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A 3-year randomised trial of liraglutide 3·0 mg for type 2 diabetes risk reduction and weight management

Carel W. le Roux, F.R.C.P., Arne Astrup, M.D., Ken Fujioka, M.D., Frank Greenway, M.D., David C.W. Lau, F.R.C.P.C., Luc Van Gaal, M.D., Rafael Violante Ortiz, M.D., John P.H. Wilding, F.R.C.P., Trine V. Skjøth, M.D., Linda Shapiro Manning, M.D., and Xavier Pi-Sunyer, M.D., on Behalf of the SCALE Obesity and Prediabetes NN8022-1839 Study Group*

From Diabetes Complications Research Centre, Conway Institute, University College Dublin, Ireland (Prof C W le Roux FRCP); Department of Nutrition, Exercise and Sports, University of Copenhagen, Frederiksberg C, Denmark (Prof A Astrup DMSc); Division of Endocrinology, Department of Nutrition and Metabolic Research, Scripps Clinic, La Jolla, California, CA (K Fujioka MD); Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA (Prof F Greenway MD); Departments of Medicine and Biochemistry & Molecular Biology, University of Calgary, Calgary, Alberta, Canada (Prof D Lau FRCPC); Department of Endocrinology, Diabetology and Metabolic Diseases, Antwerp University Hospital, Antwerp, Belgium (Prof L Van Gaal MD), Departamento Endocrinología, Instituto Mexicano del Seguro Social, Ciudad Madero, México (R Violante Ortiz MD); Department of Obesity and Endocrinology, University of Liverpool, Liverpool, England (Prof J Wilding FRCP); Novo Nordisk A/S, Soeborg, Denmark (T V Skjøth MD, L Shapiro Manning MD); and Division of Endocrinology and Obesity Research Center, Columbia University, New York, NY (Prof X Pi-Sunyer MD).

*A complete list of investigators in the Satiety and Clinical Adiposity – Liraglutide Evidence in individuals with and without diabetes (SCALE) Obesity and Prediabetes NN8022-1839 study group is provided in the Supplementary Appendix, available at thelancet.com.

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Address reprint requests to: Professor Carel W. le Roux, F.R.C.P., Ph.D., Diabetes Complications Research Centre, Conway Institute, University College Dublin, Belfield, Dublin 4, Ireland.
Telephone: +447970719453. Email: carel.leroux@ucd.ie

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Summary

Background:

Liraglutide 3·0 mg reduced body weight and improved glucose metabolism after the 56-week period of this trial, one of four trials comprising the SCALE programme. The primary objective of the 3-year SCALE Obesity and Prediabetes trial was to evaluate the proportion of individuals with prediabetes who were diagnosed with type 2 diabetes.

Methods:

In this 3-year double-blind trial, 2254 adults with prediabetes and a body-mass index of at least 30 kg/m^2, or at least 27 kg/m^2 with comorbidities, were randomised 2:1, using a telephone or web-based system, to once-daily subcutaneous liraglutide 3·0 mg or placebo, as an adjunct to a reduced-calorie diet and increased physical activity. Time to diabetes onset after 160 weeks was the primary endpoint, evaluated in randomised treated individuals with at least one post-baseline assessment. The trial was conducted at 191 sites in 27 countries and is registered with ClinicalTrials.gov, number NCT01272219.

Findings:

The study ran between June 1, 2011, and March 2, 2015; 791 of 1505 (52·6%) participants randomised to liraglutide and 337 of 749 (45·0%) randomised to placebo completed 3 years. By week 160, 26 of 1472 individuals in the liraglutide group *vs* 46 of 738 in the placebo group were diagnosed with diabetes while on treatment. For the 26 individuals in the liraglutide group, the mean time from randomisation to diagnosis was approximately 99±47 weeks *vs* 87±47 weeks for the 46 individuals in the placebo group. Taking the different diagnosis frequencies between the treatment groups into account, the time to onset of diabetes over 160 weeks among all randomised individuals was 2·7 times longer with liraglutide than with placebo (95% CI, 1·9 to 3·9, $p<0·0001$), corresponding to a hazard ratio of 0·21 (95% CI, 0·13 to 0·34). Liraglutide induced greater weight

loss than placebo at week 160 (-6·1±7·3% *vs* -1·9±6·3%, estimated treatment difference -4·3% [95% CI, -4·9 to -3·7], p<0·0001). Serious adverse events were reported by 15·1% of randomised treated individuals in the liraglutide group *vs* 12·9% in the placebo group.

Interpretation:

This trial provides results for up to 3 years of treatment, with the limitation that withdrawn individuals were not followed up after discontinuation. Liraglutide 3·0 mg may provide health benefits in terms of reduced diabetes risk in individuals with obesity and prediabetes.

Funding:

Novo Nordisk, Denmark.

Research in context

Evidence before this study

We searched PubMed from Jan 1, 1990, to April 30, 2016, using the terms “obesity” and “liraglutide” and “randomised clinical trial”. We found 45 articles assessing liraglutide treatment, including one phase 1 study, seven randomised controlled studies and seven review articles that evaluated liraglutide at a dose of 3·0 mg for weight management. Of those, one randomised controlled study was performed in individuals with and without prediabetes over a 56-week treatment period. According to study design, individuals who had prediabetes at screening continued on treatment for a further two years, and are the subject of the current report.

Added value of this study

Few trials of anti-obesity medications have been performed over 3 years. This study provides clinically important long-term data on the efficacy and safety of liraglutide 3·0 mg in individuals with prediabetes treated for 3 years followed by a 12-week off-treatment follow-up period. Treatment with liraglutide 3·0 mg over 3 years was associated with a reduced risk of type 2 diabetes, weight loss and improvements in glycaemic control in individuals with prediabetes. Liraglutide 3·0 mg was generally well tolerated and no new safety signals were observed as compared to the previous evaluation after 56 weeks of treatment.

Implications of all the available evidence

Treatment with once-daily subcutaneous liraglutide 3·0 mg for 3 years, combined with a reduced-calorie diet and increased physical activity, may not only provide a sustained clinically relevant weight loss, but also additional health benefits in terms of reduced risk of type 2 diabetes, as well as improvements in glycaemic control in a high-risk group of individuals with prediabetes and overweight/obesity.

Introduction

Prediabetes and obesity are risk factors for type 2 diabetes mellitus[1–3] and its complications.[3] The prevalence of diabetes is increasing,[1–3] and 5–10% of people with prediabetes develop diabetes yearly.[4] Weight loss through lifestyle intervention, with or without pharmacotherapy, can reduce the risk of developing diabetes.[4–9]

Once-daily subcutaneous liraglutide 3·0 mg, as an adjunct to a reduced-calorie diet and increased physical activity, is approved for weight management in several regions including North America and Europe. Liraglutide promotes weight loss through reduced appetite and energy intake.[10] The 56-week part of the current trial was reported previously and evaluated the efficacy and safety of liraglutide 3·0 mg for weight loss over 56 weeks.[11] Liraglutide 3·0 mg provided substantial weight loss in individuals with or without prediabetes who had obesity or overweight with comorbidities, and reduced type 2 diabetes incidence. Individuals who had prediabetes at screening continued on treatment in the trial for a further two years, and are the subject of the current report.

This 3-year trial aimed to evaluate the effect of liraglutide 3·0 mg in delaying the onset of type 2 diabetes in individuals with prediabetes, as well as on weight loss and safety over 3 years.

Methods

Study design

SCALE Obesity and Prediabetes was conducted as part of a large global phase 3a clinical development programme of 4 randomised, double-blind, placebo-controlled trials with over 5000 participants that was designed to investigate the efficacy and safety of liraglutide 3·0 mg, a glucagon-like peptide-1 (GLP-1) receptor agonist (RA), for weight management .[11-14] We conducted the study at 191 sites in 27 countries in Europe, North and South America, Asia, Africa and

Australia. The study design is shown in the appendix p 9. The protocol was approved by local ethics committees or institutional review boards and is available with the full article text at thelancet.com. The study was conducted according to the Declaration of Helsinki[15] and Good Clinical Practice.[16] The 56-week period of the trial evaluated the efficacy and safety of liraglutide 3·0 mg for weight management in individuals with and without prediabetes.[11] The methodology is summarised below. From week 56, individuals with prediabetes at screening continued on treatment for a further two years, with a 12-week off-treatment follow-up period. Thus individuals with prediabetes were on treatment for up to 3 years.

Participants

We enrolled adults aged ≥18 years with stable body weight and a body-mass index (BMI) of ≥30 kg/m^2, or ≥27 kg/m^2 with treated or untreated dyslipidaemia and/or hypertension. Each individual provided written informed consent before participation. Key exclusion criteria were type 1 or 2 diabetes, medications causing significant weight gain or loss, bariatric surgery, history of pancreatitis, major depressive or other severe psychiatric disorders, and family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma. Detailed eligibility and exclusion criteria are provided in the appendix p 31.

Randomisation and masking

Participants were randomly assigned, in a 2:1 ratio, to receive liraglutide 3·0 mg or placebo. Randomisation was performed using a sponsor-provided telephone or web-based system. The sponsor generated the random allocation sequence, and the trial investigators enrolled individuals, and assigned them to treatment. Participants were stratified at screening by BMI (≥30 *vs* <30 kg/m^2) and according to whether or not they had prediabetes. Those who had prediabetes and completed 56 weeks of treatment continued for an additional 104 weeks of treatment, allowing for a total of 160

147 weeks of treatment. Participants without prediabetes were on treatment for 56 weeks, followed by a
148 12-week re-randomised period; results for this period of the trial have been reported previously.[11]
149 Participants without prediabetes are not included in the current report, thus the stratification factor
150 was not included in the statistical analysis. Participants and investigators were blinded to treatment
151 allocation during the entire trial (160 weeks plus the 12-week off-treatment follow-up period),
152 whereas the sponsor was unblinded to treatment allocation at week 56.
153
154 *Procedures and treatments*
155 The current report covers participants with prediabetes who were randomised to treatment for the full
156 3-year period. The diagnosis of prediabetes was based on fulfilment of at least one of the three
157 American Diabetes Association (ADA) 2010 criteria: glycated haemoglobin 5·7−6·4% both
158 inclusive and/or fasting plasma glucose ≥5·6 mmol/L and ≤6·9 mmol/L and/or 2-hour post-challenge
159 plasma glucose ≥7·8 mmol/L and ≤11·0 mmol/L.[17] Diagnosis of diabetes was confirmed by two
160 consecutive measurements of the same type of criteria: glycated haemoglobin ≥6·5% and/or fasting
161 plasma glucose ≥7·0 mmol/L and/or 2-hour post-challenge plasma glucose ≥11·1 mmol/L.[17]
162 Liraglutide and placebo were provided in prefilled FlexPen devices (Novo Nordisk A/S, Bagsværd,
163 Denmark), starting at 0·6 mg with weekly 0·6-mg incremental increases to 3·0 mg. All trial
164 participants received standardised lifestyle intervention counselling from randomisation to end of
165 follow-up, at approximately monthly intervals (appendix p 3). Participants were advised to achieve at
166 least 150 minutes of physical activity per week and to reduce their daily energy intake to 500 kcal
167 below their individualised energy requirement.
168
169 *Efficacy and safety endpoints*
170 The primary objective was to evaluate the proportion of individuals with type 2 diabetes at 160
171 weeks, with time to onset of diabetes as the primary endpoint. This was the fourth coprimary

endpoint of the trial; the first three coprimary endpoints, mean weight loss and the proportion of participants losing ≥5% and >10% of their baseline body weight, were met at week 56.[11] Secondary endpoints included changes from baseline to week 160 in glycaemic control parameters, mean and categorical body weight, BMI, waist circumference, cardiometabolic biomarkers, and health-related quality of life, assessed using validated questionnaires.[18-20] Additional methodology, including timing of assessments, is described in the appendix p 3.

Specific adverse events with increased prevalence among people with obesity, or of relevance to the GLP-1 drug class were assessed (as described in the appendix p 33). Independent medical experts prospectively adjudicated 9 of 17 event types in a blinded manner. We report adverse events that occurred during the 160-week trial period, from the first treatment day to 14 days after the last treatment day, unless otherwise stated.

Statistical analysis

A sample size of 3600 randomised individuals, 2400 to liraglutide 3·0 mg and 1200 to placebo, was chosen to provide an assessment of the safety and efficacy of liraglutide 3·0 mg over 3 years. This provided enough power for the primary endpoint of the 3-year trial, the fourth coprimary endpoint, which was the long-term efficacy of liraglutide 3·0 mg in delaying onset of diabetes in individuals with a diagnosis of prediabetes at screening, as reported here. Superiority for liraglutide 3·0 mg *vs* placebo was tested in a hierarchical manner with respect to the four coprimary endpoints to control for multiple testing, whereby the second, third and fourth endpoints were tested only if the previous endpoint had achieved statistical significance.

For the power estimation, a conservative approach was chosen using the binary endpoint type 2 diabetes "yes *vs* no" assessed in completers during the 160 weeks of treatment and analysed with a two-sided Chi-square test with a 5% significance level.

It was assumed that the annual conversion rate to type 2 diabetes of the individuals with prediabetes would be 7% in the placebo group and 2·1% in the liraglutide 3·0 mg group, i.e., 70% lower. After 160 weeks of treatment, the percentage of individuals with diabetes was therefore estimated to be 1-(1-0·07)^3 or 20% among individuals in the placebo group, and 1-(1-0·021)^3 or 6% among those in the liraglutide group. The drop-out rate during the 160 weeks of treatment was assumed to be 65% in both groups.

The prespecified efficacy analyses used data from the full-analysis set of all randomised individuals who received at least one treatment dose and had at least one post-baseline assessment. The safety-analysis set included all randomised individuals who received at least one treatment dose. Missing values were imputed using last-observation-carried-forward for post-baseline measurements. The primary endpoint of the 3-year trial was analysed using a Weibull model, using methods for the analysis of interval-censored time-to-event data. The Weibull model included treatment, sex and baseline BMI stratum as fixed effects, and baseline fasting glucose value as a covariate. Mean changes in continuous endpoints were analysed using an analysis of covariance. Categorical changes for dichotomous endpoints were analysed with logistic regression. Sensitivity analyses were performed to assess the robustness of the primary analysis, and the analyses for mean and categorical weight loss (appendix p 36).

The handling of missing data has progressed since the prespecified analyses were defined,[21] therefore additional post-hoc analyses were specified to further address the issue. A post-hoc Cox regression

analysis was done at week 172 in which diabetes status was imputed for all withdrawn individuals. It was firstly assumed that 1% of withdrawn individuals in the liraglutide 3·0 mg group had undiagnosed diabetes at withdrawal (based on the five additional cases observed in the 12-week off-treatment follow-up period), whereas it was assumed that none of those withdrawn in the placebo group did so. It was secondly assumed that the risk of developing diabetes after withdrawal in individuals who did not have diabetes at withdrawal (diagnosed or undiagnosed) was the same in both treatment groups.

Five prespecified subgroup analyses were performed to investigate whether baseline BMI (four categories) had any effect on weight or glycated haemoglobin level (see the appendix p 4). All statistical analyses in the trial were performed with SAS software, version 9·3 (SAS Institute). Additional statistical analysis details are included in the appendix. The trial is registered with ClinicalTrials.gov, number NCT01272219.

Role of the funding source

The sponsor, Novo Nordisk, participated in discussions regarding study design and protocol development, and provided logistical support during the trial. The sponsor collected the data, and planned and performed the statistical analyses, which were assessed by both authors and sponsor. The authors interpreted the data in collaboration with the sponsor, and wrote the report together with medical writing services provided by the sponsor. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

Trial population

The study was conducted between June 1, 2011, and March 2, 2015. A total of 2254 individuals with prediabetes, based on ADA 2010 criteria,[17] were randomised to 3 years of lifestyle intervention plus treatment with liraglutide 3·0 mg (n=1505) or placebo (n=749); see the trial profile in figure 1. In the liraglutide group, 791 of 1505 participants (52·6%) completed 160 weeks of treatment, as did 337 of 749 participants (45·0%) in the placebo group. A greater proportion of participants in the liraglutide group than the placebo group withdrew owing to adverse events (13·3% [199 of 1501 participants] *vs* 6·2% [46 of 747]). A smaller proportion of participants in the liraglutide group than in the placebo group withdrew owing to ineffective therapy (1·9% [29 of 1505 participants] *vs* 4·8% [36 of 749]) or withdrew their consent to remain in the trial (21·5% [324 of 1505] *vs* 31·1% [233 of 749]). Individuals who withdrew were slightly younger than the average trial population; otherwise, no noteworthy differences in baseline characteristics or medical history were observed (appendix p 35). The full-analysis set comprised 1472 participants in the liraglutide group and 738 participants in the placebo group.

Baseline characteristics of each group were similar (table 1; additional characteristics are shown in the appendix p 35).

Type 2 diabetes diagnosis

By week 160, 26 of 1472 individuals in the liraglutide group *vs* 46 of 738 in the placebo group were diagnosed with diabetes while on treatment. Figure 2A shows the Kaplan-Meier plot of cumulative probability of a diagnosis of diabetes taking censoring into account; 3% of individuals in the liraglutide group *vs* 11% in the placebo group were diagnosed with diabetes by week 160.

For the 26 individuals in the liraglutide group, the mean time from randomisation to diagnosis was approximately 99±47 weeks *vs* 87±47 weeks for the 46 individuals in the placebo group, in a post-hoc analysis. Taking the different diagnosis frequencies between the treatment groups into account, the time to onset of diabetes over 160 weeks among all randomised individuals, while on treatment, was 2·7 times longer with liraglutide than with placebo (95% confidence interval [CI], 1·9 to 3·9, p<0·0001) (appendix p 10). Hence the time to any specific percentile (for instance 1% or 10%) of the randomised population that will be diagnosed with diabetes is prolonged by a factor of 2·7 for individuals treated with liraglutide instead of placebo, corresponding to a hazard ratio of 0·21 (95% CI, 0·13 to 0·34) and a risk reduction of approximately 80% for liraglutide *vs* placebo.

Results were consistent across sensitivity analyses, and the treatment difference remained statistically significant after the 12-week off-treatment follow-up period, with five *vs* one additional individuals being diagnosed with diabetes with liraglutide *vs* placebo, respectively (appendix p 11). An additional post-hoc analysis was done at week 172 that addressed the lack of follow-up information for withdrawn participants, and assumed that 1% of those withdrawn in the liraglutide group had undiagnosed diabetes at withdrawal, whereas none of those in the placebo group did. The analysis provided a hazard ratio of 0·34, 95% CI, 0·22 to 0·53, p<0·0001, corresponding to a risk reduction of approximately 66%.

Regression to normoglycaemia

While on treatment, more individuals in the liraglutide 3·0 mg group (970 of 1472; 66%) than the placebo group (268 of 738; 36%) had regressed from prediabetes to normoglycaemia by week 160 (odds ratio 3·6 [95% CI, 3·0 to 4·4], p<0·0001; figure 2B), corresponding to a number-needed-to-treat of 3. After a 12-week treatment cessation, some individuals in the liraglutide group reverted to prediabetes but 740 of 1472 randomised and exposed individuals (50%) still had normoglycaemia at

week 172 compared to 263 of 738 (36%) of those in the placebo group (odds ratio 1·9 [95% CI, 1·6 to 2·3], p<0·0001).

Glycaemic control

While on treatment, measures of insulin resistance and beta-cell function improved in the liraglutide group *vs* the placebo group at week 160 (appendix p 37), and glycated haemoglobin, fasting glucose, and fasting insulin levels were lower with liraglutide than with placebo (table 2). Effects on fasting insulin and HOMA-IR were sustained after treatment cessation from week 160–172; effects on fasting glucose and glycated haemoglobin were not (figure 2C).

Body weight

Liraglutide induced greater weight loss than placebo at week 160 while on treatment (-6·1±7·3% *vs* -1·9±6·3%, estimated treatment difference -4·3% [95% CI, -4·9 to -3·7], p<0·0001). Weight loss with liraglutide treatment was sustained over 3 years (figure 3A). Greater mean and categorical weight loss were achieved in the liraglutide group *vs* the placebo group (table 2 and figure 3). After treatment cessation at week 160, some weight was regained in the liraglutide group, although the treatment difference was still significant at week 172 (-3·2% [95% CI, -4·3 to -2·2], p<0·0001; appendix p 38).

Several sensitivity analyses confirmed the superiority of liraglutide over placebo on mean weight loss, as presented in the appendix p 37. Treatment effects for weight-related endpoints and glycated haemoglobin were consistent across BMI subgroups (appendix p 18).

Of note, more than 90% of individuals in each treatment group who were diagnosed with diabetes lost less body weight than the treatment group mean at the time of diagnosis (appendix p 20).

317

318 *Cardiometabolic variables*

319 Systolic blood pressure was significantly decreased with liraglutide *vs* placebo at week 160 while on
320 treatment; diastolic blood pressure was not (table 2). Effects on fasting lipids and cardiovascular
321 biomarkers were generally modest (appendix p 39), but levels of high-sensitivity C-reactive protein
322 were substantially lower with liraglutide *vs* placebo (-36·9% *vs* -11·0%; estimated treatment
323 difference -29% [95% CI, -34 to -23], p<0·0001).

324

325 *Health-related quality of life*

326 Liraglutide 3·0 mg was associated with higher mean scores on the SF-36 physical component
327 summary score and the Impact of Weight on Quality of Life–Lite total score, indicating improved
328 health-related quality of life *vs* placebo (appendix p 39).

329

330 *Safety and tolerability*

331 Gastrointestinal disorders, 93% of mild or moderate severity, were the most common side effects in
332 the liraglutide 3·0 mg group (table 3), and also the most common cause of withdrawal (118 of 1501
333 individuals [7·9%] in the liraglutide group *vs* 11 of 747 [1·5%] in the placebo group) (see the
334 appendix p 23 for adverse events leading to discontinuation of ≥0·2% individuals in either group).
335 More serious adverse events were reported in the liraglutide group than the placebo group (table 3).
336 Adverse event incidence generally declined during the trial (appendix p 25). Four individuals died —
337 two in the liraglutide group (due to cardiac arrest and metastatic cholangiocarcinoma) and two in the
338 placebo group (pulmonary failure and cancer, primary tumour unknown).

339

340 As previously reported,[11] gallbladder-related events were more common with liraglutide than with
341 placebo (occurring in 74 of 1501 individuals [4·9%], 2·9 events per 100 patient-years of observation

(PYO) *vs* 13 of 747 individuals [1·7%], 1·2 events per 100 PYO). More cases of cholelithiasis and cholecystitis occurred at relatively constant rates over 3 years in the liraglutide group. Weight loss among individuals with gallbladder-related events in the liraglutide group was generally greater than the treatment group mean (appendix p 28).

Pancreatitis and neoplasms were assessed over 172 weeks, as described in the appendix p 5. Overall, 12 pancreatitis cases (eleven graded as mild, one as moderately severe),[22] were confirmed by adjudication, occurring in ten of 1501 individuals in the liraglutide group (0·7%; 0·3 events per 100 PYO), and in two of 747 placebo-group individuals (0·3%; 0·1 events per 100 PYO). Eight events in the liraglutide group occurred in the first year, (appendix p 26). Five individuals (four in the liraglutide group) had gallstone-related pancreatitis, with liver enzyme levels at least three times the upper limit of the normal range; three individuals (two in the liraglutide group) had gallstones on imaging.[23]

The incidence of adjudicated and confirmed neoplasms was similar in both treatment groups (2·2 *vs* 2·4 events per 100 PYO). As reported previously,[11] a numerical imbalance was observed for malignant and pre-malignant breast neoplasms: ten events in nine women in the liraglutide group, seven occurring in the first year, and no events in the placebo group (appendix p 27). Most women with events had above-average weight loss (appendix p 42). There were no cases of medullary thyroid carcinoma or C-cell hyperplasia. Liraglutide treatment did not increase median serum calcitonin concentrations.

Resting pulse increased in the liraglutide group at week 160 by approximately 2 beats per minute (table 2). Increases of >5, 10 and 20 beats per minute on at least two consecutive visits are shown in the appendix p 42. Prespecified cardiovascular events (appendix p 33) occurred in 242 of 1501

individuals in the liraglutide group (16·1%; 12·1 events per 100 PYO) *vs* 142 of 747 individuals in the placebo group (19·0%; 15·1 events per 100 PYO). The incidence of adjudication-confirmed major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was similarly low in both treatment groups (0·19 *vs* 0·20 events per 100 PYO).

No between-group differences were observed for psychiatric disorders, or questionnaire-based depression or suicidal behaviour scores. However, seven individuals treated with liraglutide (*vs* none treated with placebo) reported eight suicidal ideation events and one individual in the placebo group (*vs* none in the liraglutide group) reported suicidal depression. There was one suicide attempt in each treatment group (appendix p 6).

Results from the 12-week observational follow-up period and additional safety information, including results on hypoglycaemia, anti-liraglutide antibodies and pregnancies, are provided in the appendix.

Discussion

In individuals with overweight or obesity and prediabetes, 3 years of continued treatment with once-daily liraglutide 3·0 mg, as an adjunct to diet and exercise, was associated with lower risk of a type 2 diabetes diagnosis and greater sustained weight loss compared with placebo.

Generally, lifestyle intervention can induce a 40-70% diabetes relative-risk reduction, and enhance insulin sensitivity and beta-cell function in individuals with prediabetes at high-risk of developing type 2 diabetes.[4] In both the Diabetes Prevention Program (DPP) and Finnish Diabetes Prevention Study (DPS), lifestyle intervention compared with placebo was associated with a 58% reduction in the risk of diabetes after 3 years.[6,7] Furthermore, the DPP showed that metformin treatment was

associated with a 31% risk reduction compared with placebo.[6] In a pharmacotherapy trial in individuals with obesity, four years of treatment with orlistat was associated with a 37% reduced risk of diabetes , concomitant with a mean 5·8 kg weight loss *vs* 3·0 kg with placebo.[8] Moreover, two years of treatment with phentermine/topiramate provided a reduction *vs* placebo in the annualised incident rate of type 2 diabetes of 71% or 79%, depending on the dose, in individuals with prediabetes and/or the metabolic syndrome.[9] Mean weight loss was 10·9 and 12·1% for the two phentermine/topiramate doses *vs* 2·5% with placebo. Finally, pioglitazone reduced the conversion of impaired glucose tolerance to type 2 diabetes by 72% compared with placebo after a median 2·4 year follow-up period, though was associated with significant weight gain.[24] The present study addresses both weight-loss mediated and direct glucose-dependent insulinotropic effects of liraglutide 3·0 mg on the progression to type 2 diabetes. Liraglutide was associated with an approximate 80% risk reduction relative to placebo (hazard ratio 0·21) in the onset of type 2 diabetes. However, the primary analysis did not take into account the lack of follow-up information for withdrawn individuals. Therefore, a post-hoc analysis was done that made assumptions about those withdrawn individuals, and provided a risk reduction of approximately 66% relative to placebo (hazard ratio 0·34).

Whether the lack of a response to treatment for some individuals in the current trial was related to individual participant characteristics, or due to other factors, is unclear. Most individuals who were diagnosed with diabetes lost less body weight than the treatment group mean at the time of diagnosis.

Regression from prediabetes to normoglycaemia was observed in 66% of individuals in the liraglutide group while on treatment over 160 weeks, and was associated with a lower risk of diabetes.[5] Similar results have been observed previously with liraglutide and other GLP-1 RAs.[11, 25–27] The combination of weight loss and glycaemic improvements achieved with liraglutide and

lifestyle intervention likely contributed to the greater regression to normoglycaemia and longer time to onset of diabetes observed. Furthermore, findings from the DPP Outcomes Study demonstrate that regression to normoglycaemia by any means is associated with a 56% lower risk of diabetes.[5,28] Collectively these results support the beneficial use of pharmacotherapy to lower the risk of diabetes with the potential to reduce cardiovascular risk factors in individuals with obesity and prediabetes.[4]

Compared to the DPP, which recruited individuals with impaired fasting glucose and impaired glucose tolerance, we enrolled a lower-risk, less progressed population as we allowed for fulfilment of any one of three ADA 2010 diagnostic criteria[17] at enrolment. This, together with the weight loss achieved, may partly explain the lower diabetes incidence of 11% observed in our lifestyle placebo group, compared to the cumulative incidence of 14·4% at 3 years seen in the DPP for the lifestyle intervention group and 28·9% in the placebo group.[6]

The improvements previously observed[11] in body weight, glycaemia and cardiometabolic risk factors were generally sustained over 3 years. Similar improvements in many of these parameters, such as high-sensitivity C-reactive protein, have been observed with several GLP-1 receptor agonists,[29,30] including liraglutide.[12-14] After 12 weeks of treatment cessation, effects on glycated haemoglobin and fasting glucose disappeared with liraglutide, whereas fasting insulin remained low and unchanged, supporting differential (direct *vs* indirect) effects of liraglutide on glucose metabolism and diabetes risk. As the participants lost more weight with liraglutide than placebo, it will be important for future studies to quantify the relative contributions of weight loss *vs* the direct effects of liraglutide on glucose homeostasis with respect to diabetes risk reduction.

The safety profile over 3 years was in line with that observed over the initial 56-week period.[11] The numerical imbalance in gallbladder-related events, including cholelithiasis and cholecystitis events

that occurred at relatively constant rates over 3 years in the liraglutide group, is currently under investigation. Obesity and weight loss are both associated with an increased risk of gallstone formation.[31] Greater weight loss was generally observed among individuals in the liraglutide group who reported gallbladder-related events compared to the overall liraglutide population mean. The cause of the greater number of breast neoplasms in the liraglutide group, 70% of which occurred during the first year, is still unclear, but weight loss may have increased detection. The underlying mechanism for the increased resting pulse with liraglutide is also unknown; a direct chronotropic effect of liraglutide on the sino-atrial node has been suggested.[32]

The prevalence of obesity and type 2 diabetes and their associated major comorbidities and healthcare costs highlight the need for effective treatments. Adverse events in the current trial were mostly predictable based on the known effects of GLP-1 RAs, including more gastrointestinal disorders with liraglutide than with placebo, notably nausea, diarrhoea, constipation and vomiting. Furthermore, the increased pulse associated with liraglutide, as observed with other GLP-1 RAs, did not lead to an increased cardiovascular risk in a large cardiovascular-outcomes trial with liraglutide doses up to 1·8 mg.[33] In general, liraglutide has a well-documented safety profile based on clinical trials in over 5000 individuals with obesity and a large clinical development programme in individuals with diabetes, [33] including extensive post-marketing data. While the frequencies of gallbladder-related events and pancreatitis were greater in the liraglutide group than in the placebo group, the incidence of both was relatively low and will be monitored regularly in the post-marketing setting by routine pharmacovigilance. Overall, the long-term efficacy and safety results for the current trial support that the benefits of treatment with liraglutide 3·0 mg outweigh the risks in this already at-risk population of individuals with obesity or overweight with comorbidities. Data provided here will enable clinicians to attenuate the risks of individuals while optimising the benefits.

Although the 3-year retention rate of 53% in the liraglutide group and 45% in the placebo group can be considered successful and comparable to another long-term obesity trial,[8] the missing data due to participant withdrawal is a limitation when interpreting the primary endpoint and reported adverse events. However, a post-hoc analysis accounting for the lack of follow-up information demonstrated an approximately 66% lower risk of diabetes with liraglutide compared to placebo, the magnitude of which compares favourably with the 58% lower risk observed in the DPP[6] and DPP Outcomes Study,[28] with higher retention and longer follow-up.

In conclusion, 3 years of treatment with once-daily subcutaneous liraglutide 3·0 mg, as an adjunct to a reduced-calorie diet and increased physical activity, reduced the risk of type 2 diabetes in individuals with overweight or obesity and prediabetes, and promoted greater weight loss and improvements in glycaemic control and cardiometabolic risk factors compared with placebo. Liraglutide 3·0 mg, as a GLP-1 RA, provides a different treatment option for individuals with obesity or overweight, with or without type 2 diabetes, having direct glucose-dependent effects on insulin secretion and weight-loss mediated effects on improved insulin resistance. Liraglutide 3·0 mg was generally well tolerated. However, post-market surveillance will be exercised to ensure detection of potential side effects with a very low incidence.

Contributors

All authors were involved in the design or conduct of the study, the preparation of the manuscript, and the decision to submit it for publication, and all verify the accuracy and completeness of the data and analyses. The first draft of the manuscript was written by the medical writer Angela Stocks, PhD, (employee of Larix, funded by Novo Nordisk), who provided editorial and medical writing services in collaboration with all authors and based on an outline that all authors provided input to.

Declaration of interests

CleR has been an advisory board member for Fractyl, Herbalife and Novo Nordisk, and has received speaker's fees from Boehringer Ingelheim, Janssen, Johnson & Johnson, Medtronic, and Sanofi. AA has received research grants from Novo Nordisk, been an advisory board member for BioCare and Novo Nordisk, and received consultancy fees from Arena Pharmaceuticals, Basic Research, Gelesis, Omega ACO, Orexigen Therapeutics, Pathway Genomics, and S-Biotek. KF has received research grants from Eisai, Enteromedics, Novo Nordisk, Orexigen, and Shire, consultancy fees from Ambra, Eisai, Gelesis, KVK-tech, Nazura, Novo Nordisk, Orexigen, Takeda and Zafgen, and speaker's fees from Abbott, Novo Nordisk, Shire, and Takeda. FG has received research grants from Novo Nordisk, been an advisory board member for Baronova, Curves-Jenny Craig, General Nutrition Corporation, Nerium, Novo Nordisk, Orexigen Therapeutics, Pamlab and Zafgen, received consultancy fees from Basic Research, Eisai, Goodrich & Rosati, Neothetics, Sonsoni, and Wilson, received stock options from Microbiome Therapeutics and Neothetics, has stock in Plensat, and has licenced patents for Neuroquest, as well as other patents issued or pending. DL has received research grants from AstraZeneca, Boehringer Ingelheim, Merck and Novo Nordisk, consultancy fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Roche, Sanofi, Shire and Valiant, and speaker's fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi and Valiant. LVG has received research grants from the EU (Hepadip + Resolve consortium), been an advisory board member or consultant for and received speaker's fees

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610 10.1056/NEJMoa1603827.
611

612 **Table 1. Baseline characteristics of all randomised individuals.***

Characteristic	Liraglutide 3·0 mg (N=1505)	Placebo (N=749)
Sex – n (%)		
Female	1141 (75·8)	573 (76·5)
Male	364 (24·2)	176 (23·5)
Age – years	47·5±11·7	47·3±11·8
Race – n (%)†		
White	1256 (83·5)	628 (83·8)
Black or African-American	146 (9·7)	71 (9·5)
Asian	75 (5·0)	39 (5·2)
American Indian or Alaska Native	5 (0·3)	2 (0·3)
Native Hawaiian or other Pacific Islander	1 (<0·1)	1 (0·1)
Other	22 (1·5)	8 (1·1)
Hispanic or Latino ethnic group – n (%)†	143 (9·5)	70 (9·3)
Weight – kg	107·5±21·6	107·9±21·8
Body-mass index – kg/m^2	38·8±6·4	39·0±6·3
Body-mass index categories – n (%)		
27-29·9 – overweight	39 (2·6)	23 (3·1)
30-34·9 – obesity class I	427 (28·4)	197 (26·3)
35-39·9 – obesity class II	492 (32·7)	245 (32·7)
≥40 – obesity class III	547 (36·3)	284 (37·9)
Waist circumference (all participants) (cm)	116·5±14·4	116·7±13·9
Females (n=1141 *vs* 573)	113·9±13·0	113·8±12·7
Males (n=364 *vs* 176)	124·9±15·0	126·1±13·7)
Glycated haemoglobin – %	5·8±0·3	5·7±0·3
Fasting glucose – mmol/L	5·5±0·6	5·5±0·5

2-hour plasma glucose during OGTT – mmol/L	7·4±1·8	7·4±1·7
Fasting insulin – pmol/L	127·6±76·5	125·1±79·1
Blood pressure – mm Hg		
Systolic	124·7±12·9	125·0±12·8
Diastolic	79·4±8·4	79·8±8·3
Cholesterol – mmol/L		
Total	5·0±19·0	5·1±19·0
LDL-cholesterol	2·9±27·9	3·0±28·0
HDL-cholesterol (all participants)	1·3±26·1	1·3±26·4
Females (n=1139 *vs* 572)	1·4±25·3	1·4±25·1
Males (n=363 *vs* 176)	1·1±22·1	1·1±25·1
VLDL-cholesterol	0·7±46·8	0·7±51·3
Non-HDL cholesterol	3·6±24·9	3·7±25·0
Free fatty acids – mmol/L	0·47±39·6	0·48±38·4
Triglycerides – mmol/L	1·5±54·1	1·5±66·6
Dyslipidaemia – n (%)‡	499 (33·2)	249 (33·2)
Hypertension – n (%)‡	635 (42·2)	312 (41·7)
Dyslipidaemia and hypertension – n (%)‡	317 (21·1)	156 (20·8)

*Data are observed means ± SD or number (%). For fasting insulin and lipids, data are geometric means and coefficients of variation. HDL=high-density lipoprotein. LDL=low-density lipoprotein. OGTT=oral glucose-tolerance test. SD=standard deviation. VLDL=very low density lipoprotein.

†Race and ethnic group were self-reported. Participants from France (44 in all) did not report race or ethnic group.

‡The diagnoses of dyslipidaemia and hypertension were based on reported medical history.

Table 2: Changes in body weight and cardiometabolic risk factors between baseline and week 160.*

Endpoint	Liraglutide 3·0 mg (N=1472)	Placebo (N=738)	Estimated treatment difference, liraglutide *vs* placebo (95% CI)†	p value
Change in body weight				
% of body weight	-6·1±7·3	-1·9±6·3	-4·3 (-4·9 to -3·7)	<0·0001
Kilograms of body weight	-6·5±8·1	-2·0±7·3	-4·6 (-5·3 to -3·9)	<0·0001
Loss of ≥5% body weight (%)‡	49·6	23·7	3·2 (2·6 to 3·9)	<0·0001
Loss of >10% body weight (%)‡	24·8	9·9	3·1 (2·3 to 4·1)	<0·0001
Loss of >15% body weight (%)‡	11·0	3·1	4·0 (2·6 to 6·3)	<0·0001
Body weight-related endpoints				
Body-mass index (kg/m^2)	-2·4±2·9	-0·7±2·6	-1·7 (-1·9 to -1·4)	<0·0001
Waist circumference (all) (cm)	-6·9±8·3	-3·4±7·5	-3·5 (-4·2 to -2·8)	<0·0001
Females (n=1110 *vs* 565)	-7·2±8·3	-3·1±7·3	-4·0 (-4·8 to -3·2)	<0·0001
Males (n=362 *vs* 173)	-5·9±8·1	-4·3±8·0	-1·9 (-3·4 to -0·5)	0·0080
Glycaemic control parameters				
Glycated haemoglobin (% points)	-0·35±0·32	-0·14±0·34	-0·21 (-0·24 to -0·18)	<0·0001
Fasting glucose (mmol/L)	-0·37±0·68	0·05±0·62	-0·41 (-0·46 to -0·36)	<0·0001
Fasting insulin (%)	-8·3	1·7	-10·1 (-14·3 to -5·6)	<0·0001
Fasting C-peptide (%)	-4·1	-3·2	-1·3 (-4·4 to 2·0)	0·44
PG AUC during OGTT (h*mmol/L)	-2·5±6·3	-0·16±7·2	-2·4 (-3·0 to -1·8)	<0·0001
Insulin AUC during OGTT (%)	-0·3	-11·4	11·0 (4·8 to 17·7)	0.0004
C-peptide AUC during OGTT (%)	-1·7	-10·2	8·8 (4·5 to 13·4)	<0·0001
2-hour PG during OGTT (mmol/L)	-1·6±2·1	-0·2±2·2	-1·4 (-1·6 to -1·3)	<0·0001
Vital signs				
Systolic blood pressure (mm Hg)	-3·2±13·0	-0·5±13·7	-2·8 (-3·8 to -1·8)	<0·0001

Diastolic blood pressure (mm Hg)	-2·3±9·0	-1·9±9·3	-0·6 (-1·3 to 0·1)	0·09
Pulse (beats per minute)	2·1±10·0	-0·02±9·8	2·0 (1·2 to 2·7)	<0·0001

*Data are observed means ± SD, unless otherwise stated, using available data from the full-analysis set, with last-observation-carried-forward (LOCF) imputation. For insulin and C-peptide, data were log-transformed for analysis and presented as the relative changes from baseline and relative treatment differences. Post-hoc analysis was performed for weight loss greater than 15%. Changes from baseline to week 172, after a 12-week observational follow-up period, are presented in the appendix p 38.

AUC=area under the curve. OGTT=oral glucose-tolerance test. PG=plasma glucose.

†Estimated treatment differences for all endpoints, except pulse, are from an analysis of covariance with available data from the full-analysis set, with LOCF imputation. The full-analysis set comprised individuals who underwent randomisation, were exposed to at least one treatment dose, and had at least one assessment after randomisation (44 individuals were excluded from the full-analysis set: 38 due to lack of an assessment and 6 due to no exposure). Data on pulse are based on the safety-analysis set, which included all individuals who underwent randomisation and were exposed to at least one treatment dose.

‡Loss of at least 5%, more than 10%, and more than 15% of body weight were analysed by logistic regression with data from the full-analysis set (n=1467 in the liraglutide group and n=734 in the placebo group), with LOCF imputation, and are presented as the proportions of participants (%) and odds ratios.

Table 3: Adverse events and serious adverse events.*

Event	Liraglutide 3·0 mg (N=1501)			Placebo (N=747)		
	Participants n (%)	Events (n)	Event rate per 100 years of observation	Participants n (%)	Events (n)	Event rate per 100 years of observation
Total number of adverse events	1421 (94·7)	15759	489·6	668 (89·4)	6350	431·9
Adverse events in ≥5% of individuals	1322 (88·1)	8240	256·0	579 (77·5)	2837	193·0
Gastrointestinal disorders						
Nausea	614 (40·9)	961	29·9	125 (16·7)	166	11·3
Diarrhoea	379 (25·2)	610	19·0	107 (14·3)	145	9·9
Constipation	331 (22·1)	419	13·0	85 (11·4)	100	6·8
Vomiting	295 (19·7)	472	14·7	40 (5·4)	53	3·6
Dyspepsia	154 (10·3)	192	6·0	35 (4·7)	40	2·7
Abdominal pain	114 (7·6)	152	4·7	38 (5·1)	50	3·4
Abdominal pain upper	112 (7·5)	139	4·3	39 (5·2)	47	3·2
Gastroesophageal reflex disease	98 (6·5)	110	3·4	18 (2·4)	20	1·4
Eructation	85 (5·7)	95	3·0	4 (0·5)	4	0·3
Flatulence	81 (5·4)	94	2·9	20 (2·7)	23	1·6

General disorders and administration site conditions						
Fatigue	152 (10·1)	188	5·8	57 (7·6)	66	4·5
Injection site haematoma	91 (6·1)	102	3·2	60 (8·0)	68	4·6
Oedema peripheral	53 (3·5)	60	1·9	47 (6·3)	58	3·9
Infections and infestations						
Nasopharyngitis	396 (26·4)	755	23·5	209 (28·0)	405	27·5
Upper respiratory tract infection	235 (15·7)	388	12·1	119 (15·9)	212	14·4
Influenza	181 (12·1)	252	7·8	79 (10·6)	122	8·3
Gastroenteritis	142 (9·3)	173	5·4	46 (6·2)	53	3·6
Sinusitis	128 (8·5)	173	5·4	65 (8·7)	111	7·6
Urinary tract infection	121 (8·1)	176	5·5	43 (5·8)	62	4·2
Bronchitis	114 (7·6)	139	4·3	62 (8·3)	82	5·6
Investigations						
Lipase increased	146 (9·7)	208	6·5	23 (3·1)	25	1·7
Metabolism and nutrition disorders						
Decreased appetite	164 (10·9)	176	5·5	26 (3·5)	27	1·8
Musculoskeletal and connective tissue disorders						
Back pain	200 (13·3)	287	8·9	120 (16·1)	162	11·0
Arthralgia	184 (12·3)	229	7·1	97 (13·0)	135	9·2

Pain in extremity	108 (7·2)	127	3·9	54 (7·2)	64	4·4
Nervous system disorders						
Headache	270 (18·0)	427	13·3	122 (16·3)	219	14·9
Dizziness	146 (9·7)	195	6·1	54 (7·2)	72	4·9
Respiratory, thoracic and mediastinal disorders						
Cough	111 (7·4)	132	4·1	59 (7·9)	85	5·8
Oropharyngeal pain	74 (4·9)	81	2·5	44 (5·9)	52	3·5
Vascular disorders						
Hypertension	75 (5·0)	87	2·7	47 (6·3)	57	3·9
Total number of serious adverse events	227 (15·1)	350	10·9	96 (12·9)	143	9·7
Serious adverse events in ≥0·4% of individuals						
Cholelithiasis	20 (1·3)	21	0·7	6 (0·8)	6	0·4
Cholecystitis acute	9 (0·6)	9	0·3	1 (0·1)	1	<0·1
Cholecystitis	6 (0·4)	6	0·2	0	0	0
Osteoarthritis	12 (0·8)	14	0·4	5 (0·7)	6	0·4
Intervertebral disc protrusion	6 (0·4)	6	0·2	1 (0·1)	1	<0·1
Back pain	4 (0·3)	4	0·1	3 (0·4)	3	0·2
Fall	0	0	0	4 (0·5)	4	0·3
Cellulitis	3 (0·2)	3	0·1	3 (0·4)	3	0·2

Obesity	1 (<0·1)	1	<0·1	3 (0·4)	3	0·2

*Adverse events (grouped by their system organ class) and serious adverse events that occurred up to and including week 162 among individuals in the safety-analysis set are included and are presented by their preferred terms from the Medical Dictionary for Regulatory Activities. Events are included if they had an onset date on or after the first day that study drug was administered and no later than 14 days after the last day the study drug was administered.

Figure legends

Figure 1: Trial flow diagram

The 3-year trial population consisted of all individuals with prediabetes, except for those that were incorrectly stratified: 37 entered the re-randomised period of the 56-week part of the trial, reported previously,[15] and are not included below, and 6 with normoglycaemia entered the 3-year part of the trial and are included below.

Figure 2: Liraglutide 3·0 mg and glycaemic status.

Panel A shows Kaplan-Meier estimates of the proportion of participants who received a diagnosis of type 2 diabetes during the course of the trial. Glycaemic status was defined according to American Diabetes Association 2010 criteria.[21] All individuals for whom diabetes was diagnosed had prediabetes at screening, except for one in the placebo group, who had normoglycaemia. The numbers along the graph lines show the cumulative number of individuals who received a diagnosis of diabetes over the course of 172 weeks. The time until 1% were diagnosed with diabetes was 90 weeks with liraglutide 3·0 mg and 24 weeks with placebo (post-hoc analysis). Participants were off treatment during the 12-week observational follow-up period, but still on diet and exercise. The numbers of participants at risk (i.e., remaining in the trial) are shown below the week numbers on the x axis. Panel B shows the proportion of participants with prediabetes at screening who regressed to having normoglycaemia over the course of 172 weeks. Panel C shows changes in fasting plasma glucose (left) and fasting serum insulin (right) over the course of 172 weeks. Relative changes in fasting glucose (%) are shown in the appendix p 15. Changes in fasting glucose translated into a similar corresponding pattern for glycated haemoglobin changes. Changes in HOMA-IR followed a similar pattern as fasting insulin changes. Data shown are the observed means with standard error bars (fasting glucose) or with 95% confidence intervals (fasting insulin), and the separate symbols represent the 160-week changes using last-observation-carried-forward (LOCF) imputation.

Figure 3: Liraglutide 3·0 mg and body weight.

Panel A shows the mean relative change in body weight for individuals in the full-analysis set who completed each scheduled visit. Data shown are the observed means with standard error bars, and the separate symbols in the boxes represent the 160-week weight change using last-observation-carried-forward (LOCF) imputation. The full-analysis set comprised individuals who underwent randomisation, were exposed to at least one treatment dose, and had at least one assessment after randomisation (44 participants were excluded from the full-analysis set: 38 due to lack of an assessment and 6 due to no exposure). Panel B shows the proportions of participants who lost at least 5%, more than 10%, and more than 15% of their baseline body weight at week 160. Data shown are the observed means for the full-analysis set, with LOCF. Findings from a logistic-regression analysis showed an odds ratio of 3·2 (95% CI, 2·6 to 3·9) for at least 5% weight loss and an odds ratio of 3·1 (95% CI, 2·3 to 4·1) for more than 10% weight loss. The analysis for achieving more than 15% weight loss was performed post-hoc (odds ratio 4·0 [95% CI, 2·6 to 6·3]).