# A randomised, phase 2, placebo- and active-controlled dose-ranging study of semaglutide for treatment of obesity

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| **Research in context**  *Evidence before this study*  We performed an online (PubMed) literature review of relevant articles and reviews of obesity and its management published within the last 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 review confirmed the limited 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. Hitherto, data have been restricted to liraglutide (five studies) and exenatide (one study).  *Implications of all the available evidence*  The evidence serves 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 tolerability that supports its further evaluation for this indication. |

# Abstract

**Background** Obesity is a major public health issue, and new pharmaceuticals for weight management are needed. We assessed the efficacy and safety of the glucagon-like peptide 1 (GLP-1) analogue semaglutide to promote weight loss in individuals with obesity without diabetes.

**Methods** We performed a phase 2, multinational, double-blinded, 52-week randomised study of once-daily subcutaneous semaglutide (0·05, 0·1, 0·2, 0·3, or 0·4 mg/day), with liraglutide (3·0 mg/day) and placebo controls, with diet and exercise counselling (NCT02453711). At each dose, participants were randomised 6:1 active treatment:placebo; placebo groups were pooled for analysis. Semaglutide was incrementally escalated to final dosing every 4 weeks (q4w) or 2 weeks (exploratory). The primary endpoint was percentage weight loss at week 52. The primary analysis was an intention-to-treat ANCOVA estimate with missing data derived from placebo.

**Findings** 957 individuals were randomised (102–103 per active arm; 136 placebo). Mean baseline characteristics were: age 47 years, weight 111 kg, BMI 39 kg/m2. Weight data were available for 93% (891/957) at week 52. Estimated mean weight loss was –2·3% (placebo) *vs* –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) on q4w escalation. All comparisons were p≤0·001 *vs* placebo and remained significant after adjustment for multiple testing. Mean weight reductions on ≥0·2 mg semaglutide were all p<0·01 *vs* liraglutide (–7·8%). Estimated weight loss ≥10% occurred in 10% (placebo) *vs* 37–65% on ≥0·1 mg semaglutide (q4w; 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 superior to placebo at all doses.

**Funding** Novo Nordisk A/S.

# Introduction

Obesity has grown into a major public health issue across the globe, and its characterisation as a chronic disease by many major health institutions1–3 reflects the impact of a complex, multifactorial epidemic with many genetic, physiological, behavioural, and cultural contributions.4 The clinical complications of obesity encompass a range of disorders—including metabolic (diabetes, hypertension, non-alcoholic steatohepatitis), mechanical (obstructive sleep apnoea, orthopaedic problems), and mental health complications (anxiety, 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 body weight,5 and global health expenditure on obesity-related complications is estimated to reach a remarkable $1·2 trillion by 2025 when adjusted for 2014 purchasing power.6 Almost half of this sum will be spent in the United States alone.6

Preventive strategies have had limited success7 and though a weight loss of 5–10% of body mass reduces obesity-related complications and improves quality of life,8,9 this 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 or 1·8 mg daily. It was subsequently approved in many countries for weight management at a higher dose of 3·0 mg daily, in combination with diet and exercise interventions.

Significant weight loss among 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 up to 1·0 mg once-weekly.15–17 Herein, we report the weight-loss efficacy and safety of once-daily semaglutide given for 52 weeks at different doses to individuals with obesity in a randomised clinical trial with both active (liraglutide) and placebo controls.

# Methods

## Study design

NN9536-4153 (ClinicalTrials.gov NCT02453711) was a phase 2, randomised, double-blinded, placebo- and active-controlled (liraglutide 3·0 mg daily), multinational, multicentre, parallel-group dose-ranging trial. The trial examined weight loss and safety in adults with obesity but without diabetes, treated with various daily doses of semaglutide compared with placebo or liraglutide, all as adjuncts to diet and physical activity counselling. The protocol is included in the supplementary appendix.

The study consisted of a 1-week screening period, 52 weeks of treatment, and a post-treatment follow-up of 7 weeks. Participants received semaglutide at one of five daily doses (0·05, 0·1, 0·2, 0·3, or 0·4 mg), liraglutide (3·0 mg), or placebo, as once-daily subcutaneous injections. Semaglutide was initiated at 0·05 mg per day and incrementally escalated to the next dosing level every 4 weeks (q4w) until reaching the final dose. Two additional fast-escalation arms (0·3 and 0·4 mg) were escalated every 2 weeks (q2w). Liraglutide was initiated at 0·6 mg per day and escalated by 0·6 mg per week to 3·0 mg. All participants received advice about a hypocaloric diet plus monthly dietary and physical activity counselling. The dose escalation schedules are shown in supplementary appendix figure S1.

The study was conducted between October 2015 and April 2017 in eight countries and 71 clinical sites: Australia (5 sites), Belgium (5), Canada (9), Germany (6), Israel (7), Russian Federation (10), UK (8), and USA (21). A full list of principal investigators is given in table S1 of the supplementary appendix.

The study was sponsored by Novo Nordisk A/S (Søborg, Denmark) and undertaken 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/independent ethics committee for each clinical site. All participants provided written informed consent prior to study procedures. The sponsor was responsible for study management, central statistical data monitoring, and all analyses.

## Participants

Eligible participants were adults (≥18 years old) without diabetes, with a body mass index (BMI) ≥30 kg/m2 and no endocrine cause for obesity (e.g. 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 prior unsuccessful non-surgical weight-loss attempt and been free from major depressive symptoms (defined as a screening Patient Health Questionnaire-9 [PHQ-9] score below 15). To ensure sufficient enrolment of males, female recruitment was capped at 70%. Full inclusion and exclusion criteria are given in the protocol.

## Randomisation and masking

For each active-treatment group (semaglutide or liraglutide), there was a matching placebo group of equal injection volume and escalation schedule. Randomisation to each active group or matching placebo was stratified by sex and performed in a 6:1 active:placebo ratio using an interactive web response system and on-demand allocation with a block size of 56. The randomisation schedule was prepared by the Sponsor. All placebo arms were pooled for subsequent analyses. Treatment assignment was blinded to participants, investigators, and the Sponsor with respect to active *vs* placebo treatment, but not towards the target dose of drug or placebo.

## Procedures

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. Body weight, vital signs, and adverse events were monitored at every visit, while waist and hip circumference were measured at screening, baseline, and every 4 weeks, plus 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 hours prior to attendance. Changes from baseline in the use of antihypertensive or lipid-lowering medications (decrease, increase, no change) were assessed at weeks 16, 28, 40 and 52. For English-speaking participants in the USA only, patient-reported outcomes were assessed using 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 these, assessment by an event adjudication committee was required for fatal events, coronary or cerebrovascular events (myocardial ischaemia, coronary revascularisation, stroke, transient ischaemic attack, hospitalisation for heart failure, or unstable angina), pancreatitis, neoplasms, and thyroidectomy. Other thyroid events, injection site reactions, and acute gallbladder disease were 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 level ≤3·9 mmol/L at a site visit, and graded according to American Diabetes Association criteria.19

Nutritional compliance was assessed and nutritional/physical activity counselling provided by qualified research staff every 4 weeks. Participants were advised to follow a daily energy intake limit approximately 500 kcal below their total energy expenditure, estimated as described elsewhere20 from basal metabolic rate and a physical activity level of 1·3. A maintenance diet without an energy deficit was recommended if BMI declined to ≤22 kg/m2. 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 minutes per week without specifying exercise intensity.

Individuals discontinuing randomised 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 post-discontinuation. Early discontinuers were also encouraged to attend a week 52 visit as “retrieved” participants for determination of body weight, blood pressure, and adverse events, but did not attend intermediate visits.

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.

## Outcomes

The primary endpoint was the relative percentage change in body weight from baseline to week 52. Prespecified secondary endpoints included categorical weight loss ≥5% or ≥10% of baseline, absolute weight change, waist circumference, waist-to-hip ratio, and body mass index; change in glucose metabolism (HbA1c, fasting glucose), cardiovascular risk factors (blood pressure, lipids, C-reactive protein); changes in SF-36 scores, compliance with nutritional counselling, proportions of subjects with changes in antihypertensive or lipid-lowering medications, and the number of adverse events. Categorical weight loss ≥15% or ≥20% of baseline was assessed post hoc.

## Statistical analysis

The primary analysis comprised all randomised participants, 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 week 52 were imputed from the pooled placebo arm 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 analysis of covariance (ANCOVA) model with treatment, region, and sex as factors and the baseline value of the endpoint as covariate. Resulting estimates and standard deviations were pooled using Rubin’s approach.21 Pairwise treatment differences, 95% CIs, and p values were provided. Comparisons of the primary endpoint between the placebo pool and the five semaglutide doses on q4w escalation only were adjusted for multiple testing using Dunnett’s method.22,23 All other comparisons were unadjusted. Categorical weight loss ≥5% or ≥10% of baseline was evaluated as part of the prespecified analysis plan using J2R-MI and logistic regression with the same factors and covariate as the primary endpoint analysis. Categorical weight loss of ≥15% or ≥20% was similarly assessed post hoc. In addition to the primary analysis at week 52, ANCOVA estimation (with J2R-MI) of percentage weight change from baseline was performed at all treatment visits.

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

The overall study size was determined by the number of individuals in each active-treatment 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 statistically 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 liraglutide 3·0 mg24—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. Further, 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 >99% would result.

## Role of the funding source

The trial was designed by the trial sponsor, Novo Nordisk A/S, in collaboration with the study investigators. Data collection and analysis were performed by representatives of the trial sponsor. All authors had full access to the data, were involved in the development and approval of the manuscript, and had final responsibility for the decision to submit the manuscript for publication. The manuscript was prepared by the authors with assistance from a medical writer funded by the sponsor. The authors assume responsibility for the accuracy and completeness of the data and vouch for the fidelity of the trial to the protocol.

# Results

## Patient disposition

In total, 1111 people were screened and 957 randomised. The most common reasons (n>10) for non-randomisation among the 154 screened but not treated were hypo/hyperthyroidism (n=37), diabetes (n=26), investigator judgment (n=13), high blood pressure (n=13), and a PHQ-9 score ≥15 (n=12).

Baseline characteristics of the 957 randomised participants are shown in table 1. Overall, the treatment groups appeared well balanced for body weight and other baseline characteristics.

Figure 1 shows participant disposition throughout the trial. Overall, 81% (777/957) completed 52 weeks of treatment, while 19% (180/957) discontinued treatment early—18% (147/821) of those on active treatment and 24% (33/136) on placebo. Discontinuations were primarily for adverse events (8% [77/957]), loss to follow-up (3% [33/957]), participant choice (3% [29/957]), or protocol violations (2% [22/957]; supplementary appendix table S2).

One treatment completer had no weight data at week 52, and most (64%; 115/180) of those who discontinued early subsequently attended the week 52 visit as retrieved participants. Overall, therefore, 93% of participants (891/957) had available weight data at week 52 and 7% (66/957) were imputed in the primary analysis.

## Efficacy

In the primary analysis, estimated (J2R-MI, ANCOVA) and observed percentage reductions in body weight across the treatment period were semaglutide dose-dependent. At week 52, estimated mean weight reductions from baseline on semaglutide (figure 2A) ranged from 6·0% (standard error [SE] 0.85; 0·05 mg) to 13·8% (SE 0.83; 0·4 mg) on q4w escalation, 11·4% (SE 0.85; 0·3 mg) and 16·3% (SE 0.83; 0·4 mg) on q2w escalation, and 7·8% (SE 0.85) and 2·3% (SE 0.74) on liraglutide 3·0 mg and placebo, respectively. Observed reductions without imputation for all individuals with available week 52 data (including retrieved participants) were similar to the estimated outcomes, while 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 weight than placebo at week 52, and these remained significant in the semaglutide q4w escalation groups after adjustment for multiple comparisons (figure 2C). Among the q4w escalation groups, doses of more than 0·1 mg of semaglutide resulted in significantly greater weight loss at week 52 than liraglutide 3·0 mg (11·2–13·8% semaglutide versus 7·8% liraglutide; figure 2D). Weight loss for the highest doses of semaglutide appeared to continue through the full 52 weeks of treatment (supplementary appendix figure S2). The effect of q2w *vs* q4w dose escalation was inconsistent. Although a somewhat higher estimated week 52 weight loss was seen for 0·4 mg dosing on the q2w schedule (treatment difference *vs* q4w: –2·45% [95% CI –4·76% to –0·13%]), no effect of escalation speed was noted at 0·3 mg (treatment difference q2w *vs* q4w: –0·21% [95% CI –2·56% to 2·14%]).

MMRM-estimated weight reductions in the secondary analysis were slightly greater than in the primary analysis, and similar to observed on-treatment data (supplementary appendix figures S3 and S4). The difference between these two analyses can be interpreted as a measure of treatment effect lost due to early discontinuation.

Estimated (logistic regression, J2R-MI) and observed weight loss of at least 5%, 10%, 15%, or 20% of baseline were also semaglutide dose-dependent (figure 3). In prespecified analyses, 54–83% on semaglutide 0·05–0·4 mg/day and q4w escalation had an estimated loss ≥5% at week 52, *vs* 23% on placebo and 66% on liraglutide (all semaglutide p<0·0001 versus placebo), while 19–65% lost ≥10% *vs* 10% on placebo and 34% on liraglutide (p<0·0001 *vs* placebo for all semaglutide >0·05 mg). In post-hoc analyses, 7–41% on semaglutide q4w escalation had an estimated loss ≥15%, *vs* 5% on placebo and 15% on liraglutide, and 4–27% lost ≥20%, *vs* 2% on placebo and 4% on liraglutide (statistically significant *vs* placebo for all semaglutide >0·05 mg). Observed categorical weight loss without imputation was similar to the estimated outcomes for all those with available data, and slightly higher than estimated for those still on treatment at week 52 (figure 3). Among participants still receiving semaglutide at week 52 (q4w escalation), 60–91% had a weight loss ≥5%, and 21–74% lost ≥10% (*vs* 23% [24/103] and 10% [10/103], respectively, on placebo, and 72% [62/86] and 41% [35/86], respectively, on liraglutide), while 9–50% lost ≥15%, and 5–35% lost ≥20% (*vs* 4% [4/103] and 2% [2/103], respectively, on placebo, and 20% [17/86] and 6% [5/86], respectively, on liraglutide).

Other key secondary outcomes at week 52, excluding patient-reported outcomes, are shown in table 2 and in figures S5–S8 of the supplementary appendix. Consistent improvements in glucose metabolic and most anthropometric outcomes except for waist-to-hip ratio were observed on active treatment, with semaglutide dose-related reductions. Systolic and diastolic blood pressure decreased with all active treatment, with p<0·05 reductions *vs* placebo in systolic pressure for liraglutide and all semaglutide doses above 0·05 mg. Overall there appeared to be a trend towards improvements in other cardiac-associated outcomes (lipids, high-sensitivity C-reactive protein) among subjects receiving semaglutide compared with placebo, but without a clear association between the degree of improvement and the dose level.

Overall, 259 participants completed the SF-36 questionnaire at both baseline and week 52 (23–33 per active group, 38 pooled placebo). Dose-dependent trends towards greater improvements in the physical component and physical functioning scores were observed for semaglutide versus placebo, but no differences or trends were noted for the mental component score.

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) for q4w escalation, and 3·52 (0·3 mg) and 3·72 (0·4 mg) for q2w escalation, compared with 3·04 on liraglutide. Treatment differences for 0·3 mg (q2w escalation only), 0·4 mg (q2w and q4w escalation), and liraglutide were all p<0·05.

Between 75 and 88 individuals in each active-treatment arm, and 102 who received placebo, 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 q4w escalation were –4·9% (SD 6.2; 0·05 mg) to –13·5% (SD 7.9; 0·4 mg); for q2w escalation, –12·0% (SD 7.9; 0·3 mg) and –15·5% (SD 9.3; 0·4 mg); for liraglutide 3·0 mg, –7·7% (SD 6.9); and for pooled placebo, –1·8% (SD 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 (supplementary appendix figure S9).

There were no clear differences observed at week 52 in the number of subjects who changed their use of either antihypertensive or lipid-lowering medication (supplementary appendix table S3). 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 for placebo. Mean compliance scores across all semaglutide dosing groups at week 52 ranged from 6·85 (SD 2·47; 0·3 mg q4w) to 7·36 (SD 2·22 [0·4 mg q4w] and SD 1·85 [0·3 mg q2w]), versus 6·87 (SD 2·07) for liraglutide 3·0 mg and 6·09 (SD 2·39) for the pooled placebo group.

## Safety

A summary of adverse events on treatment is shown in table 3. 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 arms than in the pooled placebo group. Gastrointestinal events—primarily nausea (supplementary appendix figure S10)—were the most common adverse events observed on active treatment with either semaglutide or liraglutide.

Overall, most reported adverse events were of mild (69% [4125/5986]) or moderate (28% [1665/5986]) intensity. Events of severe intensity were uncommon and neither these nor events classed as serious adverse events showed any association with either active treatment or semaglutide dose. There was a single death, not considered related to study treatment by the investigator. A 40-year-old woman in the semaglutide 0·4 mg fast-escalation group 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 (supplementary appendix figure S11). In contrast, discontinuations due to adverse events were generally low but were highest for the highest semaglutide doses, and were higher in all active-treatment arms than on placebo. Most adverse event-related discontinuations were for gastrointestinal-related events, which were semaglutide dose-related and which were more common during the dose-escalation period in each treatment group than after the final dose had been reached (supplementary appendix figures S12).

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, primarily cholelithiasis or cholecystitis, increased across the semaglutide dosing range (1·9–6·9%, versus 0% on liraglutide 3·0 mg, and 3·7% on placebo).

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 semaglutide on a q2w escalation schedule, while at 0·4 mg/day the incidence of these and of gastrointestinal disorders were numerically lower for q2w than q4w escalation.

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 and/or cholecystitis: one individual was on placebo, two were on semaglutide 0·3 mg (q2w escalation), and one was on semaglutide 0·05 mg. 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). Four individuals were receiving semaglutide and one placebo, and all but one had a prior history of heart disease. No event was considered likely to be treatment related by the investigators (supplementary appendix table S4). In addition, a consistent increase in mean pulse rate of up to 4 beats/min at week 52 compared with placebo was observed for all semaglutide doses above 0·05 mg and for liraglutide 3·0 mg (supplementary appendix figure S13). This increase was not semaglutide dose-dependent and was similar for both semaglutide and liraglutide treatment.

Twenty-one confirmed neoplasms occurred in 19 individuals across the trial period (including off-treatment follow-up) in both the active (n=12 semaglutide, n=3 liraglutide) and pooled placebo groups (n=4; supplementary appendix table S5). There was no group imbalance reported in the type or incidence of neoplasms, there were no pancreatic neoplasms, and no breast neoplasms were observed in semaglutide-treated individuals.

There were few hypoglycaemic episodes reported in any treatment group (supplementary appendix table S6) and none were graded as severe.

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.

# Discussion

Weight loss on semaglutide is primarily due to reduced energy intake resulting from appetite suppression and enhanced satiety, and at a 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.26 This study was the first assessment of semaglutide for weight management, as opposed to previous studies focussing on glycaemic control in type 2 diabetes. In these individuals without diabetes, semaglutide 0·05–0·4 mg/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/day at doses of 0·2 mg/day or above.

The primary analysis was based on intent-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 randomised 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- 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 good agreement with observed on-treatment data at week 52.

The 7·8% weight loss in the liraglutide arm in this study was comparable with other similar-length studies of liraglutide 3·0 mg for weight management,24,27 but was significantly less than the 11–14% reductions seen with semaglutide doses ≥0·2 mg/day on q4w escalation. 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 (≈6%), lorcaserin (≈6%), phentermine/topiramate (≈8–10%), and naltrexone/bupropion (≈5%).4 At these higher semaglutide doses, an estimated 75–83% lost ≥5% of their baseline weight and 56–65% lost ≥10%, while in post-hoc analyses an estimated 29–41% lost ≥15%, and 11–27% lost ≥20% of their baseline weight. For all in-trial participants at week 52, observed proportions with ≥15% and ≥20% weight loss were 32–42% and 14–29%, respectively, for semaglutide doses of 0·2 mg/day or above and q4w escalation, while for those still on treatment at week 52 the observed proportions with ≥15% weight loss were 33–50% and with ≥20% 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 stands in contrast to earlier studies of anti-obesity medications including liraglutide,28 lorcaserin,29 and naltrexone/bupropion,30 where treatment response plateaued at an earlier timepoint, and suggests that longer studies may 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 on semaglutide that were statistically greater than placebo at all doses tested. Most secondary cardiovascular and glucose homeostasis factors were better on semaglutide or liraglutide than placebo, though 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 over placebo in physical outcome scores that became statistically 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 and/or obesity. 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, though the proportion of discontinuations for gastrointestinal events on any active treatment (2·9–12·7% across groups) was low compared with the overall incidence of gastrointestinal events (62–82%). Gallbladder disorders showed a possible dose-related trend on 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 comparable among individuals on liraglutide or on semaglutide doses above 0·05 mg/day. These 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/day and 0·4 mg/day were escalated on both q2w and q4w schedules, no firm conclusions could be made about the comparative safety and efficacy of the exploratory q2w groups. For 0·3 mg/day, efficacy outcomes on q2w escalation were comparable with q4w, but faster escalation was associated with more adverse events. By contrast, at 0·4 mg/day q2w escalation generally had higher efficacy outcomes but somewhat fewer adverse events than q4w.

Limitations of the current study include the impossibility of blinding participants and site staff to the assigned dose due to the differing volumes and dose escalation periods, although at each dosing level they remained blinded for active drug or placebo. This may potentially have introduced bias into the reporting of adverse events (high doses) or treatment discontinuation (low doses). Adherence to diet recommendations was assessed monthly on a numeric 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 lost was not performed.

These data for semaglutide 0·05–0·4 mg/day confirm earlier findings of significant weight loss with semaglutide 0·5 mg/week or 1·0 mg/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 establish 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 demonstrated 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. Phase 3 studies are ongoing.

# Contributors

JPHW, CGC, CHJ, and MK contributed to the design of the study. PMO, 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 received grants and personal fees from Novo Nordisk during the conduct of the study, as well as grants from Weight Watchers International, and received personal fees from Janssen, Vindico CME, WebMD and the Robard Corporation. ALB has received fees from Novo Nordisk, unrelated to the submitted work. BM received grants from Novo Nordisk during the conduct of the study, and is the primary investigator on two Novo Nordisk trials. She received grants and personal fees from Novo Nordisk, personal fees from Boehringer Ingelheim, Janssen, Eli Lilly and Merck Sharp & Dohme outside of the submitted work. OM reports 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 reports personal fees and non-financial support from Novo Nordisk, Eli Lilly, Valeant, Merck 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 received non-financial support from Novo Nordisk during the conduct of the study, and 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 reports grants from Novo Nordisk during the conduct of the study; grants, and personal fees and other financial support from Novo Nordisk and AstraZeneca, grants and personal fees from Takeda, personal fees and other from Boehringer Ingelheim, Sanofi, Eli Lilly, Orexigen, Napp/Mundipharma and Janssen, and other financial support from Astellas, outside of the submitted work.

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# Data Sharing

|  |  |
| --- | --- |
| Will individual participant data be available (Including data dictionaries)? | Individual participant data will be shared in data sets in a de-identified/anonymised format. |
| What data in particular will be shared? | Data sets from Novo Nordisk sponsored clinical research completed after 2001 for product indications approved in both the EU and US. |
| What other documents will be available? | Study protocol and redacted Clinical Study Report (CSR) will be available according to Novo Nordisk data sharing commitments. |
| When will data be available (start and end dates)? | The data will be available permanently after research completion and approval of product and product use in both EU and US. No end date. |
| With whom will data be shared? | With bona fide researchers submitting a research proposal requesting access to data. |
| For what types of analyses? | For use as approved by the Independent Review Board according to the IRB Charter (see novonordisk-trials.com) |
| By what mechanism will data be made available | Access request proposal form and the access criteria can be found at novonordisk-trials.com. The data will be made available on a specialised SAS data platform. |

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***Table 1:* Participant baseline characteristics**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **SEMA**  **0·05 mg**  **(n=103)** | **SEMA**  **0·1 mg**  **(n=102)** | **SEMA**  **0·2 mg**  **(n=103)** | **SEMA**  **0·3 mg**  **(n=103)** | **SEMA**  **0·4 mg**  **(n=102)** | **SEMA**  **0·3 mg FE**  **(n=102)** | **SEMA**  **0·4 mg FE**  **(n=103)** | **LIRA**  **3·0 mg**  **(n=103)** | **PBO**  **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 [13]  (18–86) |
| Male, n (%) | 36 (35·0) | 36 (35·3) | 37 (35·9) | 37 (35·9) | 36 (35·3) | 36 (35·3) | 36 (35·0) | 36 (35·0) | 48 (35·3) | 338 (35·3) |
| Race, n (%)  White  Black/African-American  Other  Not applicable\* | 88 (85·4)  5 (4·9)  2 (1·9)  8 (7·8) | 76 (74·5)  7 (6·9)  2 (2·0)  17 (16·7) | 72 (69·9)  10 (9·7)  1 (1·0)  20 (19·4) | 74 (71·8)  3 (2·9)  4 (3·9)  22 (21·4) | 71 (69·6)  10 (9·8)  2 (2·0)  19 (18·6) | 76 (74·5)  0  4 (3·9)  22 (21·6) | 68 (66·0)  7 (6·8)  3 (2·9)  25 (24·3) | 78 (75·7)  9 (8·7)  2 (1·9)  14 (13·6) | 97 (71·3)  10 (7·4)  5 (3·7)  24 (17·6) | 700 (73·1)  61 (6·4)  25 (2·6)  171 (17·9) |
| Weight, 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/m2 | 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/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) |
| HbA1c, % | 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) |
| hs-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 [113·4] (0·2–105·5) |
| Country of residence, n (%)  Australia  Belgium  Canada  Germany  Israel  Russian Federation  United Kingdom  United States | 10 (9·7)  4 (3·9)  4 (3·9)  7 (6·8)  15 (14·6)  17 (16·5)  8 (7·8)  38 (36·9) | 6 (5·9)  8 (7·8)  9 (8·8)  5 (4·9)  13 (12·7)  13 (12·7)  17 (16·7)  31 (30·4) | 6 (5·8)  16 (15·5)  4 (3·9)  7 (6·8)  6 (5·8)  14 (13·6)  17 (16·5)  33 (32·0) | 8 (7·8)  11 (10·7)  11 (10·7)  8 (7·8)  7 (6·8)  12 (11·7)  9 (8·7)  37 (35·9) | 4 (3·9)  11 (10·8)  8 (7·8)  5 (4·9)  9 (8·8)  10 (9·8)  12 (11·8)  43 (42·2) | 6 (5·9)  8 (7·8)  14 (13·7)  9 (8·8)  8 (7·8)  13 (12·7)  12 (11·8)  32 (31·4) | 2 (1·9)  16 (15·5)  9 (8·7)  9 (8·7)  6 (5·8)  14 (13·6)  15 (14·6)  32 (31·1) | 4 (3·9)  10 (9·7)  4 (3·9)  7 (6·8)  9 (8·7)  15 (14·6)  10 (9·7)  44 (42·7) | 10 (7·4)  12 (8·8)  12 (8·8)  12 (8·8)  10 (7·4)  16 (11·8)  13 (9·6)  51 (37·5) | 56 (5·9)  96 (10·0)  75 (7·8)  69 (7·2)  83 (8·7)  124 (13·0)  113 (11·8)  341 (35·6) |

\*Belgian and Canadian sites only (racial data not recorded). Data are mean [SD] (range), or †Geometric mean [CV] (range), unless otherwise specified. BMI=body mass index, FE=fast (2-weekly) dose escalation, HbA1c=haemoglobin A1c, HDL=high-density lipoprotein, hs-CRP=high-sensitivity C-reactive protein, LDL=low-density lipoprotein, LIRA=liraglutide, PBO=placebo, SEMA=semaglutide, VLDL=very low-density lipoprotein.

***Table 2:* Key secondary endpoints**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **SEMA**  **0·05 mg**  **(n=103)** | **SEMA**  **0·1 mg**  **(n=102)** | **SEMA**  **0·2 mg**  **(n=103)** | **SEMA**  **0·3 mg**  **(n=103)** | **SEMA**  **0·4 mg**  **(n=102)** | **SEMA**  **0·3 mg FE**  **(n=102)** | **SEMA**  **0·4 mg FE**  **(n=103)** | **LIRA**  **3·0 mg**  **(n=103)** | **PBO**  **Pooled**  **(n=136)** |
| Body weight, 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) |
| 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) |
| BMI, kg/m2 | –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) |
| HbA1c, % | –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, mmHg  Systolic  Diastolic | –4·46 (1·20)  *p=0.0691*  –2·55 (0·84)  *p=0.3441* | –5·76 (1·18)  *p=0.0078*  –2·65 (0·82)  *p=0.2937* | –6·26 (1·19)  *p=0.0030*  –4·09 (0·83)  *p=0.0181* | –6·41 (1·19)  *p=0.0021*  –2·98 (0·83)  *p=0.1751* | –5·81 (1·16)  *p=0.0065*  –3·61 (0·80)  *p=0.0511* | –6·07 (1·19)  *p=0.0044*  –2·20 (0·83)  *p=0.5205* | –10·26 (1·16)  *p<0.0001*  –5·52 (0·80)  *p=0.0002* | –5·45 (1·18)  *p=0.0135*  –2·70 (0·82)  *p=0.2736* | –1·58 (1·04)  –1·50 (0·73) |
| Lipids, ratio week 52 to BL  Total cholesterol  HDL-cholesterol  LDL-cholesterol  VLDL-cholesterol  Triglycerides | 0·96 (0·02)  *p=0.6599*  0·99 (0·01)  *p=0.7457*  0·97 (0·02)  *p=0.9466*  0·90 (0·03)  *p=0.2526*  0·89 (0·04)  *p=0.2322* | 0·95 (0·01)  *p=0.2065*  1·02 (0·01)  *p=0.3227*  0·93 (0·02)  *p=0.1882*  0·89 (0·03)  *p=0.1405*  0·88 (0·03)  *p=0.1560* | 0·93 (0·01)  *p=0.0472*  1·02 (0·01)  *p=0.3600*  0·93 (0·02)  *p=0.1867*  0·81 (0·03)  *p=0.0015*  0·81 (0·03)  *p=0.0020* | 0·93 (0·01)  *p=0.0253*  1·02 (0·01)  *p=0.2943*  0·92 (0·02)  *p=0.0754*  0·85 (0·03)  *p=0.0187*  0·85 (0·03)  *p=0.0250* | 0·93 (0·01)  *p=0.0606*  1·00 (0·01)  *p=0.8892*  0·93 (0·02)  *p=0.2428*  0·81 (0·03)  *p=0.0009*  0·80 (0·03)  *p=0.0010* | 0·93 (0·02)  *p=0.0663*  1·00 (0·02)  *p=0.9470*  0·92 (0·02)  *p=0.1158*  0·87 (0·04)  *p=0.0784*  0·87 (0·04)  *p=0.0877* | 0·92 (0·01)  *p=0.0067*  1·01 (0·01)  *p=0.4836*  0·91 (0·02)  *p=0.0363*  0·81 (0·03)  *p=0.0006*  0·80 (0·03)  *p=0.0006* | 0·96 (0·01)  *p=0.5062*  1·00 (0·01)  *p=0.8656*  0·95 (0·02)  *p=0.6358*  0·91 (0·03)  *p=0.3168*  0·90 (0·03)  *p=0.3298* | 0·97 (0·01)  1·00 (0·01)  0·97 (0·02)  0·95 (0·03)  0·95 (0·03) |
| hs-CRP, ratio week 52 to BL | 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 *vs* placebo (unadjusted for multiple comparisons).Table excludes categorical weight loss and patient-reported outcome data discussed in main text. All analyses by ANCOVA with J2R-MI of missing data. ANCOVA=analysis of covariance, BL=baseline, BMI=body mass index, FE=fast (2-weekly) dose escalation, hs-CRP=high-sensitivity C-reactive protein, HbA1c=haemoglobin A1c, HDL=high-density lipoprotein, J2R-MI, jump-to-reference multiple imputation, LDL=low-density lipoprotein, LIRA=liraglutide, PBO=placebo, SEM=standard error of the mean, SEMA=semaglutide, VLDL=very low-density lipoprotein.

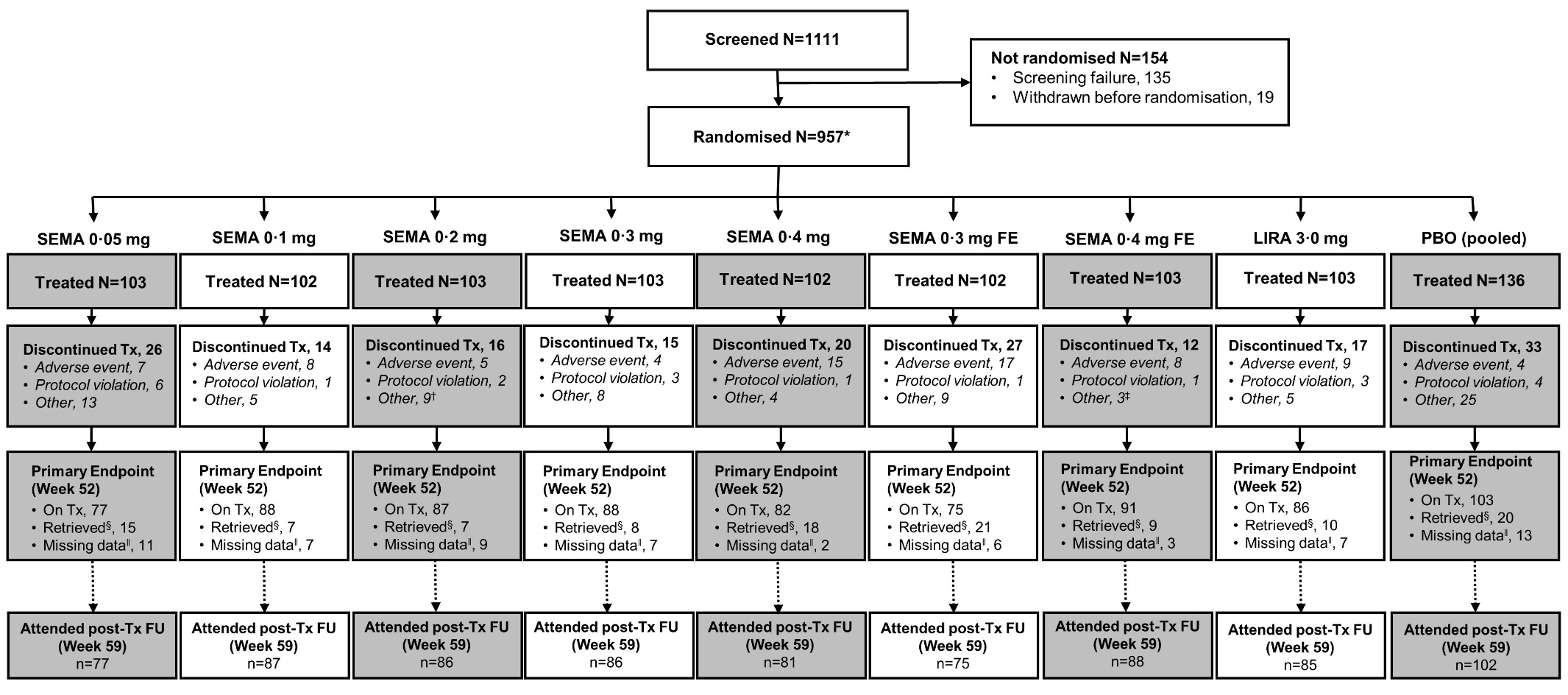
***Table 3:* On-treatment safety overview**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **SEMA**  **0·05 mg**  **(n=103)** | **SEMA**  **0·1 mg**  **(n=102)** | **SEMA**  **0·2 mg**  **(n=103)** | **SEMA**  **0·3 mg**  **(n=103)** | **SEMA**  **0·4 mg**  **(n=102)** | **SEMA**  **0·3 mg FE**  **(n=102)** | **SEMA**  **0·4 mg FE**  **(n=103)** | **LIRA**  **3·0 mg**  **(n=103)** | **PBO**  **Pooled**  **(n=136)** |
| Individuals with ≥1 adverse event | 93 (90·3) | 94 (92·2) | 96 (93·2) | 93 (90·3) | 98 (96·1) | 98 (96·1) | 96 (93·2) | 88 (85·4) | 107 (78·7) |
| Individuals with ≥1 serious adverse event | 13 (12·6) | 8 (7·8) | 5 (4·9) | 6 (5·8) | 13 (12·7) | 6 (5·9) | 7 (6·8) | 4 (3·9) | 11 (8·1) |
| Individuals with ≥1 adverse event of severe intensity | 13 (12·6) | 17 (16·7) | 12 (11·7) | 14 (13·6) | 17 (16·7) | 16 (15·7) | 13 (12·6) | 13 (12·6) | 16 (11·8) |
| Individuals with ≥1 adverse event leading to discontinuation  Discontinuation for ≥1 gastrointestinal adverse event | 7 (6·8)  6 (5·8) | 8 (7·8)  5 (4·9) | 5 (4·9)  3 (2·9) | 4 (3·9)  4 (3·9) | 15 (14·7)  13 (12·7) | 17 (16·7)  12 (11·8) | 8 (7·8)  8 (7·8) | 9 (8·7)  4 (3·9) | 4 (2·9)  2 (1·5) |
| 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 | 0 |
| Most common events†  Nausea  Diarrhoea  Constipation  Nasopharyngitis  Vomiting  Decreased appetite  Headache  Eructation | 32 (31·1)  20 (19·4)  13 (12·6)  16 (15·5)  8 (7·8)  8 (7·8)  7 (6·8)  4 (3·9) | 42 (41·2)  25 (24·5)  22 (21·6)  23 (22·5)  18 (17·6)  17 (16·7)  15 (14·7)  8 (7·8) | 45 (43·7)  35 (34·0)  26 (25·2)  19 (18·4)  24 (23·3)  13 (12·6)  10 (9·7)  14 (13·6) | 43 (41·7)  27 (26·2)  18 (17·5)  15 (14·6)  11 (10·7)  13 (12·6)  10 (9·7)  8 (7·8) | 49 (48·0)  39 (38·2)  24 (23·5)  19 (18·6)  18 (17·6)  14 (13·7)  21 (20·6)  7 (6·9) | 55 (53·9)  28 (27·5)  19 (18·6)  16 (15·7)  21 (20·6)  18 (17·6)  14 (13·7)  17 (16·7) | 50 (48·5)  28 (27·2)  29 (28·2)  20 (19·4)  23 (22·3)  20 (19·4)  11 (10·7)  10 (9·7) | 46 (44·7)  29 (28·2)  24 (23·3)  16 (15·5)  11 (10·7)  12 (11·7)  15 (14·6)  6 (5·8) | 24 (17·6)  16 (11·8)  6 (4·4)  16 (11·8)  6 (4·4)  5 (3·7)  15 (11·0)  1 (0·7) |
| Events of special interest  Gastrointestinal disorders  Gallbladder disorders  Hepatic events  Injection site reactions  Allergic reactions  Neoplasms (EAC confirmed in-trial)‡  Hypoglycaemic episodes  Pancreatitis (EAC confirmed on-treatment) | 64 (62·1)  2 (1·9)  2 (1·9)  7 (6·8)  5 (4·9)  3 (2·9)  1 (1·0)  1 (1·0) | 72 (70·6)  2 (2·0)  3 (2·9)  9 (8·8)  9 (8·8)  1 (1·0)  4 (3·9)  0 | 72 (69·9)  3 (2·9)  2 (1·9)  6 (5·8)  7 (6·8)  3 (2·9)  4 (3·9)  0 | 72 (69·9)  3 (2·9)  2 (1·9)  5 (4·9)  3 (2·9)  0  5 (4·9)  0 | 84 (82·4)  6 (5·9)  1 (1·0)  8 (7·8)  8 (7·8)  4 (3·9)  9 (8·8)  0 | 84 (82·4)  7 (6·9)  3 (2·9)  8 (7·8)  8 (7·8)  0  8 (7·8)  2 (2·0) | 78 (75·7)  2 (1·9)  0  10 (9·7)  3 (2·9)  1 (1·0)  10 (9·7)  0 | 77 (74·8)  0  2 (1·9)  10 (9·7)  13 (12·6)  3 (2·9)  4 (3·9)  0 | 52 (38·2)  5 (3·7)  9 (6·6)  10 (7·4)  10 (7·4)  4 (2·9)  8 (5·9)  1 (0·7) |

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

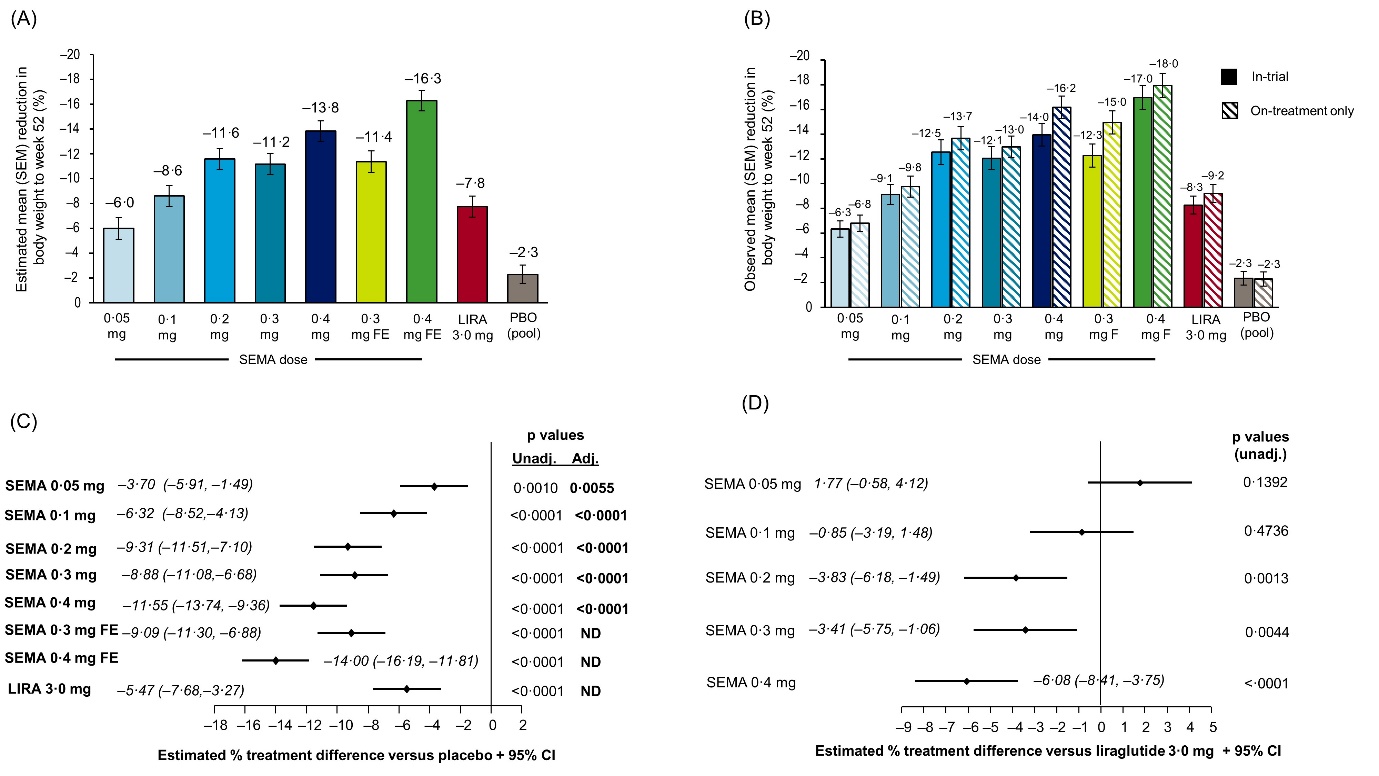
***Figure 1:* Participant disposition**

FE=fast (2-weekly) dose escalation, FU=follow-up, LIRA=liraglutide, PBO=placebo, SEMA=semaglutide, Tx=treatment. \*All randomised patients received treatment. †Includes 1 pregnancy. ‡Includes 1 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.



***Figure 2:* Percentage weight loss at week 52: (A) estimated mean changes from baseline (primary endpoint); (B) Observed mean changes from baseline; (C) estimated semaglutide/liraglutide treatment differences versus placebo; (D) estimated semaglutide treatment differences (q4w dose escalation) versus liraglutide 3·0 mg**

Estimated changes are ANCOVA-modelled with J2R-MI 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. adj.=p value adjusted for multiple comparisons (Dunnett’s method), ANCOVA=analysis of covariance, FE=fast (2-weekly) dose escalation, J2R-MI, jump-to-resistance multiple imputation, LIRA=liraglutide, ND=not determined, PBO=placebo, q4w=every 4 weeks, SEM=standard error of the mean, SEMA=semaglutide, unadj.=unadjusted.



***Figure 3:* Categorical weight loss at week 52: Estimated and observed reductions ≥5% and ≥10% (Panels A, C, E), and ≥15% and ≥20% (Panels B, D, F) of baseline weight**

Analyses of ≥15% and ≥20% are post hoc. Estimations are by logistic regression on all individuals with available data at week 52, with J2R-MI of missing data. Observed data are without imputation. In-trial data are for all individuals with available data at week 52, on- or off-treatment. On-treatment data are for those still on treatment at week 52 only. FE=fast (2-weekly) dose escalation, J2R-MI=jump-to-reference multiple imputation, LIRA=liraglutide, LR=logistic regression, PBO=placebo, SEMA=semaglutide. \*p<0·0500 *vs* placebo. †<0·0001 *vs* placebo.  
