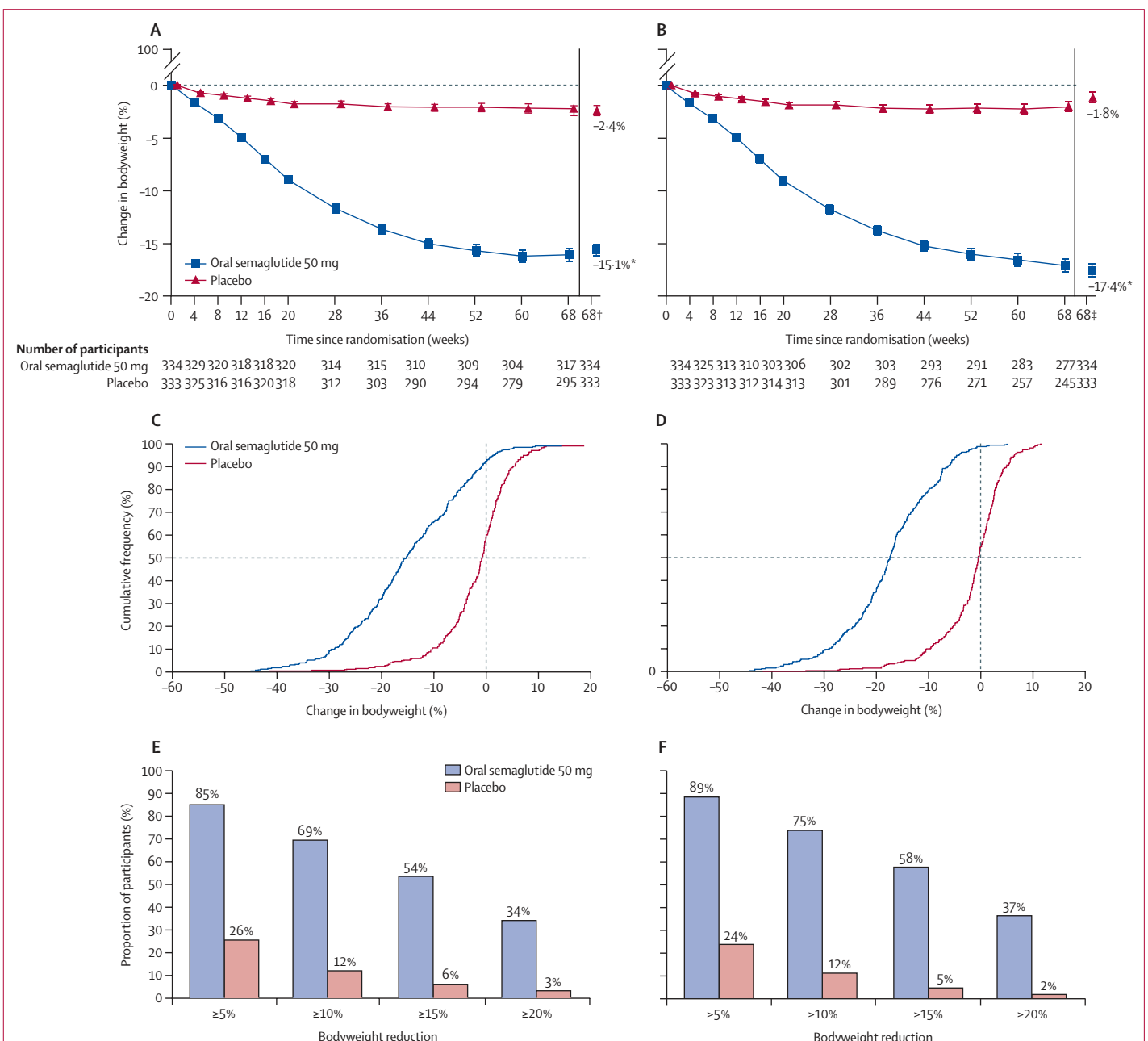

Figure 2: **Change in the bodyweight-related coprimary and confirmatory secondary efficacy endpoints from baseline to week 68**
Data are observed (ie, as-measured) mean changes from baseline in bodyweight (A and B; error bars are SE and numbers below the graphs are the number of participants contributing to the mean), the cumulative distribution of observed and imputed (where observations were missing) mean changes from baseline in bodyweight (C and D), and observed proportions of participants achieving bodyweight reductions of at least 5%, 10%, 15%, and 20% (E and F) for the in-trial (A, C, and E) and on-treatment (B, D, and F) observation periods, all for the full-analysis set. (C) Missing observations were handled according to methods used for the treatment policy estimand. (D) Missing observations and observations after first trial product discontinuation or use of another bodyweight-lowering therapy were handled in accordance with methods for the trial product estimand. *p<0·0001 for the estimated treatment difference versus placebo. †Estimated mean changes in bodyweight at week 68 for the treatment policy estimand. ‡Estimated mean changes in bodyweight at week 68 for the trial product estimand.

assessed using a logistic regression model fitted with the same factor and covariate as used in the other analyses. Similar to the previous semaglutide trials, the additional estimands will be referred to as the trial product estimand.

Adverse events are only presented descriptively. The statistical analysis plan and amendments are available in the appendix (pp 122–48). This trial is complete and is registered with ClinicalTrials.gov, NCT05035095.

Role of the funding source

Novo Nordisk, the funder, designed the trial, oversaw its conduct, monitored trial sites, collected and analysed the data, and assumed the role of the data monitoring committee (as agreed with regulatory agencies considering the well characterised safety profile of semaglutide); investigators were responsible for trial-related medical decisions and data collection. This article was drafted and revised under the guidance of the authors who were responsible for all decisions regarding publication, with medical writing and editorial support paid for by the funder.

Results

From Sept 13 to Nov 22, 2021, 709 participants were screened, of whom 667 were randomly assigned to oral semaglutide 50 mg (n=334) or placebo (n=333), and were included in the intention-to-treat analysis (figure 1). Most participants completed treatment (ie, were on treatment at week 68; 546 [82%] of 667; 287 [86%] of 334 with oral semaglutide 50 mg and 259 [78%] of 333 with placebo) and most completed the trial (ie, attended the end-of-trial visit at week 75, regardless of treatment completion; 627 [94%]; figure 1). Other bodyweight-lowering therapies were used by 18 participants during the trial (one in the oral semaglutide 50 mg group, 17 in the placebo group). Among participants who completed treatment on oral semaglutide 50 mg, 229 (80%) of 285 (week 68 dosing information was missing for one participant, and one was reported as receiving no dose) were on the 50 mg dose at week 68 (appendix p 25). Most participants in the oral semaglutide 50 mg group appeared to tolerate the standard dose-escalation protocol, with 232 (76%) of 306 on the 50-mg dose by the end of week 20.

Baseline characteristics were well balanced across the treatment groups (table 1). For the total population, mean age was 50 years, bodyweight was 105·4 kg, BMI was 37·5 kg/m², and waist circumference was 113·6 cm. 494 (74%) of 667 participants were White, 43 (6%) were Black or African American, and 72 (11%) were Asian. 485 (73%) participants were female and 182 (27%) were male. Overall, 613 participants had a BMI of at least 30 kg/m², and 54 had a BMI of at least 27 kg/m² but less than 30 kg/m² plus bodyweight-related complications or comorbidities (table 1).

Mean bodyweight decreased over the course of the trial in each treatment group (figure 2A, B; cumulative distribution plots in figure 2C, D). For the treatment

	Oral semaglutide 50 mg (n=334)	Placebo (n=333)	Treatment comparison	
			OR or ETD (95% CI)	p value for confirmatory analyses
Coprimary endpoints				
Change in bodyweight, %	−15·1 (0·5); n=317	−2·4 (0·5); n=295	ETD* −12·7 (−14·2 to −11·3)	p<0·0001
Participants with 5% or more bodyweight reduction†	269/317 (85%)	76/295 (26%)	OR 12·6 (8·5 to 18·7)	p<0·0001
Confirmatory secondary endpoints				
Participants with 10% or more bodyweight reduction†	220/317 (69%)	35/295 (12%)	OR 14·7 (9·6 to 22·6)	p<0·0001
Participants with 15% or more bodyweight reduction†	170/317 (54%)	17/295 (6%)	OR 17·9 (10·4 to 30·7)	p<0·0001
Participants with 20% or more bodyweight reduction†	107/317 (34%)	8/295 (3%)	OR 18·5 (8·8 to 38·9)	p<0·0001
Change in IWQOL-Lite-CT Physical Function score, points	14·7 (1·1); n=309	4·2 (1·1); n=281	ETD 10·5 (7·5 to 13·6)	p<0·0001
Change in SF-36v2 Physical Functioning score, points	2·5 (0·3); n=309	0·2 (0·3); n=281	ETD 2·3 (1·4 to 3·2)	p<0·0001
Supportive secondary endpoints				
Change in bodyweight, kg	−15·5 (0·5); n=317	−2·5 (0·5); n=295	ETD −13·0 (−14·6 to −11·5)	..
Change in BMI, kg/m²	−5·6 (0·2); n=317	−0·9 (0·2); n=295	ETD −4·7 (−5·3 to −4·2)	..
Change in waist circumference, cm	−13·0 (0·5); n=317	−3·0 (0·5); n=295	ETD −10·0 (−11·4 to −8·6)	..
Change in HbA_{1c}, percentage-point	−0·2 (0·0); n=311	0·1 (0·0); n=286	ETD −0·3 (−0·3 to −0·2)	..
Change in fasting plasma glucose, mmol/L	−0·5 (0·0); n=314	−0·1 (0·0); n=294	ETD −0·4 (−0·5 to −0·3)	..
Change in fasting serum insulin, %‡	−33·1; n=309	−8·1; n=287	ETD −27·2 (−33·4 to −20·4)	..
Change in blood pressure, mm Hg				
Systolic	−6·6 (0·7); n=317	−0·3 (0·7); n=295	ETD −6·3 (−8·3 to −4·3)	..
Diastolic	−2·4 (0·5); n=317	−0·6 (0·5); n=295	ETD −1·9 (−3·2 to −0·6)	..
Change in lipids, %‡				
Total cholesterol	−2·3; n=315	0·2; n=293	ETD −2·4 (−5·0 to 0·2)	..
HDL cholesterol	4·9; n=314	0·2; n=293	ETD 4·8 (2·2 to 7·3)	..
LDL cholesterol	−0·6; n=314	1·7; n=293	ETD −2·2 (−5·9 to 1·7)	..
VLDL cholesterol	−22·2; n=314	−5·1; n=293	ETD −18·0 (−22·6 to −13·2)	..
Free fatty acids	−14·4; n=309	3·5; n=287	ETD −17·3 (−24·3 to −9·6)	..
Triglycerides	−22·3; n=314	−5·3; n=293	ETD −17·9 (−22·5 to −13·1)	..
Change in high-sensitivity C-reactive protein, %‡	−57·3; n=315	−13·8; n=293	ETD −50·4 (−57·1 to −42·6)	..
Participants with 14·6-point change or more in IWQOL-Lite-CT Physical Function score†§	149/298 (50%)	87/278 (31%)	OR 2·8 (1·9 to 4·1)	..

(Table 2 continues on next page)

	Oral semaglutide 50 mg (n=334)	Placebo (n=333)	Treatment comparison	
			OR or ETD (95% CI)	p value for confirmatory analyses
(Continued from previous page)				
Participants with 3·7-point change or more in SF-36v2 Physical Functioning score†§	113/303 (37%)	56/280 (20%)	OR 2·9 (1·9 to 4·5)	..
Participants whose BMI changed from 30 kg/m² or more at baseline to less than 30 kg/m²†	129/294 (44%)	19/268 (7%)	OR 14·4 (8·0 to 25·9)	..
Glycaemic status†				
HbA_{1c} less than 5·7%	274/311 (88%)	139/286 (49%)	NA	..
HbA_{1c} 5·7% or more to less than 6·5%	36/311 (12%)	143/286 (50%)	NA	..
HbA_{1c} 6·5% or more	1/311 (0%)	4/286 (1%)	NA	..

Data are estimated mean (SE) changes for each parameter for the treatment policy estimand, unless stated otherwise, for the full-analysis set. The treatment policy estimand assessed the treatment effect in all participants who had undergone randomisation, regardless of adherence to their assigned treatment or the use of other bodyweight-lowering therapies (ie, anti-obesity medications or bariatric surgery), on the basis of data from the in-trial observation period. Corresponding data for the trial product estimand (which assessed the treatment effect assuming that participants received their assigned treatment for the trial duration without use of other bodyweight-lowering therapies) are shown in the appendix (p 13). Numbers of participants with an observation at week 68 are denoted by n for each endpoint. The number of participants with imputed data can be calculated by subtracting n from the number in the full-analysis set, provided in the column headers. ETD=estimated treatment difference. FDA=US Food and Drug Administration. HbA_{1c}=glycated haemoglobin. IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version. N/A=not assessed. OR=odds ratio. SF-36v2=Short Form-36v2 Health Survey acute version. STEP=Semaglutide Treatment Effect in People with Obesity. *The treatment comparison for the mean percentage change in bodyweight is expressed in percentage points. †Data are observed (ie, as measured) n (%) from the in-trial observation period, and the treatment comparison is the estimated ORs for the treatment policy estimand (ORs were not estimated for the change in glycaemic status). Proportions by glycaemic status may not total 100 because of rounding. ‡These measures were initially analysed on a log scale as an estimated ratio to the baseline value (within trial groups) and estimated treatment ratios (between trial groups). For interpretation, the ratios to the baseline value are expressed as relative percentage changes, and the treatment ratios are expressed as estimated relative percentage differences between groups, calculated with the use of the following formula: (estimated ratio − 1) × 100. §Thresholds represent meaningful, within-participant improvements, derived using anchor-based methods in accordance with FDA guidance,[19] on the basis of data from the STEP 1 trial.[20]

Table 2: **Coprimary, confirmatory secondary, and supportive secondary efficacy endpoints at week 68**

policy estimand (ie, the effect based on exactly how the treatments were taken), the estimated mean bodyweight change from baseline at week 68 was –15·1% (SE 0·5) with oral semaglutide 50 mg versus –2·4% (0·5) with placebo (coprimary endpoint; estimated treatment difference –12·7 percentage points, 95% CI –14·2 to –11·3, p<0·0001; table 2). Corresponding changes for the trial product estimand (ie, the effect if the treatments were taken as intended) were –17·4% (0·5) with oral semaglutide 50 mg versus –1·8% (0·5) with placebo (estimated treatment difference –15·6 percentage points, –17·1 to –14·2; appendix p 13). In the subgroup analyses, there were significant treatment-by-subgroup interactions on the change in bodyweight for sex (p=0·0003) and baseline bodyweight (p=0·032), but not baseline BMI (appendix p 16).

The observed number of participants reaching at least 5% bodyweight reduction from baseline to week 68 was 269 (85%) of 317 with oral semaglutide 50 mg and 76 (26%) of 295 with placebo during the in-trial observation period, and 247 (89%) of 277 with oral semaglutide 50 mg and 60 (24%) of 245 with placebo during the on-treatment observation period (table 2; figure 2E, F; appendix p 13). The odds of reaching this outcome were significantly greater with oral semaglutide 50 mg versus placebo for both the treatment policy (coprimary endpoint; odds ratio [OR] 12·6, 95% CI 8·5–18·7; p<0·0001) and trial product (OR 55·2, 33·0–92·4) estimands (table 2, appendix p 13). Similarly, participants receiving oral semaglutide 50 mg versus placebo were significantly more likely to reach at least 10%, 15%, and 20% bodyweight reductions for both estimands (confirmatory secondary endpoints; table 2; figure 2E, F, appendix p 13). Estimated proportions of participants derived from the logistic regression model for the treatment policy estimand are shown in the appendix (p 17).

The greater bodyweight reduction with oral semaglutide 50 mg over placebo was accompanied by significant improvements in the participant-reported outcomes IWQOL-Lite-CT Physical Function and SF-36v2 Physical Functioning scores for both estimands (confirmatory secondary endpoints; table 2; appendix pp 13, 26, 27). In addition, participants were significantly more likely to reach clinically relevant changes in these measures with oral semaglutide 50 mg than with placebo (table 2; appendix p 13).

Data for the other supportive secondary endpoints are shown (table 2) for the treatment policy estimand (corresponding data for the trial product estimand is presented in the appendix p 13). Of note, there were improvements in absolute bodyweight (in kg), BMI, waist circumference, glucose homoeostasis (HbA_{1c}, fasting plasma glucose, and fasting serum insulin), blood pressure, fasting lipids (HDL cholesterol, VLDL cholesterol, free fatty acids, and triglycerides), and high-sensitivity C-reactive protein with oral semaglutide 50 mg compared with placebo (table 2; figure 3A–E; appendix pp 13, 28). Participants who had a baseline BMI of 30 kg/m² or more were more likely to reach a BMI less than 30 kg/m² at week 68 with oral semaglutide 50 mg than with placebo (table 2; appendix p 13). Among the participants with baseline prediabetes, a greater proportion had an HbA_{1c} of less than 5·7% by week 68 with oral semaglutide 50 mg than with placebo (table 2; figure 3F; appendix p 13, 28). Although rates were low, a greater proportion of participants had stopped or decreased their blood pressure-lowering medication at week 68 with oral semaglutide 50 mg than placebo (appendix p 18).

In terms of safety, the number of participants reporting adverse events was 307 (92%) of 334 with oral semaglutide 50 mg and 285 (86%) of 333 with placebo (table 3). Serious adverse events were reported by 32 (10%) participants with oral semaglutide 50 mg and 29 (9%) with placebo. Slightly more participants in the oral semaglutide 50 mg group than the placebo group permanently discontinued

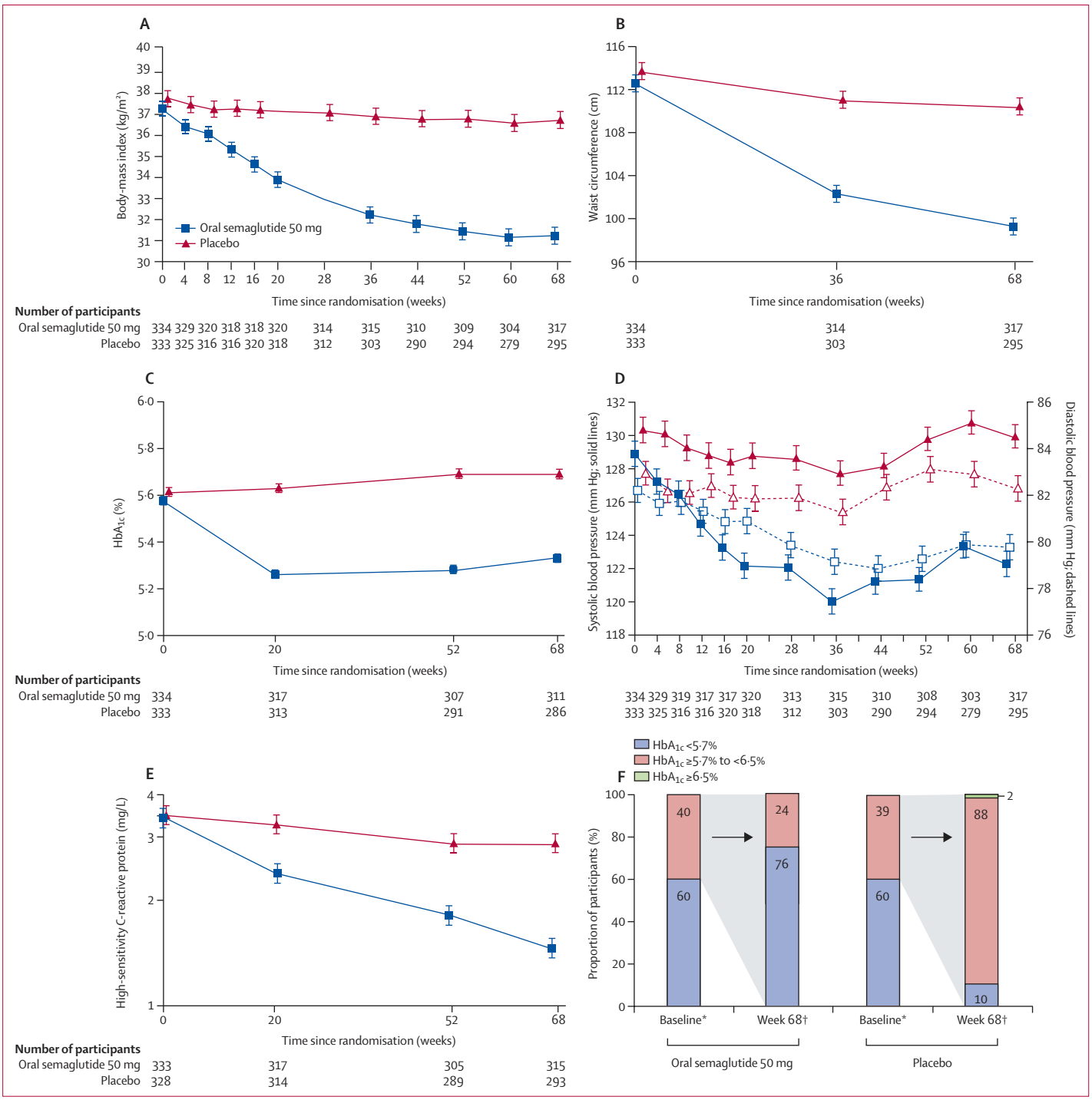

***Figure 3*: Change in the BMI, waist circumference, HbA_{1c}, blood pressure, high-sensitivity C-reactive protein, and glycaemic status supportive secondary efficacy endpoints from baseline to week 68**

Data are observed (ie, as-measured) mean absolute values of BMI (A), waist circumference (B), HbA_{1c} (C), systolic and diastolic blood pressure (D; error bars are SE), geometric mean values of high-sensitivity C-reactive protein (E; y-axis is on a logarithmic scale, error bars are SE calculated on a logarithmic scale and back transformed to a linear scale), and observed proportions of participants by glycaemic status at baseline and, in people with baseline prediabetes, at week 68 (F) from the in-trial observation period, all for the full-analysis set. (A–E) Numbers below the graphs are the number of participants contributing to the mean and geometric mean. (F) Proportions might not total 100 because of rounding. Corresponding data for the on-treatment observation period are shown in the appendix (p 28). HbA_{1c}=glycated haemoglobin. *Baseline glycaemic status in all participants with normoglycaemia and prediabetes. Presence of type 2 diabetes at screening was an exclusion criterion. However, five participants (n=2, oral semaglutide 50 mg; n=3, placebo) developed an HbA_{1c} of 6·5% or more between screening and baseline; these participants are not shown in the figure. †Week 68 glycaemic status in participants with baseline prediabetes.

trial product because of adverse events (mostly gastrointestinal related with oral semaglutide 50 mg; table 3; appendix p 29). No deaths occurred.

The most frequently reported events with oral semaglutide 50 mg were gastrointestinal related (nausea, constipation, diarrhoea, and vomiting) and COVID-19 (table 3). The gastrointestinal adverse events were typically transient and mild to moderate in severity and resolved without permanent trial product discontinuation (appendix p 30). The reporting of gastrointestinal-related events with oral semaglutide 50 mg peaked during the dose escalation phase (appendix p 30).

Gallbladder-related disorders (mostly cholelithiasis) were reported by 13 (4%) of 334 participants with oral semaglutide 50 mg and 4 (1%) of 333 participants with placebo. There were no pancreatitis events in either treatment group. Cardiovascular disorders were reported by 39 (12%) participants with oral semaglutide 50 mg and 44 (13%) with placebo. There was an imbalance in benign and malignant neoplasm events between groups, reported by 30 (9%) participants with oral semaglutide 50 mg and 17 (5%) with placebo (appendix p 19). Malignant neoplasms occurred in 5 (2%) participants with oral semaglutide 50 mg and 4 (1%) with placebo, indicating the imbalance was driven by benign neoplasms. Benign neoplasms events were dispersed across organs, with no clustering in any specific system organ class (appendix p 19). There was also an imbalance in adverse events related to a clinical picture of altered skin sensation, reported by 42 (13%) participants with

	Oral semaglutide 50 mg (n=334)			Placebo (n=333)		
	n	Number of events	Event rate*	n	Number of events	Event rate*
Any adverse events	307/334 (92%)	2500	561·3	285/333 (86%)	1577	366·7
Serious adverse events	32/334 (10%)	44	9·9	29/333 (9%)	48	11·2
Adverse events leading to trial product discontinuation	19/334 (6%)	27	6·1	12/333 (4%)	17	4·0
Gastrointestinal disorders	12/334 (4%)	19	4·3	5/333 (2%)	7	1·6
Fatal events†	0	..	..	0	..	..
Adverse events reported in 5% of patients or more by MedDRA preferred term						
Nausea	173/334 (52%)	331	74·3	51/333 (15%)	64	14·9
COVID-19	120/334 (36%)	128	28·7	116/333 (35%)	122	28·4
Constipation	92/334 (28%)	123	27·6	50/333 (15%)	71	16·5
Diarrhoea	89/334 (27%)	169	37·9	56/333 (17%)	70	16·3
Vomiting	80/334 (24%)	154	34·6	12/333 (4%)	14	3·3
Decreased appetite	56/334 (17%)	61	13·7	24/333 (7%)	26	6·0
Dyspepsia	47/334 (14%)	64	14·4	17/333 (5%)	19	4·4
Headache	46/334 (14%)	80	18·0	29/333 (9%)	36	8·4
Nasopharyngitis	38/334 (11%)	54	12·1	49/333 (15%)	73	17·0
Abdominal pain upper	32/334 (10%)	45	10·1	12/333 (4%)	16	3·7
Eructation	32/334 (10%)	42	9·4	7/333 (2%)	7	1·6
Gastro-oesophageal reflux disease	29/334 (9%)	35	7·9	11/333 (3%)	12	2·8
Dizziness	27/334 (8%)	33	7·4	16/333 (5%)	19	4·4
Influenza	26/334 (8%)	37	8·3	18/333 (5%)	21	4·9
Abdominal distension	25/334 (7%)	26	5·8	16/333 (5%)	19	4·4
Fatigue	24/334 (7%)	28	6·3	20/333 (6%)	23	5·3
Alopecia	23/334 (7%)	25	5·6	9/333 (3%)	9	2·1
Abdominal pain	22/334 (7%)	28	6·3	16/333 (5%)	19	4·4
Arthralgia	22/334 (7%)	26	5·8	38/333 (11%)	42	9·8
Flatulence	19/334 (6%)	22	4·9	13/333 (4%)	15	3·5
Upper-respiratory-tract infection	19/334 (6%)	26	5·8	20/333 (6%)	29	6·7
Urinary-tract infection	19/334 (6%)	27	6·1	8/333 (2%)	8	1·9
Gastroenteritis	18/334 (5%)	22	4·9	10/333 (3%)	10	2·3
Back pain	16/334 (5%)	20	4·5	24/333 (7%)	37	8·6
Sinusitis	12/334 (4%)	13	2·9	18/333 (5%)	25	5·8
Hypertension	10/334 (3%)	12	2·7	22/333 (7%)	24	5·6

(Table 3 continues on next page)

	Oral semaglutide 50 mg (n=334)			Placebo (n=333)		
	n	Number of events	Event rate*	n	Number of events	Event rate*
(Continued from previous page)						
Safety areas of interest‡						
Gastrointestinal disorders	268/334 (80%)	1136	255·1	154/333 (46%)	382	88·8
Cardiovascular disorders†	39/334 (12%)	49	10·4	44/333 (13%)	56	12·0
Psychiatric disorders§	31/334 (9%)	35	7·9	34/333 (10%)	37	8·6
Benign and malignant neoplasms†¶	30/334 (9%)	38	8·1	17/333 (5%)	24	5·2
Allergic reactions	26/334 (8%)	35	7·9	17/333 (5%)	23	5·3
Gallbladder-related disorders	13/334 (4%)	15	3·4	4/333 (1%)	5	1·2
Hepatobiliary disorders§	13/334 (4%)	15	3·4	4/333 (1%)	5	1·2
Cholelithiasis‖	11/334 (3%)	12	2·7	4/333 (1%)	4	0·9
Hepatic disorders	6/334 (2%)	7	1·6	9/333 (3%)	10	2·3
Malignant neoplasms†	5/334 (1%)	6	1·3	4/333 (1%)	5	1·1
Hypoglycaemia†	3/334 (1%)	4	0·8	1/333 (0%)	1	0·2
Acute pancreatitis	0	..	..	0	..	..
Acute renal failure	0	..	..	2/333 (1%)	2	0·5

Data are observed (ie, as measured) n (%) and number of events from the on-treatment observation period (the time from the first dose of trial product to 49 days after the last dose for safety analyses, excluding any temporary interruptions) for the safety-analysis set, unless stated otherwise. GLP-1=glucagon-like peptide-1. MedDRA=Medical Dictionary for Regulatory Activities (version 25.1). *Number of events per 100 patient-years. †Data are from the in-trial observation period (the time from randomisation to the last contact with a trial site, regardless of trial product discontinuation or use of other bodyweight-lowering therapies—ie, medications or bariatric surgery). ‡Prespecified based on therapeutic experience with GLP-1 receptor agonists and regulatory requirements, identified by searching adverse event data for relevant MedDRA terms, unless stated otherwise. §MedDRA system organ class. ¶Benign and malignant adverse events by MedDRA system organ class and preferred term are shown in the appendix (p 19). ‖MedDRA preferred term.

Table 3: **Adverse events**

oral semaglutide 50 mg and 4 (1%) with placebo (appendix pp 21, 31; additional data on safety focus areas are presented in table 3).

Pulse increased by 4·1 (SE 0·5) beats per minute with oral semaglutide 50 mg during the trial and decreased by 0·4 (0·5) beats per minute with placebo (appendix p 22). There were no other clinically relevant changes following physical examinations or electrocardiograms, nor in haematology or biochemistry values (appendix p 22).

Discussion

The OASIS 1 trial showed that in adults with overweight or obesity, oral semaglutide 50 mg taken once per day as an adjunct to diet and physical activity was significantly more effective at meaningfully reducing bodyweight than placebo. Bodyweight was reduced by 15·1% from baseline with oral semaglutide 50 mg, 12·7 percentage points more than placebo. Assuming it was taken as intended, the estimated bodyweight reduction with oral semaglutide 50 mg was 17·4%. Also, more than three times the number of participants treated with oral semaglutide 50 mg reached a clinically meaningful reduction in bodyweight of at least 5% than with placebo (85% *vs* 26%), which is a minimum regulatory requirement for an effective anti-obesity medication.[21] In addition, more than two-thirds of participants had bodyweight reductions of at least 10%, more than half had reductions of at least 15%, and a third had reductions of at least 20% with oral semaglutide 50 mg, all more than with placebo. All of the prespecified endpoints in the statistical testing hierarchy were met, indicating that oral semaglutide 50 mg was superior to placebo in reducing bodyweight and improving physical functioning. These findings were accompanied by improvements in cardiometabolic risk factors.

With the caveat that indirect comparisons between trials should be interpreted with caution owing to differences in designs, lengths, populations, and analysis methods, the magnitude of bodyweight reduction achieved with oral semaglutide 50 mg appears to be greater than has previously been reported with oral anti-obesity medications.[22] However, large head-to-head clinical trials are required to confirm this. Furthermore, the magnitude of placebo-corrected bodyweight reduction with oral semaglutide 50 mg was notably similar to that reported in the STEP 1 trial (12·4 percentage points) with subcutaneous semaglutide 2·4 mg once per week,[20] which was of similar design and had a similar population to OASIS 1. Subcutaneous semaglutide 2·4 mg exerts its effects on bodyweight by increasing feelings of satiety, improving control of eating, and reducing food cravings, all of which result in lowering energy intake.[23] Oral semaglutide 50 mg probably has similar effects on appetite, food-related behaviour, and gastric emptying, which are currently being investigated in an ongoing trial (NCT05236517).

Variability in the magnitude of response to anti-obesity medications is a well known phenomenon.[24] We found

significant treatment-by-subgroup interactions on the change in bodyweight for sex and baseline bodyweight with oral semaglutide 50 mg versus placebo, with similar findings previously reported with subcutaneous semaglutide 2·4 mg.[25] Further analyses on larger datasets are needed to investigate whether other participant characteristics could affect response to oral semaglutide 50 mg. Considering obesity is a chronic, relapsing disease requiring long-term treatment, people using anti-obesity medications often also experience bodyweight regain after treatment cessation.[26] However, the sustainability of the effect of a treatment will depend on the active pharmacotherapeutic ingredient. 2-year trials have shown bodyweight regain with continued use of both lorcaserin and orlistat.[27,28] Data with subcutaneous semaglutide 2·4 mg indicate that continued treatment is required to maintain its bodyweight-related benefits.[29,30] However, these effects are maintained with up to 2 years of use.[31] The long-term sustainability of the bodyweight reduction with oral semaglutide 50 mg might therefore be similar to that with the subcutaneous formulation, but this will require longer-term trials to be conducted, considering efficacy endpoints were only assessed up to week 68 in OASIS 1.

Obesity treatment is central to the prevention and management of multiple obesity-related complications and comorbidities.[1,3] Oral semaglutide 50 mg was able to substantially improve cardiometabolic risk factors including waist circumference, HbA_{1c}, blood pressure, and lipids (HDL cholesterol, VLDL cholesterol, free fatty acids, and triglycerides), which could have contributed to the observed reduction in the need for blood pressure-lowering medication, and the greater number of participants with baseline prediabetes reverting to normoglycaemia at week 68 compared with placebo. Furthermore, the reductions in both fasting plasma glucose and serum insulin concentrations were consistent with an improvement in insulin sensitivity. Similar findings have been seen with subcutaneous semaglutide 2·4 mg,[20] with greater reductions in these parameters observed at greater levels of bodyweight reduction.[32]

In addition to metabolic improvements, oral semaglutide 50 mg resulted in a 57·3% reduction in high-sensitivity C-reactive protein, a marker of systemic inflammation that can be used to assess future cardiovascular risk.[33] From the baseline value of 3·4 mg/dL, this level of reduction would equate to an improvement in relative risk category from high (defined as more than 3 mg/dL) to intermediate (defined as 1–3 mg/dL) risk,[33] which has also previously been reported with subcutaneous semaglutide 2·4 mg.[34] Combined, oral semaglutide at doses up to 14 mg and subcutaneous semaglutide at doses up to 1 mg have already been shown to provide cardiovascular benefits in people with type 2 diabetes.[35] These effects are being further investigated with oral semaglutide (up to 14 mg) in people with type 2 diabetes in the ongoing Semaglutide Cardiovascular Outcomes Trial (SOUL; NCT03914326), and with subcutaneous semaglutide 2·4 mg in people with overweight or obesity without type 2 diabetes in the ongoing Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity (SELECT) trial (NCT03574597). There are currently no equivalent ongoing outcome trials with oral semaglutide 50 mg in people with overweight or obesity without type 2 diabetes, but data from SOUL and SELECT will provide further insight into the effects of semaglutide on cardiovascular outcomes.

The safety profile of oral semaglutide 50 mg was generally in line with subcutaneous semaglutide 2·4 mg,[8] and with that of the GLP-1 receptor agonist class as a whole.[36] As seen previously with subcutaneous semaglutide 2·4 mg,[37] gastrointestinal-related adverse events, including upper gastrointestinal events such as gastro-oesophageal reflux disease and dyspepsia, were more common than with placebo and were associated with the dose escalation period. It is not impossible that the greater rate of gastrointestinal adverse events with oral semaglutide 50 mg compared with placebo contributed to the greater bodyweight reductions. Previous analyses with subcutaneous semaglutide 2·4 mg have shown that less than one percentage point of the bodyweight reduction achieved with semaglutide was because of gastrointestinal adverse events.[37] Similar analyses would be required to confirm this with oral semaglutide 50 mg. The proportion of participants who prematurely discontinued trial product was consistent with that seen with subcutaneous semaglutide 2·4 mg in STEP 1.[20] More participants reported events related to a clinical picture of altered skin sensation in the oral semaglutide 50 mg group compared with placebo. These events were generally mild to moderate in severity, occurred during escalation to the higher doses, and resolved without requiring permanent treatment discontinuation. There was also an imbalance in benign neoplasm events between treatment groups, which was not observed in the Peptide Innovation for Early Diabetes Treatment (PIONEER) PLUS trial (NCT04707469) of oral semaglutide 25 mg and 50 mg in people with type 2 diabetes.[38] There are no data available that could explain this imbalance, and so it will be monitored in future trials, such as the SELECT trial, as well as post-marketing surveillance of semaglutide. COVID-19 was a frequent adverse event in both treatment groups in the trial, probably as a result of frequent testing during the trial period.

Of the participants who completed their treatment with oral semaglutide, 80% did so on the 50 mg dose suggesting acceptable tolerability. A small number of participants (9%) were on the 25 mg dose at week 68. For this group, the final dose might not be representative of

their exposure throughout the trial and their responses would not correspond to a non-selected population. Treatment effects in this group were therefore not assessed. Oral semaglutide 25 mg will instead be investigated in the ongoing OASIS 4 trial (NCT05564117).

These results, and their similarity to those with subcutaneous semaglutide 2·4 mg, indicate that oral semaglutide 50 mg represents another effective treatment option that could allow patients to use a treatment that meets their preferences. As evidenced in populations with type 2 diabetes, patients differ in their preference for injectable and oral GLP-1 receptor agonist medications,[39,40] suggesting increasing the options available to those with obesity could be of benefit. Indeed, whereas oral semaglutide 50 mg is the first oral GLP-1 receptor agonist to be tested for the treatment of obesity, others are also under investigation, albeit at an earlier stage, including orforglipron, danuglipron, and lotiglipron. Compared with the subcutaneous formulation, a greater amount of semaglutide is needed for the oral formulation because of its lower bioavailability. However, new studies are ongoing to increase bioavailability. The differences in environmental impact (eg, plastic consumption) remain to be quantified.

A strength of the trial was the overall high retention rate (94%), ensuring the primary analyses were robust. In the past, trials of other anti-obesity medications have suffered from high attrition rates (up to 40%), which can affect the reliability of their results.[41] For this reason, retention was an important focus for the sponsor, investigators, and trial staff to ensure data integrity. The two different estimands were also used to show the effect of oral semaglutide 50 mg both as it was taken by all of the trial participants and when it was taken as intended.[16]

The trial had several limitations. First, the trial population might not reflect the general population with overweight or obesity in all countries, considering the predominance of female and White participants in the trial demographics. This could affect the generalisability of the results, as individuals from other groups who were not adequately represented might respond differently to oral semaglutide 50 mg. Second, the trial had strict eligibility criteria, which excluded people with conditions that are often comorbid with or related to obesity, such as type 2 diabetes.[1,2] As OASIS 1 was the first trial to evaluate oral semaglutide 50 mg in people with obesity, the aim of the eligibility criteria was to ensure the trial population was representative of the general population, while balancing safety considerations and minimising participant characteristics that could have confounded the results. For type 2 diabetes specifically, the effects of oral semaglutide 25 mg and 50 mg in people with type 2 diabetes were instead investigated in the PIONEER PLUS trial.[38] Third, adherence to the treatment regimen was not formally assessed, and there was no strict monitoring of the timing of the administration of the trial product. Fourth, the protocol allowed flexibility in the implementation of the lifestyle intervention, which could have resulted in site-specific differences in its application.

In conclusion, oral semaglutide 50 mg taken once per day, the first oral GLP-1 receptor agonist to be investigated for the treatment of obesity in adults with overweight or obesity, was shown to induce substantial, clinically meaningful bodyweight reductions as an adjunct to diet and physical activity. Oral semaglutide 50 mg led to a mean bodyweight reduction of 15·1% compared with 2·4% in the placebo group, and greater percentages of participants reaching bodyweight reduction targets of at least 5%, 10%, 15%, and 20%. Bodyweight reductions were accompanied by significant improvements in cardiometabolic risk factors compared with placebo. These results indicate that oral semaglutide 50 mg could provide an effective, future option for people with overweight or obesity who would benefit from a GLP-1 receptor agonist.

Contributors

PNL and TH-H contributed to the trial design. TH-H did the statistical analysis. FKK, RDdV, TH-H, PNL, JR, DMR, and WTG did the trial. FKK, JR, DMR, and WTG collected the data. All authors interpreted the data. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication. All authors contributed to the 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. FKK and TH-H have accessed and verified the underlying data reported in the manuscript.

Declaration of interests

FKK has consulted for 89bio, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Pharmacosmos, Sanofi, Structure Therapeutics, Zealand Pharma, and Zucara; received research grants from Chr Hansen, Novo Nordisk, and Zealand Pharma; received honoraria for lectures, presentations, and educational events from 89bio, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Pharmacosmos, Sanofi, Structure Therapeutics, Zealand Pharma, and Zucara; received support for attendance at scientific meetings from Bayer, Boehringer Ingelheim, and Novo Nordisk; has participated in data safety monitoring boards or advisory boards for 89bio, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi, Structure Therapeutics, Zealand Pharma, and Zucara; and has received study drugs for clinical trials from Boehringer Ingelheim, Chr Hansen, Eli Lilly, Novo Nordisk, and Sanofi. FKK is a minority shareholder in Antag Therapeutics, a co-owner of the weight loss clinic Medicinsk Vægttabsbehandling ApS, and holds a patent for GIP peptide analogues (assignee University of Copenhagen; patent EP3189072B1, European Patent Office). VRA has received medical writing support from Novo Nordisk; consultancy fees from Applied Therapeutics, Fractyl, Novo Nordisk, Pfizer, and Sanofi; research grant support (to institution) from Applied Therapeutics, Eli Lilly, Fractyl, Novo Nordisk, and Sanofi; and support for attendance at investigator meetings and scientific conferences for related presentations from Eli Lilly, Fractyl, and Novo Nordisk. VRA's spouse is an employee of Janssen. RDdV and TH-H are employees of, and shareholders in, Novo Nordisk. PNL is an employee of Novo Nordisk. JR has received grants or research support from Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi, Merck, Oramed, Novartis, Novo Nordisk, Pfizer, and Sanofi; has served on scientific advisory boards and received honorarium or consulting fees from Applied Therapeutics, Boehringer Ingelheim, Eli Lilly, Hanmi, Novo Nordisk, Oramed, Sanofi, Structure Therapeutics, Terns Pharma, and Zealand Pharma; and has received honoraria for lectures from Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi. DMR has received medical writing support from Novo Nordisk; has been a clinical investigator for AstraZeneca, Boehringer Ingelheim, and Novo Nordisk; has received consulting fees from Boehringer Ingelheim, Kayentis, and Novo Nordisk; has acted as an unpaid consultant for Eli Lilly; has received honoraria as a speaker from Boehringer Ingelheim and Novo Nordisk; has received personal fees from the American Diabetes Association, the Endocrine

Society, Medscape, PeerView, and Prime Therapeutics for the development of continuing medical education materials; has received support for attendance at scientific congresses by the American Diabetes Association, the Endocrine Society, Medscape, Novo Nordisk, PeerView, and Prime Therapeutics; has participated in scientific advisory boards for Boehringer Ingelheim and Novo Nordisk; and is a shareholder in Eli Lilly. WTG has received medical writing support from Novo Nordisk; has served as a site principal investigator for multicentred clinical trials sponsored by his university and funded by Eli Lilly, Epitomee, Neurovalens, Novo Nordisk, and Pfizer; has served as a consultant on advisory boards for Alnylam Pharmaceuticals, Boehringer Ingelheim, Eli Lilly, Fractyl Health, Inogen, Merck, Novo Nordisk, and Pfizer; and has served on the executive committee of the American Association of Clinical Endocrinology (term expired May, 2021).

Data sharing

Individual participant data will be shared in datasets in a deidentified, anonymised format. Shared data will include datasets from clinical research sponsored by Novo Nordisk completed after 2001 for product indications approved in both the EU and the USA. The study protocol and redacted clinical study report will be made available according to Novo Nordisk data-sharing commitments. These data will be available permanently after research completion and approval of product and product use in both the EU and the USA (no end date). Data will be shared with bona-fide researchers submitting a research proposal requesting access to data, for use as approved by the Independent Review Board (IRB) according to the IRB charter. These data can be accessed via an access request proposal form. The data will be made available on a specialised SAS data platform.

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