

Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial



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Summary

Background Obesity is a major public health issue, and new pharmaceuticals for weight management are needed. Therefore, we evaluated the efficacy and safety of the glucagon-like peptide-1 (GLP-1) analogue semaglutide in comparison with liraglutide and a placebo in promoting weight loss.

Methods We did a randomised, double-blind, placebo and active controlled, multicentre, dose-ranging, phase 2 trial. The study was done in eight countries involving 71 clinical sites. Eligible participants were adults (≥ 18 years) without diabetes and with a body-mass index (BMI) of 30 kg/m² or more. We randomly assigned participants (6:1) to each active treatment group (ie, semaglutide [0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg; initiated at 0.05 mg per day and incrementally escalated every 4 weeks] or liraglutide [3.0 mg; initiated at 0.6 mg per day and escalated by 0.6 mg per week]) or matching placebo group (equal injection volume and escalation schedule to active treatment group) using a block size of 56. All treatment doses were delivered once-daily via subcutaneous injections. Participants and investigators were masked to the assigned study treatment but not the target dose. The primary endpoint was percentage weight loss at week 52. The primary analysis was done using intention-to-treat ANCOVA estimation with missing data derived from the placebo pool. This study is registered with ClinicalTrials.gov, number NCT02453711.

Findings Between Oct 1, 2015, and Feb 11, 2016, 957 individuals were randomly assigned (102–103 participants per active treatment group and 136 in the pooled placebo group). Mean baseline characteristics included age 47 years, bodyweight 111.5 kg, and BMI 39.3 kg/m². Bodyweight data were available for 891 (93%) of 957 participants at week 52. Estimated mean weight loss was -2.3% for the placebo group versus -6.0% (0.05 mg), -8.6% (0.1 mg), -11.6% (0.2 mg), -11.2% (0.3 mg), and -13.8% (0.4 mg) for the semaglutide groups. All semaglutide groups versus placebo were significant (unadjusted $p \leq 0.0010$), and remained significant after adjustment for multiple testing ($p \leq 0.0055$). Mean bodyweight reductions for 0.2 mg or more of semaglutide versus liraglutide were all significant (-13.8% to -11.2% vs -7.8%). Estimated weight loss of 10% or more occurred in 10% of participants receiving placebo compared with 37–65% receiving 0.1 mg or more of semaglutide ($p < 0.0001$ vs placebo). All semaglutide doses were generally well tolerated, with no new safety concerns. The most common adverse events were dose-related gastrointestinal symptoms, primarily nausea, as seen previously with GLP-1 receptor agonists.

Interpretation In combination with dietary and physical activity counselling, semaglutide was well tolerated over 52 weeks and showed clinically relevant weight loss compared with placebo at all doses.

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Introduction

Obesity has become a major public health issue across the globe, and its characterisation as a chronic disease by many major health institutions^{1–3} reflects the impact of a complex, multifactorial condition with many genetic, physiological, behavioural, and cultural contributions.⁴ The clinical complications of obesity encompass a range of disorders—including metabolic (diabetes, hypertension, and non-alcoholic steatohepatitis), mechanical (obstructive sleep apnoea and orthopaedic problems), and mental health complications (anxiety and depression), as well as

others such as cardiovascular disease and certain cancers—that include some of the most common causes of morbidity and mortality in the world. Their costs, both human and financial, escalate with increasing bodyweight,⁵ and global health expenditure on obesity-related complications is estimated to reach a remarkable US\$1.2 trillion by 2025 when adjusted for 2014 purchasing power.⁶ Almost half of this sum will be spent in the USA alone.⁶

Preventive strategies have had little success⁷ and although a weight loss of 5–10% of body mass reduces obesity-related complications and improves quality of

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Research in context**Evidence before this study**

We searched PubMed for relevant articles and reviews of obesity and its management published within the past 10 years using search terms including but not limited to “obesity”, “anti-obesity”, “pharmacotherapy”, “weight management”, and “glucagon-like peptide 1”. Particular attention was given to published studies involving semaglutide and liraglutide. Our literature review confirmed the small number of effective pharmacotherapeutic interventions for obesity management.

Added value of this study

The findings of this study add to the clinical data for the use of glucagon-like peptide-1 agonists for the treatment of obesity

as distinct from their use to treat type 2 diabetes. Previously, data have been restricted to liraglutide (five studies) and exenatide (one study).

Implications of all the available evidence

Findings from this study serve to confirm that semaglutide, as well as liraglutide, can promote significant dose-related weight loss in combination with dietary and exercise interventions, and that semaglutide has a promising balance between efficacy and safety, supporting the need for further evaluation of this indication.

See Online for appendix

life,^{8,9} this goal can be difficult to achieve and sustain with lifestyle interventions alone.^{10,11} Drugs to promote and maintain weight loss have existed since the 1930s,¹² but many have been associated with serious adverse events. Indeed, more than 20 anti-obesity agents initially approved for clinical use have subsequently been withdrawn from global or regional distribution for side-effects including serious cardiotoxicity, psychiatric disturbances, and dependency.¹²

Several better tolerated agents remain available, with five compounds currently approved for weight management in the USA and three in Europe.⁴ One compound approved in these and other regions is liraglutide, an analogue of human glucagon-like peptide-1 (GLP-1), a hormone regulator of glucose-dependent insulin secretion and glucagon release that also modulates appetite, satiety, and energy intake.^{13,14} Initially, liraglutide was approved for treatment of type 2 diabetes at a subcutaneous dose of 1.2 mg or 1.8 mg per day. It was subsequently approved in many countries for weight management at a higher dose of 3.0 mg per day, in combination with diet and exercise interventions. Marked weight loss in patients with type 2 diabetes has also been observed in studies of semaglutide, a longer-acting GLP-1 analogue recently approved in Europe, Japan, and North America for treatment of type 2 diabetes at subcutaneous doses of up to 1.0 mg per week.¹⁵⁻¹⁷ Here, we aimed to evaluate the weight-loss efficacy and safety of semaglutide given once-daily for 52 weeks at different doses to individuals with obesity in comparison with both an active control (liraglutide) and placebo.

Methods**Study design and participants**

We did a randomised, double-blind, placebo and active controlled, multicentre, parallel-group, dose-ranging, phase 2 trial. The study was done in eight countries involving 71 clinical sites: Australia (n=5), Belgium (n=5), Canada (n=9), Germany (n=6), Israel (n=7), Russia (n=10), the UK (n=8), and the USA (n=21). A full list of principal

investigators is given in the appendix (p 4). The study was done in accordance with Good Clinical Practice and the ethical principles originating in the Declaration of Helsinki. The protocol and informed consent document were approved by the institutional review board or independent ethics committee for each clinical site. The protocol is included in the appendix.

Eligible participants were adults who were 18 years or older without diabetes, and with a body-mass index (BMI) of 30 kg/m² or more that was not of endocrine aetiology (eg, Cushing's syndrome). Self-reported body-weight must not have fluctuated by more than 5 kg in the 90 days before screening. Eligible individuals must have undergone at least one previous unsuccessful non-surgical weight-loss attempt and been free from major depressive symptoms (defined as a screening Patient Health Questionnaire-9 [PHQ-9] score <15). To ensure sufficient enrolment of men, recruitment of women was capped at 70%. Full inclusion and exclusion criteria are given in the protocol. All participants provided written informed consent.

Randomisation and masking

We randomly assigned participants (6:1) to each active treatment group (ie, semaglutide or liraglutide) or matching placebo group using an interactive web response system and on-demand allocation with a block size of 56. We stratified the randomisation by sex. The randomisation schedule was prepared by the sponsor. Participants, investigators, and the sponsor were masked to the assigned study treatment, with respect to active versus placebo treatment, but were not masked towards the target dose of drug or placebo.

Procedures

Participants received semaglutide at one of five doses (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg) or liraglutide (3.0 mg) as once-daily subcutaneous injections. For each active treatment group (semaglutide or liraglutide), there was a matching placebo group of equal injection volume

as well as escalation and dosing schedule. Study medication, including placebo, was provided as prefilled FlexPen devices (Novo Nordisk A/S, Søborg, Denmark) by the study sponsor. Training in their handling and use was given at the baseline visit. Semaglutide was initiated at 0.05 mg per day and incrementally escalated to the next dosing level every 4 weeks until reaching the final dose. Two additional fast-escalation groups of semaglutide (0.3 mg and 0.4 mg) were escalated every 2 weeks, which was exploratory. Liraglutide was initiated at 0.6 mg per day and escalated by 0.6 mg per week to 3.0 mg. The dose escalation schedules are shown in the appendix (p 10).

The study consisted of a 1-week screening period, 52 weeks of treatment, and a post-treatment follow-up of 7 weeks. Study visits occurred at screening, baseline (randomisation visit; day 1), every 2 weeks through week 20, and every 4 weeks thereafter through week 52 (end of treatment), plus a follow-up visit at week 59. Bodyweight, vital signs, and adverse events were monitored at every visit, whereas waist and hip circumferences were measured at screening, at baseline, every 4 weeks, and at the follow-up visit. Laboratory parameters were monitored at baseline and weeks 4, 16, 28, 40, and 52. These were fasting visits in which participants were required to abstain from food or drink (except water) for at least 8 h before attendance. Changes from baseline in the use of antihypertensive or lipid-lowering medications (decrease, increase, or no change) were assessed at weeks 16, 28, 40, and 52. For English-speaking participants in the USA only, patient-reported outcomes were assessed with the 36-Item Short Form Health Survey (SF-36) questionnaire¹⁸ administered at baseline and at weeks 28 and 52.

Certain preselected adverse events of interest required additional data collection, of which assessment by an event adjudication committee was required for fatal events, coronary or cerebrovascular events (myocardial ischaemia, coronary revascularisation, stroke, transient ischaemic attack, admission to hospital for heart failure, or unstable angina), pancreatitis, neoplasms, and thyroidectomy. Other thyroid events, injection-site reactions, and acute gallbladder disease were adverse events of interest not requiring adjudication. Participants were instructed in hypoglycaemic symptom recognition and management at baseline visit. Hypoglycaemic episodes were identified by self-report or a free plasma glucose concentration of 3.9 mmol/L or less at a site visit, and graded according to the American Diabetes Association criteria.¹⁹

Nutritional compliance was assessed and nutritional and physical activity counselling was provided by qualified research staff every 4 weeks. Participants were advised to follow a daily energy intake limit of approximately 500 kcal below their total energy expenditure, estimated from their basal metabolic rate using a method described elsewhere²⁰ with a physical activity level of 1.3. A

maintenance diet without an energy deficit was recommended to participants if their BMI declined to 22 kg/m² or less. Compliance was assessed on a 10-point numeric rating scale from 0 (not at all compliant) to 10 (fully compliant) monthly from week 4. Physical activity counselling was based on participant capability, emphasising a recommended minimum activity time of 150 min per week without specifying exercise intensity.

Individuals discontinuing the study treatment before week 52 were requested to undergo the same end-of-treatment procedures as those who received the full course, and to attend a follow-up visit 7 weeks after discontinuation. These individuals were also encouraged to attend a week 52 visit as retrieved participants for determination of bodyweight, blood pressure, and adverse events but not intermediate visits.

Outcomes

The primary endpoint was the relative percentage change in bodyweight from baseline to week 52. Prespecified secondary endpoints were categorical weight loss of 5% or more or 10% or more of baseline, absolute change in weight, waist circumference, waist-to-hip ratio, and BMI; change in glucose metabolism (glycated haemoglobin A_{1c}, fasting glucose), cardiovascular risk factors (blood pressure, lipids, C-reactive protein); changes in SF-36 scores; compliance with nutritional counselling; proportions of participants with changes in antihypertensive or lipid-lowering medications; and the number of adverse events. Categorical weight loss of 15% or more or 20% or more of baseline was assessed post hoc.

Statistical analysis

All matched placebo groups were pooled for analyses. The overall study size was determined by the number of individuals in each active treatment group and pooled placebo group necessary both to provide sufficient precision to distinguish between any two semaglutide doses, and to have a high power to show a significant treatment difference between the optimal semaglutide dose and placebo. Assuming an SD for percentage weight loss of approximately 7% per group—based on data for 3.0 mg of liraglutide²¹—100 individuals per group results in 90% probability that the 95% CI around the treatment difference between any two semaglutide groups would be contained within 2.5% of the point estimate. Furthermore, assuming an observed treatment difference from placebo of 9.5% among completers in the optimal dosing group, and 40% discontinuation with a 0% treatment difference, an estimated treatment difference of 8.2% (SD 8.4%) and a statistical power of more than 99% would result.

The primary analysis comprised all participants who were randomly assigned, and all available in-trial data at week 52 were included in accordance with the intention-to-treat principle. In trial at week 52 included both on-treatment and retrieved participants. Missing data at

	Semaglutide 0.05 mg (n=103)	Semaglutide 0.1 mg (n=102)	Semaglutide 0.2 mg (n=103)	Semaglutide 0.3 mg (n=103)	Semaglutide 0.4 mg (n=102)	Semaglutide 0.3 mg FE (n=102)	Semaglutide 0.4 mg FE (n=103)	Liraglutide 3.0 mg (n=103)	Placebo (pooled; n=136)	Total (n=957)
Age (years)	47 (13; 18-73)	45 (13; 21-72)	44 (11; 22-71)	47 (12; 20-77)	48 (13; 20-74)	47 (12; 23-78)	46 (14; 18-86)	49 (11; 19-72)	46 (13; 20-76)	47 (12; 18-86)
Sex										
Men	36 (35%)	36 (35%)	37 (36%)	37 (36%)	36 (35%)	36 (35%)	36 (35%)	36 (35%)	48 (35%)	338 (35%)
Race										
White	88 (85%)	76 (75%)	72 (70%)	74 (72%)	71 (70%)	76 (75%)	68 (66%)	78 (76%)	97 (71%)	700 (73%)
Black or African American	5 (5%)	7 (7%)	10 (10%)	3 (3%)	10 (10%)	0	7 (7%)	9 (9%)	10 (7%)	61 (6%)
Other	2 (2%)	2 (2%)	1 (1%)	4 (4%)	2 (2%)	4 (4%)	3 (3%)	2 (2%)	5 (4%)	25 (3%)
Not applicable*	8 (8%)	17 (17%)	20 (19%)	22 (21%)	19 (19%)	22 (22%)	25 (24%)	14 (14%)	24 (18%)	171 (18%)
Country of residence										
Australia	10 (10%)	6 (6%)	6 (6%)	8 (8%)	4 (4%)	6 (6%)	2 (2%)	4 (4%)	10 (7%)	56 (6%)
Belgium	4 (4%)	8 (8%)	16 (16%)	11 (11%)	11 (11%)	8 (8%)	16 (16%)	10 (10%)	12 (9%)	96 (10%)
Canada	4 (4%)	9 (9%)	4 (4%)	11 (11%)	8 (8%)	14 (14%)	9 (9%)	4 (4%)	12 (9%)	75 (8%)
Germany	7 (7%)	5 (5%)	7 (7%)	8 (8%)	5 (5%)	9 (9%)	9 (9%)	7 (7%)	12 (9%)	69 (7%)
Israel	15 (15%)	13 (13%)	6 (6%)	7 (7%)	9 (9%)	8 (8%)	6 (6%)	9 (9%)	10 (7%)	83 (9%)
Russia	17 (17%)	13 (13%)	14 (14%)	12 (12%)	10 (10%)	13 (13%)	14 (14%)	15 (15%)	16 (12%)	124 (13%)
UK	8 (8%)	17 (17%)	17 (17%)	9 (9%)	12 (12%)	12 (12%)	15 (15%)	10 (10%)	13 (10%)	113 (12%)
USA	38 (37%)	31 (30%)	33 (32%)	37 (36%)	43 (42%)	32 (31%)	32 (31%)	44 (43%)	51 (38%)	341 (36%)
Bodyweight (kg)	111.3 (23.2; 73.3-184.3)	111.3 (21.5; 76.4-176.0)	114.5 (24.5; 74.9-198.6)	111.5 (23.0; 79.0-196.3)	113.2 (26.4; 74.7-243.7)	108.1 (22.1; 73.1-196.0)	109.6 (21.3; 70.5-178.6)	108.7 (21.9; 70.2-175.0)	114.2 (25.4; 76.5-212.5)	111.5 (23.4; 70.2-243.7)
BMI (kg/m ²)	39.1 (6.5; 30.3-58.5)	39.6 (7.4; 30.2-74.2)	40.1 (6.9; 30.4-61.6)	39.6 (7.1; 29.8-62.1)	39.9 (8.8; 30.1-80.3)	38.2 (6.5; 29.7-61.4)	38.5 (5.9; 29.7-58.6)	38.6 (6.6; 30.4-54.9)	40.1 (7.2; 30.7-62.4)	39.3 (7.0; 29.7-80.3)
Waist circumference (cm)	117.0 (14.6; 88.4-159.5)	117.1 (13.7; 84.8-155.3)	119.1 (15.2; 90.7-166.8)	118.1 (15.1; 87.2-159.0)	119.0 (16.3; 83.3-187.0)	117.1 (13.8; 85.8-153.3)	116.8 (15.5; 82.2-164.1)	116.2 (13.8; 88.0-152.7)	119.5 (15.9; 92.2-180.0)	117.8 (14.9; 82.2-187.0)
Waist-to-hip ratio	0.94 (0.09; 0.77-1.16)	0.94 (0.09; 0.71-1.22)	0.94 (0.09; 0.76-1.17)	0.95 (0.10; 0.69-1.32)	0.94 (0.11; 0.74-1.28)	0.95 (0.10; 0.76-1.34)	0.94 (0.09; 0.71-1.20)	0.94 (0.09; 0.73-1.17)	0.93 (0.09; 0.74-1.18)	0.94 (0.09; 0.69-1.34)
HbA _{1c} (%)	5.5 (0.4; 4.7-6.4)	5.5 (0.4; 4.3-6.4)	5.4 (0.4; 4.2-6.2)	5.5 (0.4; 4.3-7.0)	5.5 (0.4; 4.4-6.6)	5.5 (0.4; 4.4-6.3)	5.5 (0.4; 4.4-6.5)	5.5 (0.4; 4.4-6.6)	5.5 (0.4; 4.8-6.5)	5.5 (0.4; 4.2-7.0)
Fasting plasma glucose (mmol/L)†	5.5 (11.7; 4.2-7.3)	5.5 (10.1; 4.3-7.0)	5.4 (14.3; 4.2-11.1)	5.4 (13.3; 4.3-8.5)	5.4 (12.4; 4.3-8.9)	5.4 (11.8; 4.4-9.8)	5.5 (15.6; 4.3-12.0)	5.5 (13.2; 3.6-8.3)	5.5 (11.3; 4.2-8.0)	5.4 (12.7; 3.6-12.0)
Total cholesterol (mmol/L)†	5.1 (20.8; 2.9-8.0)	5.0 (18.4; 2.9-7.1)	5.1 (21.4; 3.2-9.7)	5.2 (21.1; 3.1-8.3)	4.9 (20.0; 3.2-8.1)	5.1 (19.0; 2.6-7.8)	5.1 (20.8; 3.4-10.3)	5.1 (18.7; 3.1-9.2)	5.1 (18.3; 2.9-8.2)	5.1 (19.8; 2.6-10.3)
HDL cholesterol (mmol/L)†	1.2 (31.1; 0.5-2.6)	1.3 (24.0; 0.7-2.5)	1.2 (23.8; 0.7-2.2)	1.3 (23.8; 0.6-2.1)	1.2 (24.5; 0.7-2.1)	1.2 (26.2; 0.7-2.9)	1.2 (22.3; 0.7-2.1)	1.2 (21.2; 0.7-2.0)	1.3 (23.7; 0.8-2.4)	1.2 (24.6; 0.5-2.9)
LDL cholesterol (mmol/L)†	3.0 (29.7; 1.3-5.6)	3.0 (27.1; 0.8-5.1)	3.0 (27.4; 1.5-5.7)	3.1 (30.7; 1.6-6.1)	2.9 (30.4; 1.5-6.2)	3.1 (26.6; 1.3-5.4)	3.1 (26.2; 1.6-5.3)	3.1 (25.4; 1.6-5.3)	3.1 (27.0; 1.1-5.4)	3.0 (27.8; 0.8-6.2)
VLDL cholesterol (mmol/L)†	0.7 (52.3; 0.3-2.1)	0.7 (50.3; 0.2-2.8)	0.7 (76.3; 0.2-5.5)	0.7 (45.0; 0.2-2.1)	0.6 (58.5; 0.2-3.0)	0.7 (41.2; 0.2-1.5)	0.7 (54.5; 0.3-2.8)	0.7 (58.2; 0.3-2.9)	0.7 (42.8; 0.2-1.7)	0.7 (54.0; 0.2-5.5)
Triglycerides (mmol/L)†	1.6 (59.7; 0.6-6.4)	1.4 (45.7; 0.5-4.6)	1.5 (74.4; 0.5-11.9)	1.5 (51.6; 0.5-7.1)	1.4 (63.6; 0.4-8.1)	1.5 (45.6; 0.5-5.3)	1.5 (58.7; 0.6-6.6)	1.5 (71.4; 0.6-9.9)	1.5 (44.1; 0.5-4.6)	1.5 (58.2; 0.4-11.9)
High-sensitivity CRP (mg/L)†	4.0 (121; 0.3-65.4)	4.3 (101; 0.3-34.6)	4.6 (108; 0.4-55.3)	3.8 (106; 0.2-39.9)	4.5 (100; 0.3-46.6)	4.1 (166; 0.2-105.5)	4.1 (98; 0.4-32.9)	3.9 (92; 0.3-29.4)	4.7 (94; 0.4-42.2)	4.2 (113; 0.2-105.5)

Data are mean (SD; range) or n (%), unless otherwise specified. FE=fast (2-weekly) dose escalation. BMI=body-mass index. HbA_{1c}=glycated haemoglobin A_{1c}. CV=coefficient of variation. CRP=C-reactive protein. *Belgian and Canadian sites only, as racial data were not recorded. †Geometric mean (CV; range).

Table 1: Participant baseline characteristics

week 52 were imputed from the pooled placebo group, using a jump-to-reference multiple imputation (J2R-MI) approach based on 1000 iterations of the dataset. Primary and continuous secondary endpoints were analysed using an ANCOVA model with treatment, region, and sex as factors and the baseline value of the endpoint as a covariate. Resulting estimates and SDs were pooled with Rubin's approach.²² Pairwise treatment

differences, 95% CIs, and p values were provided. Comparisons of the primary endpoint between the placebo pool and the five semaglutide dosing groups that were escalated on a 4-weekly schedule were adjusted for multiple testing with Dunnett's method.^{23,24} All other comparisons were unadjusted. Categorical weight loss of 5% or more or 10% or more of baseline was evaluated as part of the prespecified analysis plan using J2R-MI

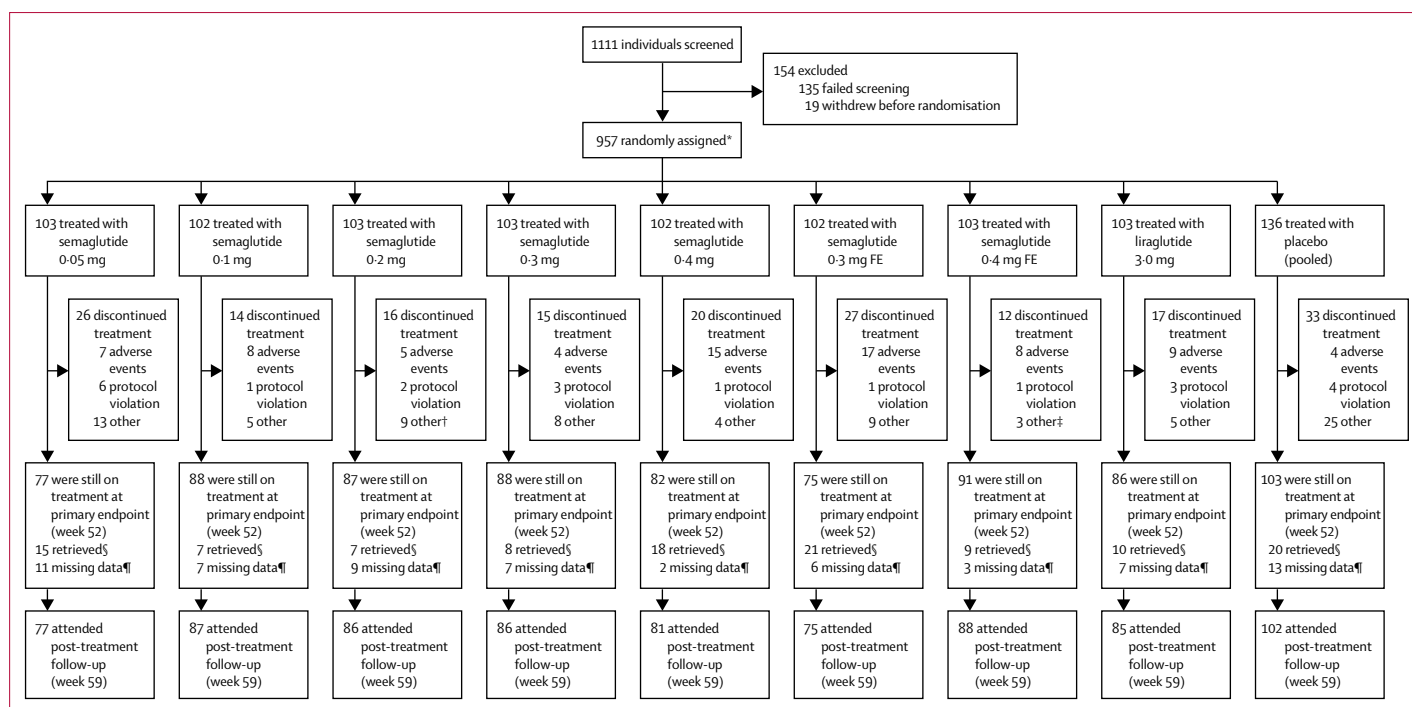


Figure 1: Trial profile

FE=fast (2-weekly) dose escalation. *All randomly assigned patients received treatment (active or placebo). †Includes one pregnancy. ‡Includes one death from metastatic ovarian cancer, not related to treatment. §Participants who discontinued treatment but returned for the week 52 weight assessment. ¶Participants who withdrew from the study and did not attend the week 52 visit.

and logistic regression with the same factors and covariate as the primary endpoint analysis. Categorical weight loss of 15% or more or 20% or more was similarly assessed post hoc. In addition to the primary analysis at week 52, ANCOVA estimation of percentage weight change from baseline, with J2R-MI, was done at all treatment visits.

The primary analysis treatment estimate reflects a treatment policy strategy by assessing all participants who were randomly assigned irrespective of adherence (intention-to-treat principle). To estimate pharmacological activity, a secondary analysis of the primary endpoint was also done, based on a mixed model for repeated measures (MMRM), to simulate a hypothetical situation whereby all participants remained on treatment for the full duration (appendix p 3). In addition to model-estimated data, observed data were summarised for all analysed endpoints and descriptive statistics provided.

We did all analyses using UNIX SAS (version 9.4) on the Statistical Computing Environment. This study is registered with ClinicalTrials.gov, number NCT02453711.

Role of the funding source

The funder of the study had a role in the study design and management, data collection, data interpretation, and data analysis. All authors had full access to the data in the study, were involved in the development and approval of the manuscript, and had final responsibility for the decision to submit for publication. The manuscript was

prepared by the authors with assistance from a medical writer funded by the sponsor.

Results

Between Oct 1, 2015, and Feb 11, 2016, 1111 people were screened and 957 were randomly assigned. Of the 154 people excluded, the most common reasons (defined as more than ten participants) were hypothyroidism or hyperthyroidism ($n=37$), diabetes ($n=26$), investigator judgment ($n=13$), high blood pressure ($n=13$), and a PHQ-9 score of 15 or more ($n=12$). Baseline characteristics appeared well balanced between randomised groups with respect to bodyweight and other details (table 1).

Figure 1 shows the participant disposition throughout the trial. Overall, 777 (81%) of 957 participants completed 52 weeks of treatment whereas 180 (19%) discontinued treatment early; 147 (18%) of 821 on active treatment and 33 (24%) of 136 on placebo. Discontinuations were primarily due to adverse events (77 [8%] of 957), loss to follow-up (33 [3%]), participant choice (29 [3%]), or protocol violations (22 [2%]; appendix p 5). One treatment completer had no data for bodyweight at week 52, and 115 (64%) of 180 who discontinued early subsequently attended the week 52 visit as retrieved participants. Overall, 891 (93%) of 957 participants had data available for bodyweight at week 52, and 66 (7%) were imputed in the primary analysis.

In the primary analysis, estimated (ANCOVA with J2R-MI) and observed percentage reductions in bodyweight

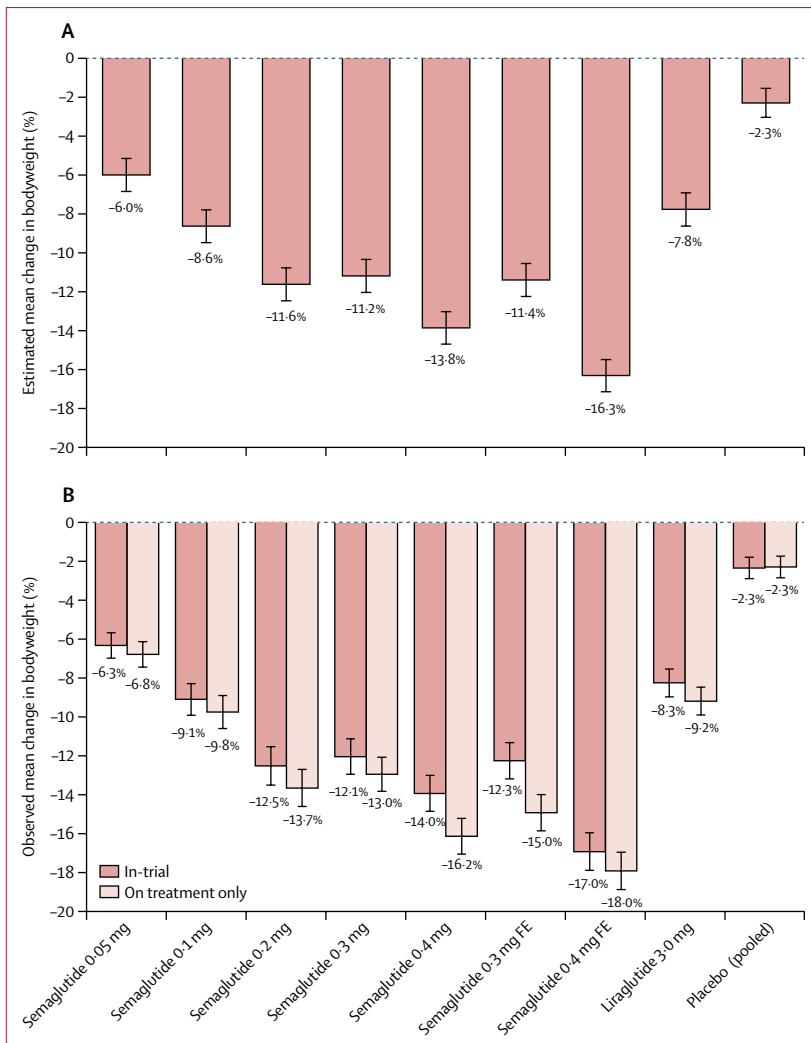


Figure 2: Estimated mean changes (A) and observed mean changes (B) in bodyweight from baseline to week 52
 Error bars are SEMs. Estimated changes (primary endpoint) are ANCOVA-modelled with jump-to-reference multiple imputation of missing data. Observed changes are without imputation and use either all available data at week 52 (in-trial) or only data from those still on treatment. FE=fast (2-weekly) dose escalation.

across the treatment period were dose-dependent for semaglutide. The estimated mean weight reductions from baseline to week 52 for participants receiving semaglutide escalated to final dose on a 4-weekly schedule ranged from 6.0% (SE 0.85; 0.05 mg) to 13.8% (SE 0.83; 0.4 mg), and for those receiving fast-escalation semaglutide (escalated on a 2-weekly schedule) were 11.4% (SE 0.85; 0.3 mg) and 16.3% (SE 0.83; 0.4 mg). The estimated bodyweight reductions were 7.8% (SE 0.85) for participants receiving liraglutide and 2.3% (SE 0.74) for those receiving placebo (figure 2A). Observed mean reductions in bodyweight without imputation for all individuals with available week 52 data, including retrieved participants, were similar to the estimated outcomes, although the observed reductions for those still on

treatment at week 52 were slightly greater (figure 2B). All active treatment groups showed significantly greater estimated reductions in bodyweight than placebo at week 52, and these reductions remained significant after adjustment for multiple testing in the semaglutide groups escalated to final dose on a 4-weekly schedule (figure 3A). For the semaglutide groups escalated every 4 weeks, doses of more than 0.1 mg of semaglutide showed significantly greater weight loss at week 52 than 3.0 mg of liraglutide (figure 3B). Weight loss for the highest doses of semaglutide appeared to continue through the full 52 weeks of treatment (appendix p 11). The effect of semaglutide escalated every 2 weeks versus every 4 weeks was inconsistent. Although a somewhat higher estimated week 52 weight loss was seen for 0.4 mg of semaglutide on a 2-weekly escalation schedule (treatment difference vs escalation every 4 weeks -2.45%, 95% CI -4.76 to -0.13), no effect of escalation speed was noted at 0.3 mg between escalation every 2 weeks and escalation every 4 weeks (treatment difference vs escalation every 4 weeks -0.21%, 95% CI -2.56 to 2.14). MMRM-estimated bodyweight reductions in the secondary analysis were slightly greater than in the primary analysis and similar to observed on-treatment data (appendix pp 12, 13). The difference between these two analyses can be interpreted as a measure of treatment effect lost because of early discontinuation.

Estimated (logistic regression, J2R-M1) weight loss and observed weight loss of at least 5%, 10%, 15%, or 20% of baseline were also dose-dependent for semaglutide (figure 4). In the prespecified analyses, 54–83% of participants receiving semaglutide 0.05–0.4 mg per day in the 4-weekly escalation groups had an estimated weight loss of 5% or more at week 52, compared with 23% receiving placebo and 66% receiving liraglutide ($p < 0.0001$ for all semaglutide dose groups vs placebo), while 19–65% of participants receiving semaglutide 0.05–0.4 mg per day on a 4-weekly dose-escalation schedule lost 10% or more bodyweight compared with 10% receiving placebo and 34% receiving liraglutide ($p < 0.0001$ for all semaglutide > 0.05 mg vs placebo; figure 4A). In the post-hoc analyses, 7–41% of participants receiving semaglutide on the 4-weekly dose-escalation schedule had an estimated weight loss of 15% or more compared with 5% receiving placebo and 15% receiving liraglutide, and 4–27% lost 20% or more compared with 2% receiving placebo and 4% receiving liraglutide ($p < 0.05$ for all semaglutide > 0.05 mg vs placebo; figure 4B). Observed categorical weight loss without imputation was similar to the estimated outcomes for all those with available data (figures 4C, 4D), and slightly higher than estimated for those still on treatment at week 52. Among participants still receiving semaglutide at week 52 (4-weekly dose escalation), 60–91% had a weight loss of 5% or more versus 23% receiving placebo and 72% receiving liraglutide, and 21–74% lost 10% or more versus 10% receiving placebo and 41% receiving

liraglutide; figure 4E). In the post-hoc analyses, 9–50% of participants receiving semaglutide on the 4-weekly dose-escalation schedule had a weight loss of 15% or more compared with 4% receiving placebo and 20% receiving liraglutide, and 5–35% lost 20% or more compared with 2% receiving placebo and 6% receiving liraglutide; figure 4F).

Other key secondary outcomes at week 52, excluding patient-reported outcomes, are shown in table 2 and the appendix (pp 14–17). Consistent dose-related improvements in glucose metabolic and most anthropometric outcomes except for waist-to-hip ratio were seen for semaglutide versus placebo. Systolic and diastolic blood pressures decreased with all active treatments with significant reductions in systolic pressure for liraglutide and all semaglutide doses greater than 0.05 mg compared with placebo. Compared with placebo, there were numeric improvements on semaglutide in other cardiac-associated outcomes (lipids and high-sensitivity C-reactive protein) that reached significance in some groups, without a clear association with dose.

Overall, 259 participants completed the SF-36 questionnaire at both baseline and week 52 (23–33 participants per active group and 38 from the pooled placebo group). Dose-dependent trends towards greater improvements in the physical component and physical functioning scores were observed for individuals receiving semaglutide compared with those receiving placebo, but no differences or trends were noted for the mental component score (data not shown). For the physical functioning score, estimated treatment differences on semaglutide versus placebo ranged from 1.01 (0.05 mg) to 3.51 (0.4 mg) in the 4-weekly escalation groups, and 3.52 (0.3 mg) to 3.72 (0.4 mg) for 2-weekly escalation, compared with 3.04 for liraglutide. Treatment differences for 0.3 mg of semaglutide in the 2-weekly escalation group, 0.4 mg of semaglutide in both escalation groups, and liraglutide were all significant.

Between 75 and 88 individuals in each active treatment group, and 102 in the placebo group, attended the 7-week post-treatment follow-up visit (figure 1). A prespecified analysis of observed weight change from baseline at week 59 showed slightly smaller mean reductions in the active treatment groups than at week 52 due to off-treatment weight regain. Mean changes at week 59 for semaglutide escalated on the 4-weekly schedule were –4.9% (SD 6.2; 0.05 mg) to –13.5% (7.9; 0.4 mg), for the 2-weekly escalation were –12.0% (7.9; 0.3 mg) and –15.5% (9.3; 0.4 mg), for liraglutide 3.0 mg was –7.7% (6.9), and for pooled placebo was –1.8% (5.5). A post-hoc analysis of participants still on treatment at week 52 (regardless of the treatment group) who also had week 59 data showed a positive correlation between the amount of weight regained off treatment and the amount lost from baseline to week 52 (appendix p 18).

There were no clear differences observed at week 52 in the number of participants who changed their use of

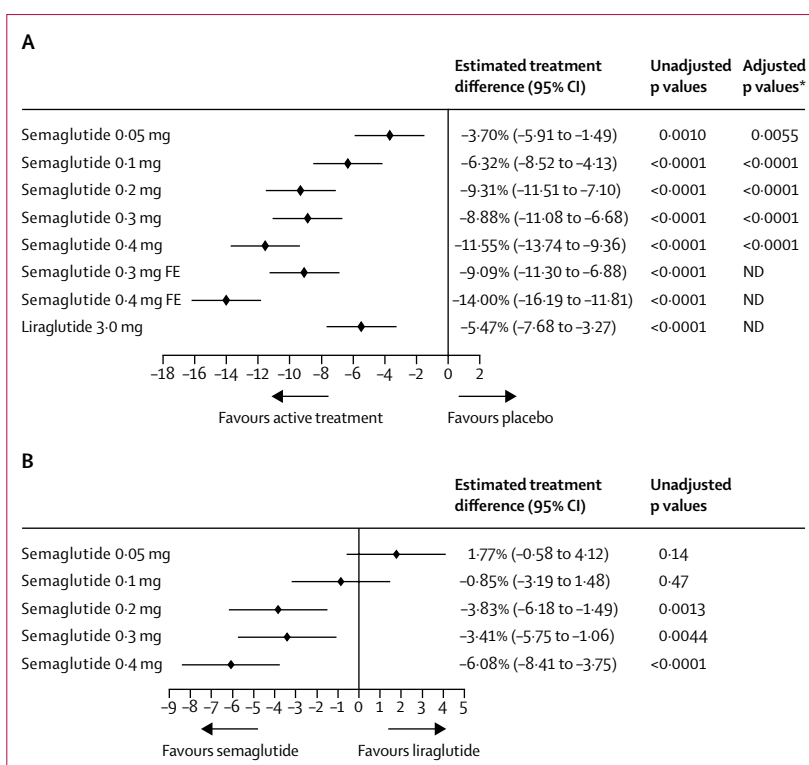


Figure 3: Estimated semaglutide and liraglutide treatment differences in bodyweight change versus placebo (A) and estimated semaglutide treatment differences (dose escalations every 4 weeks) versus liraglutide 3.0 mg (B) FE=fast (2-weekly) dose escalation. ND=not determined. *Adjusted for multiple comparisons (Dunnett's method).

either antihypertensive or lipid-lowering medications (appendix p 6). Similarly, there were no clear differences at week 52 in nutritional compliance between dosing groups, although aggregate scores were slightly higher numerically in the active treatment groups than in the placebo group. Mean compliance scores across all semaglutide dosing groups at week 52 ranged from 6.85 (SD 2.47; 0.3 mg 4-weekly escalation) to 7.36 (SD 2.22 [0.4 mg 4-weekly escalation] and SD 1.85 [0.3 mg 2-weekly escalation]), versus 6.87 (SD 2.07) for liraglutide 3.0 mg and 6.09 (SD 2.39) for the pooled placebo group.

Table 3 shows a summary of on-treatment adverse events. The proportions of any adverse events across the treatment period and their rates per 1000 patient-years of exposure broadly increased across the semaglutide dosing range and were numerically higher in all active treatment groups than in the pooled placebo group. Gastrointestinal events—primarily nausea (appendix p 19)—were the most common adverse events observed on active treatment with either semaglutide or liraglutide. Overall, most reported adverse events were of mild (4125 [69%] of 5986) or moderate (1665 [28%] of 5986) intensity. Events of severe intensity were uncommon and neither these events nor events classed as serious showed any association with either active treatment or semaglutide dose. There was a single death, which was not considered related to study

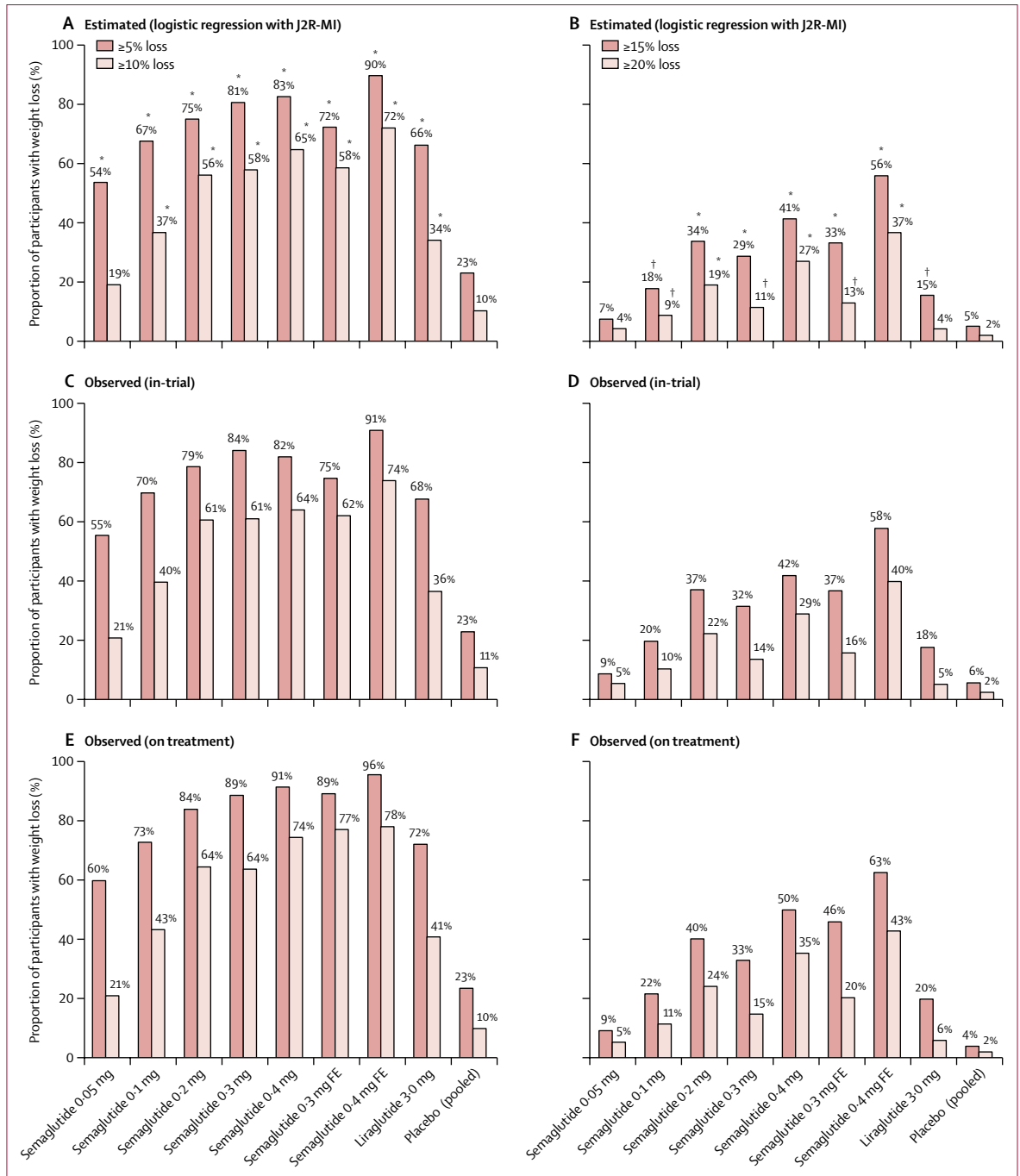


Figure 4: Estimated and observed categorical weight loss at week 52

(A, C, E) Categorical weight loss of 5% or more and 10% or more of baseline weight. (B, D, F) Categorical weight loss of 15% or more and 20% or more of baseline weight; these analyses are post hoc. Estimations are by logistic regression on all individuals with available data at week 52, with J2R-MI of missing data are without imputation. In-trial data are for all individuals with available data at week 52, on-treatment or off-treatment. On-treatment data are for those still on treatment at week 52 only. J2R-MI=jump-to-reference multiple imputation. FE=fast (2-weekly) dose escalation. * $p < 0.0001$ versus placebo. † $p < 0.05$ versus placebo.

treatment by the investigator, of a 40-year-old woman in the semaglutide 0.4 mg fast-escalation group who died on study day 119 from a combination of pneumonia (onset day 105) and stage IV metastatic ovarian cancer diagnosed on day 98.

There was no association between all-cause treatment discontinuation and semaglutide dose (appendix p 20). By contrast, discontinuations due to adverse events were generally low but were highest for the high-dose semaglutide groups, and were higher in all

	Semaglutide 0.05 mg (n=103)	Semaglutide 0.1 mg (n=102)	Semaglutide 0.2 mg (n=103)	Semaglutide 0.3 mg (n=103)	Semaglutide 0.4 mg (n=102)	Semaglutide 0.3 mg FE (n=102)	Semaglutide 0.4 mg FE (n=103)	Liraglutide 3.0 mg (n=103)	Placebo pooled (n=136)
Bodyweight (kg)	-6.66 (0.94); p=0.0007	-9.34 (0.93); p<0.0001	-12.30 (0.93); p<0.0001	-12.45 (0.93); p<0.0001	-15.15 (0.92); p<0.0001	-12.54 (0.93); p<0.0001	-17.36 (0.92); p<0.0001	-8.47 (0.93); p<0.0001	-2.48 (0.82)
BMI (kg/m ²)	-2.37 (0.33); p=0.0007	-3.36 (0.33); p<0.0001	-4.38 (0.33); p<0.0001	-4.40 (0.33); p<0.0001	-5.40 (0.33); p<0.0001	-4.48 (0.33); p<0.0001	-6.21 (0.33); p<0.0001	-3.03 (0.33); p<0.0001	-0.88 (0.29)
Waist circumference (cm)	-6.11 (0.93); p=0.0295	-8.75 (0.90); p<0.0001	-11.02 (0.89); p<0.0001	-10.91 (0.89); p<0.0001	-12.31 (0.91); p<0.0001	-11.06 (0.95); p<0.0001	-14.88 (0.88); p<0.0001	-8.35 (0.89); p<0.0001	-3.47 (0.81)
Waist-to-hip ratio	-0.01 (0.01); p=0.5360	-0.02 (0.01); p=0.6623	-0.02 (0.01); p=0.2855	-0.03 (0.01); p=0.0172	-0.02 (0.01); p=0.1109	-0.02 (0.01); p=0.3667	-0.03 (0.01); p=0.0016	-0.02 (0.01); p=0.1358	-0.01 (<0.01)
HbA _{1c} (%)	-0.13 (0.03); p=0.0043	-0.21 (0.03); p<0.0001	-0.28 (0.03); p<0.0001	-0.23 (0.03); p<0.0001	-0.29 (0.03); p<0.0001	-0.25 (0.03); p<0.0001	-0.34 (0.03); p<0.0001	-0.21 (0.03); p<0.0001	-0.01 (0.03)
Fasting plasma glucose (mmol/L)	-0.29 (0.06); p=0.0001	-0.35 (0.06); p<0.0001	-0.40 (0.06); p<0.0001	-0.39 (0.06); p<0.0001	-0.43 (0.06); p<0.0001	-0.38 (0.06); p<0.0001	-0.51 (0.06); p<0.0001	-0.35 (0.06); p<0.0001	0.01 (0.05)
Blood pressure (mm Hg)									
Systolic	-4.46 (1.20); p=0.0691	-5.76 (1.18); p=0.0078	-6.26 (1.19); p=0.0030	-6.41 (1.19); p=0.0021	-5.81 (1.16); p=0.0065	-6.07 (1.19); p=0.0044	-10.26 (1.16); p<0.0001	-5.45 (1.18); p=0.0135	-1.58 (1.04)
Diastolic	-2.55 (0.84); p=0.3441	-2.65 (0.82); p=0.2937	-4.09 (0.83); p=0.0181	-2.98 (0.83); p=0.1751	-3.61 (0.80); p=0.0511	-2.20 (0.83); p=0.5205	-5.52 (0.80); p=0.0002	-2.70 (0.82); p=0.2736	-1.50 (0.73)
Lipids (week-52-to-baseline ratio)									
Total cholesterol	0.96 (0.02); p=0.6599	0.95 (0.01); p=0.2065	0.93 (0.01); p=0.0472	0.93 (0.01); p=0.0253	0.93 (0.01); p=0.0606	0.93 (0.02); p=0.0663	0.92 (0.01); p=0.0067	0.96 (0.01); p=0.5062	0.97 (0.01)
HDL cholesterol	0.99 (0.01); p=0.7457	1.02 (0.01); p=0.3227	1.02 (0.01); p=0.3600	1.02 (0.01); p=0.2943	1.00 (0.01); p=0.8892	1.00 (0.02); p=0.9470	1.01 (0.01); p=0.4836	1.00 (0.01); p=0.8656	1.00 (0.01)
LDL cholesterol	0.97 (0.02); p=0.9466	0.93 (0.02); p=0.1882	0.93 (0.02); p=0.1867	0.92 (0.02); p=0.0754	0.93 (0.02); p=0.2428	0.92 (0.02); p=0.1158	0.91 (0.02); p=0.0363	0.95 (0.02); p=0.6358	0.97 (0.02)
VLDL cholesterol	0.90 (0.03); p=0.2526	0.89 (0.03); p=0.1405	0.81 (0.03); p=0.0015	0.85 (0.03); p=0.0187	0.81 (0.03); p=0.0009	0.87 (0.04); p=0.0784	0.81 (0.03); p=0.0006	0.91 (0.03); p=0.3168	0.95 (0.03)
Triglycerides	0.89 (0.04); p=0.2322	0.88 (0.03); p=0.1560	0.81 (0.03); p=0.0020	0.85 (0.03); p=0.0250	0.80 (0.03); p=0.0010	0.87 (0.04); p=0.0877	0.80 (0.03); p=0.0006	0.90 (0.03); p=0.3298	0.95 (0.03)
High-sensitivity CRP (week-52-to- baseline ratio)	0.71 (0.07); p=0.2370	0.65 (0.06); p=0.0441	0.57 (0.05); p=0.0022	0.66 (0.06); p=0.0604	0.54 (0.05); p=0.0004	0.58 (0.05); p=0.0032	0.44 (0.04); p<0.0001	0.72 (0.06); p=0.2411	0.82 (0.07)

Data are estimated mean (SEM) change from baseline to week 52. p values are for treatment difference versus placebo (unadjusted for multiple comparisons). Categorical weight loss and patient-reported outcome data are excluded. All analyses were done by ANCOVA with J2R-MI of missing data. FE=fast (2-weekly) dose escalation. BMI=body-mass index. HbA_{1c}=glycated haemoglobin A_{1c}. CRP=C-reactive protein. J2R-MI=jump-to-reference multiple imputation.

Table 2: Key secondary endpoints

active-treatment groups than in the placebo group. Most adverse-event-related discontinuations were for gastrointestinal-related events, which were semaglutide dose-related and more common during the dose-escalation period in each treatment group than after the final dose had been reached (appendix p 21). Other than gastrointestinal disorders, the only other type of adverse event of particular interest that appeared to show an association with semaglutide dose was gallbladder disorders. These events, primarily cholelithiasis or cholecystitis, increased across the semaglutide dosing range (2–7% vs none in the liraglutide group and 4% in the placebo group).

As with efficacy, the effect of semaglutide dose-escalation speed on safety outcomes was inconsistent. Adverse-event-related discontinuations and gallbladder disorders were numerically highest for 0.3 mg of semaglutide on the fast-escalation schedule, whereas at 0.4 mg per day the incidence of these events and of gastrointestinal disorders was numerically lower for escalation every 2 weeks than for escalation every 4 weeks.

There was no observed relationship with active treatment or semaglutide dose for pancreatitis, hepatic, thyroid or renal adverse events, injection-site or allergic reactions, cardiovascular events, mental health, or confirmed neoplasms. Five adjudicated events of acute pancreatitis on treatment occurred in four individuals, all with concurrent reports of cholelithiasis or cholecystitis, or both (table 3). All events were classified as mild according to the Atlanta criteria.²⁵

Six individual cardiovascular events in five individuals were confirmed by the event adjudication committee (one ischaemic stroke, two transient ischaemic attack, three percutaneous coronary intervention; appendix p 7). Four individuals were receiving semaglutide and one placebo, and all but one had a history of heart disease. No event was considered likely to be treatment related by the investigators. Additionally, a consistent increase in mean pulse rate of up to 4 beats per minute at week 52 compared with placebo was observed for all semaglutide doses higher than 0.05 mg and for liraglutide 3.0 mg (appendix p 22). This increase was not semaglutide

	Semaglutide 0·05 mg (n=103)	Semaglutide 0·1 mg (n=102)	Semaglutide 0·2 mg (n=103)	Semaglutide 0·3 mg (n=103)	Semaglutide 0·4 mg (n=102)	Semaglutide 0·3 mg FE (n=102)	Semaglutide 0·4 mg FE (n=103)	Liraglutide 3·0 mg (n=103)	Placebo pooled (n=136)
Individuals with ≥1 adverse event	93 (90%)	94 (92%)	96 (93%)	93 (90%)	98 (96%)	98 (96%)	96 (93%)	88 (85%)	107 (79%)
Individuals with ≥1 serious adverse event	13 (13%)	8 (8%)	5 (5%)	6 (6%)	13 (13%)	6 (6%)	7 (7%)	4 (4%)	11 (8%)
Individuals with ≥1 adverse event of severe intensity	13 (13%)	17 (17%)	12 (12%)	14 (14%)	17 (17%)	16 (16%)	13 (13%)	13 (13%)	16 (12%)
Individuals with ≥1 adverse event leading to discontinuation	7 (7%)	8 (8%)	5 (5%)	4 (4%)	15 (15%)	17 (17%)	8 (8%)	9 (9%)	4 (3%)
Discontinuation for ≥1 gastrointestinal adverse event	6 (6%)	5 (5%)	3 (3%)	4 (4%)	13 (13%)	12 (12%)	8 (8%)	4 (4%)	2 (1%)
Adverse event rate (per 1000 years of observation)	5412	6856	6948	5514	7427	7459	6247	5745	4845
Deaths	0	0	0	0	0	0	1 (1%)*	0	0
Most common events†									
Nausea	32 (31%)	42 (41%)	45 (44%)	43 (42%)	49 (48%)	55 (54%)	50 (49%)	46 (45%)	24 (18%)
Diarrhoea	20 (19%)	25 (25%)	35 (34%)	27 (26%)	39 (38%)	28 (27%)	28 (27%)	29 (28%)	16 (12%)
Constipation	13 (13%)	22 (22%)	26 (25%)	18 (17%)	24 (24%)	19 (19%)	29 (28%)	24 (23%)	6 (4%)
Nasopharyngitis	16 (16%)	23 (23%)	19 (18%)	15 (15%)	19 (19%)	16 (16%)	20 (19%)	16 (16%)	16 (12%)
Vomiting	8 (8%)	18 (18%)	24 (23%)	11 (11%)	18 (18%)	21 (21%)	23 (22%)	11 (11%)	6 (4%)
Decreased appetite	8 (8%)	17 (17%)	13 (13%)	13 (13%)	14 (14%)	18 (18%)	20 (19%)	12 (12%)	5 (4%)
Headache	7 (7%)	15 (15%)	10 (10%)	10 (10%)	21 (21%)	14 (14%)	11 (11%)	15 (15%)	15 (11%)
Ercutation	4 (4%)	8 (8%)	14 (14%)	8 (8%)	7 (7%)	17 (17%)	10 (10%)	6 (6%)	1 (1%)
Events of special interest									
Gastrointestinal disorders	64 (62%)	72 (71%)	72 (70%)	72 (70%)	84 (82%)	84 (82%)	78 (76%)	77 (75%)	52 (38%)
Gallbladder disorders	2 (2%)	2 (2%)	3 (3%)	3 (3%)	6 (6%)	7 (7%)	2 (2%)	0	5 (4%)
Hepatic events	2 (2%)	3 (3%)	2 (2%)	2 (2%)	1 (1%)	3 (3%)	0	2 (2%)	9 (7%)
Injection-site reactions	7 (7%)	9 (9%)	6 (6%)	5 (5%)	8 (8%)	8 (8%)	10 (10%)	10 (10%)	10 (7%)
Allergic reactions	5 (5%)	9 (9%)	7 (7%)	3 (3%)	8 (8%)	8 (8%)	3 (3%)	13 (13%)	10 (7%)
Neoplasms (EAC confirmed in-trial)‡	3 (3%)	1 (1%)	3 (3%)	0	4 (4%)	0	1 (1%)	3 (3%)	4 (3%)
Hypoglycaemic episodes	1 (1%)	4 (4%)	4 (4%)	5 (5%)	9 (9%)	8 (8%)	10 (10%)	4 (4%)	8 (6%)
Acute pancreatitis (EAC confirmed on-treatment)	1 (1%)	0	0	0	0	2 (2%)	0	0	1 (1%)

Data are n (%), unless otherwise specified. On-treatment data include a 7-week ascertainment window after treatment discontinuation. FE=fast (2-weekly) dose escalation. EAC=event adjudication committee. *Metastatic ovarian cancer and pneumonia on day 119 (cancer diagnosed on day 98). †Preferred term >15% in any group. ‡Includes off-treatment reports.

Table 3: On-treatment adverse events

dose-dependent and was similar for both semaglutide and liraglutide treatment.

21 confirmed neoplasms occurred in 19 individuals across the trial period (including off-treatment follow-up) in both the active and pooled placebo groups (appendix p 8). There was no group imbalance reported in the type or incidence of neoplasms, and there were no pancreatic neoplasms; no breast neoplasms were observed in semaglutide-treated individuals.

There were few hypoglycaemic episodes reported in any treatment group and none were graded as severe (appendix p 9). Compared with placebo, amylase and lipase activity increased slightly with increasing semaglutide dose. Similar increases were seen with liraglutide. No safety concerns were noted for changes in biochemistry or haematology parameters, including calcitonin, and no participant developed anti-semaglutide antibodies during the study (data not shown).

Discussion

This study was the first assessment of semaglutide for weight management, as opposed to previous studies focusing on glycaemic control in type 2 diabetes. In these individuals without diabetes, semaglutide 0·05–0·4 mg per day—combined with diet and exercise modification—resulted in dose-dependent, clinically relevant weight losses over 52 weeks that were significantly greater than placebo at all tested doses, and higher than liraglutide 3·0 mg per day at doses of 0·2 mg per day or more. Weight loss in people receiving semaglutide treatment is primarily due to reduced energy intake from appetite suppression and enhanced satiety; and at a semaglutide dose of 1·0 mg, weekly loss of both fat and lean mass has been observed, with fat loss approximately three times greater than lean mass.²⁶

Our primary analysis was based on intention-to-treat principles and included off-treatment weight data from

those who discontinued early and were assessed at week 52. Missing values in the active treatment groups were imputed from participants randomly assigned to placebo, based on the underlying assumption that those without data responded as if treated with placebo for the entire duration. The estimated results of this model were in good agreement with observed in-trial data at week 52 due to the high proportion (93%) of on-treatment and off-treatment participants retained in-trial. The secondary analysis of the primary endpoint estimated pharmacological efficacy, assuming full adherence for the trial duration, and used only on-treatment data and a prediction model that assumed discontinuers would have responded similarly to those completing treatment. These estimations were in accordance with observed on-treatment data at week 52.

The 7.8% weight loss in the liraglutide group in this study was comparable with other similar length studies of liraglutide 3.0 mg for weight management,^{21,27} but was significantly less than the 11–14% reductions seen with semaglutide doses of 0.2 mg or more per day in the groups escalated every 4 weeks. Notably, weight reductions at higher doses of semaglutide were also numerically greater than have been reported for clinically approved doses of the anti-obesity agents orlistat (about 6%), lorcaserin (about 6%), phentermine-topiramate (about 8–10%), and naltrexone-bupropion (about 5%).⁴ At these higher semaglutide doses, an estimated 75–83% of participants lost 5% or more of their baseline weight and 56–65% lost 10% or more, while in the post-hoc analyses an estimated 29–41% of participants lost 15% or more and 11–27% lost 20% or more of their baseline weight. For all in-trial participants in the 4-weekly escalation groups, observed proportions with at least 15% weight loss at week 52 were 32–42% for semaglutide doses of 0.2 mg per day or more, and 14–29% lost at least 20% of baseline weight, while for those still on treatment at week 52 the observed proportions with 15% or more weight loss were 33–50% and with 20% or more weight loss were 15–35%.

It was of note that weight reductions at the higher doses of semaglutide appeared to continue through the entire 52-week treatment period. This finding contrasts with earlier studies of anti-obesity medications including liraglutide,²⁸ lorcaserin,²⁹ and naltrexone-bupropion,³⁰ in which treatment response plateaued at an earlier timepoint, and suggests that longer studies might be needed to establish the full semaglutide treatment effect.

Most weight-related secondary outcomes, with the exception of waist-to-hip ratio, also showed dose-related improvements in the semaglutide groups that were significantly greater than placebo at all doses tested. Most secondary cardiovascular and glucose homeostasis factors were better in the semaglutide or liraglutide groups than in the placebo group, although a clear semaglutide dose association for cardiovascular risk factors was less well defined in this broadly normotensive

population without overt dyslipidaemia. Patient-reported outcome data for a subset of US participants showed dose-related improvements compared with placebo in physical outcome scores that became significant at the highest doses of semaglutide, although with the caveat of small sample sizes.

Adverse events on active treatment were similar to previous studies of semaglutide in type 2 diabetes and liraglutide in type 2 diabetes or obesity, or both. The most common adverse events, and most common causes of adverse event-related discontinuations, were gastrointestinal events, primarily nausea. Gastrointestinal events were semaglutide dose-dependent and numerically more common at the highest dose than on liraglutide 3.0 mg, although the proportion of discontinuations for gastrointestinal events on any active treatment (3–13% across groups) was low compared with the overall incidence of gastrointestinal events (62–82%). Gallbladder disorders showed a possible dose-related trend for semaglutide, but the number of events was low in all groups and exceeded placebo only at the highest doses. Small increases in pulse rates were similar among individuals receiving liraglutide or semaglutide doses higher than 0.05 mg per day. These findings showed no dose dependency and were consistent with data for other GLP-1 receptor agonists. There were no severe hypoglycaemic episodes on active treatment.

Although semaglutide 0.3 mg per day and 0.4 mg per day were given on both 2-weekly and 4-weekly escalation schedules, no firm conclusions could be made about the comparative safety and efficacy of the exploratory fast-escalation groups. For 0.3 mg per day, efficacy outcomes on 2-weekly escalation were similar to the 4-weekly schedule, but faster escalation was associated with more adverse events. By contrast, the fast-escalation schedule at 0.4 mg per day generally had higher efficacy outcomes but somewhat fewer adverse events than escalation every 4 weeks.

Limitations of the study include the impossibility of masking participants and site staff to the assigned dose because of the differing volumes and dose-escalation periods, although at each assigned dose they remained masked to the active drug or placebo. This limitation might potentially have introduced bias into the reporting of adverse events at high doses or treatment discontinuation at low doses. Adherence to diet recommendations was assessed monthly on a numerical rating scale, but a systematic evaluation of exercise activity for estimation of energy balance was not undertaken. Body composition assessment to confirm the source of the weight loss was also not done.

These data for semaglutide 0.05–0.4 mg per day confirm earlier findings of significant weight loss with semaglutide 0.5 mg per week or 1.0 mg per week in the treatment of type 2 diabetes.^{15–17} The dose relatedness of the weight loss and large reductions at higher doses in the current study support the feasibility of semaglutide for weight

management in combination with lifestyle intervention. Semaglutide was generally well tolerated, and there were no unanticipated safety or tolerability outcomes compared with studies in type 2 diabetes. Semaglutide therefore showed an attractive benefit–risk profile, particularly at the higher doses associated with greater weight loss. In conclusion, these data support the further development of semaglutide for weight management, for which phase 3 studies are ongoing (NCT03548935, NCT03552757, NCT03611582, NCT03548987).

Contributors

CGC, CHJ, MK, and JPHW contributed to the study design. PMO'N, ALB, BM, OM, SDP, SW, and JPHW contributed to the recruitment of study participants and collection of data. CGC, CHJ, and MK contributed to data analysis. All authors participated in interpretation of the data and drafting and revision of the manuscript. All authors reviewed and approved the final submitted version.

Declaration of interests

PMO'N has received grants and personal fees from Novo Nordisk during the conduct of the study; grants from Weight Watchers International; and personal fees from Janssen, Vindico CME, WebMD, and the Robard Corporation. ALB has received fees from Novo Nordisk, unrelated to the submitted work. BM has received grants from Novo Nordisk, during the conduct of the study, and is the primary investigator on two Novo Nordisk trials. BM has also received grants and personal fees from Novo Nordisk; and personal fees from Boehringer Ingelheim, Janssen, Eli Lilly, and Merck Sharp & Dohme, outside of the submitted work. OM has received grants and other financial support from Novo Nordisk and Bristol-Myers Squibb; and other financial support from Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, Janssen, Novartis, and AstraZeneca. SDP has received personal fees and non-financial support from Novo Nordisk, Eli Lilly, Valeant, Merck Sharp & Dohme, and Janssen; grants, personal fees, and non-financial support from AstraZeneca; grants and personal fees from Abbott, Boehringer Ingelheim, and Sanofi; and personal fees from Prometic. SW has received non-financial support from Novo Nordisk, during the conduct of the study; personal fees from Novo Nordisk; grants and personal fees from Janssen; and personal fees from Eli Lilly and Valeant, outside of the submitted work. CGC, CHJ, and MK are employees of Novo Nordisk A/S. JPHW has received grants from Novo Nordisk, during the conduct of the study; grants, personal fees, and other financial support from Novo Nordisk and AstraZeneca; grants and personal fees from Takeda; personal fees and other financial support from Boehringer Ingelheim, Sanofi, Eli Lilly, Orexigen, Napp/Mundipharma, and Janssen; and other financial support from Astellas, outside of the submitted work.

Data sharing

Deidentified participant data are available for this Article on a specialised SAS data platform. Datasets from Novo Nordisk will be available permanently after research completion and approval of product and product use in both the EU and USA. The study protocol and redacted clinical study report will be available according to Novo Nordisk data sharing commitments. Access to data can be made through a request proposal form and the access criteria can be found online. Data will be shared with bona fide researchers submitting a research proposal requesting access to data. Data use is subject to approval by the Independent Review Board.

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