3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial

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Summary

Background **Liraglutide 3·0 mg was shown to reduce bodyweight and improve glucose metabolism after the 56-week period of this trial, one of four trials in the SCALE programme. In the 3-year assessment of the SCALE Obesity and Prediabetes trial we aimed to evaluate the proportion of individuals with prediabetes who were diagnosed with type 2 diabetes.**

Methods **In this randomised, double-blind, placebo-controlled trial, adults with prediabetes and a body-mass index of at least 30 kg/m², or at least 27 kg/m² with comorbidities, were randomised 2:1, using a telephone or web-based system, to once-daily subcutaneous liraglutide 3·0 mg or matched placebo, as an adjunct to a reduced-calorie diet and increased physical activity. Time to diabetes onset by 160 weeks was the primary outcome, evaluated in all randomised treated individuals with at least one post-baseline assessment. The trial was conducted at 191 clinical research sites in 27 countries and is registered with ClinicalTrials.gov, number NCT01272219.**

Findings **The study ran between June 1, 2011, and March 2, 2015. We randomly assigned 2254 patients to receive liraglutide (n=1505) or placebo (n=749). 1128 (50%) participants completed the study up to week 160, after withdrawal of 714 (47%) participants in the liraglutide group and 412 (55%) participants in the placebo group. By week 160, 26 (2%) of 1472 individuals in the liraglutide group versus 46 (6%) of 738 in the placebo group were diagnosed with diabetes while on treatment. The mean time from randomisation to diagnosis was 99 (SD 47) weeks for the 26 individuals in the liraglutide group versus 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 with a hazard ratio of 0·21 (95% CI 0·13–0·34). Liraglutide induced greater weight loss than placebo at week 160 (–6·1 [SD 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 227 (15%) of 1501 randomised treated individuals in the liraglutide group versus 96 (13%) of 747 individuals in the placebo group.**

Interpretation **In this trial, we provide results for 3 years of treatment, with the limitation that withdrawn individuals were not followed up after discontinuation. Liraglutide 3·0 mg might provide health benefits in terms of reduced risk of diabetes in individuals with obesity and prediabetes.**

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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 each year 5–10% of people with prediabetes develop diabetes.[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 period of the current trial was reported previously[11] and evaluated the efficacy and safety of liraglutide 3·0 mg for weight loss after 56 weeks. Liraglutide was associated with 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 this report.

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

Methods

SCALE Obesity and Prediabetes was conducted as part of a large global phase 3a clinical development programme of four randomised, double-blind, placebo-controlled trials with more than 5000 participants that was designed to investigate the efficacy and safety of liraglutide 3·0 mg,

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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 articles, 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 done for a period of 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 for 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 with 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, might 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 or obesity.

a glucagon-like peptide-1 (GLP-1) receptor agonist, for weight management.[11–14] We did this study at 191 clinical research sites in 27 countries in Europe, North America, South America, Asia, Africa, and Australia (appendix p 9). The protocol was approved by local ethics committees or institutional review boards. We did the study 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] From week 56, individuals with prediabetes at screening continued on treatment for a further 2 years, with a 12-week off-treatment follow-up period.

See Online for appendix

Participants

We enrolled adults aged 18 years or older with stable bodyweight and a body-mass index (BMI) of at least 30 kg/m², or at least 27 kg/m² with treated or untreated dyslipidaemia, or hypertension, or both. Key exclusion criteria were type 1 or type 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. Each individual provided written informed consent before participation.

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 funder-provided telephone or web-based system. The funder generated the random allocation sequence, and the trial investigators enrolled individuals, and assigned them to treatment. Participants were stratified at screening by BMI (≥30 kg/m² *vs* <30 kg/m²) and according to whether or not they had prediabetes. Those individuals who had prediabetes and completed 56 weeks of treatment continued for an additional 104 weeks of treatment, allowing for a total of 160 weeks of treatment. Participants without prediabetes were on treatment for 56 weeks, followed by a 12-week re-randomised period; results for this period of the trial have been reported previously.[11] We did not include participants without prediabetes in this trial, thus the stratification factor is not included in the statistical analysis. Participants and investigators were masked to treatment allocation during the entire trial (160 weeks plus the 12-week off-treatment follow-up period) and visually identical devices were used for subcutaneous injection, whereas the funder was unmasked to treatment allocation at week 56.

Procedures

This report covers participants with prediabetes who were randomised to treatment for the full 3-year period. We diagnosed participants with prediabetes on the basis of fulfilment of at least one of the three American Diabetes Association (ADA) 2010 criteria: 5·7–6·4% glycated haemoglobin, or fasting plasma glucose concentration between 5·6 mmol/L and 6·9 mmol/L, or 2-h post-challenge plasma glucose concentration between 7·8 mmol/L and 11·0 mmol/L.[17] Diagnosis of diabetes was confirmed by two consecutive measurements of the same type of criteria: at least 6·5% glycated haemoglobin, or at least 7·0 mmol/L fasting plasma glucose concentration, or at least 11·1 mmol/L 2-h post-challenge plasma glucose concentration.[17] Liraglutide and placebo were provided in prefilled FlexPen devices (Novo Nordisk, Bagsværd, Denmark), starting at 0·6 mg with weekly 0·6 mg incremental increases to 3·0 mg. All trial participants received standardised lifestyle intervention counselling from randomisation to end of follow-up, about once a month (appendix p 3). Participants were advised to achieve at least 150 minutes of physical activity per week and to

reduce their daily energy intake to 500 kcal below their individualised energy requirement. Additional methodology, including timing of assessments, is described in the appendix p 3.

Outcomes

Our primary objective was to evaluate the proportion of individuals with type 2 diabetes at 160 weeks, with time to onset of diabetes as the primary endpoint. The trial had four coprimary endpoints, three of which were assessed at week 56—mean weight loss, and the proportion of participants losing at least 5% of their baseline bodyweight, and more than 10% of their baseline bodyweight.[11] Secondary endpoints included changes from baseline to week 160 in glycaemic control parameters, mean and categorical bodyweight, BMI, waist circumference, cardiometabolic biomarkers, vital signs, and health-related quality of life—assessed using validated questionnaires.[18–20]

Specific adverse events with increased prevalence among people with obesity, or of relevance to the GLP-1 drug class, were assessed (appendix p 33). Independent medical experts prospectively adjudicated nine 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 target 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 for 3 years. This size 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. Superiority for liraglutide 3·0 mg versus 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 versus no" assessed in completers during the 160 weeks of treatment and analysed with a two-sided χ^2 test with a 5% significance level.

We assumed that the annual conversion rate to type 2 diabetes of the individuals with prediabetes would be 7·0% in the placebo group and 2·1% in the liraglutide 3·0 mg group—ie, 70% lower in the liraglutide 3·0 mg group. 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 dropout rate during the 160 weeks of treatment was assumed to be 65% in both groups.

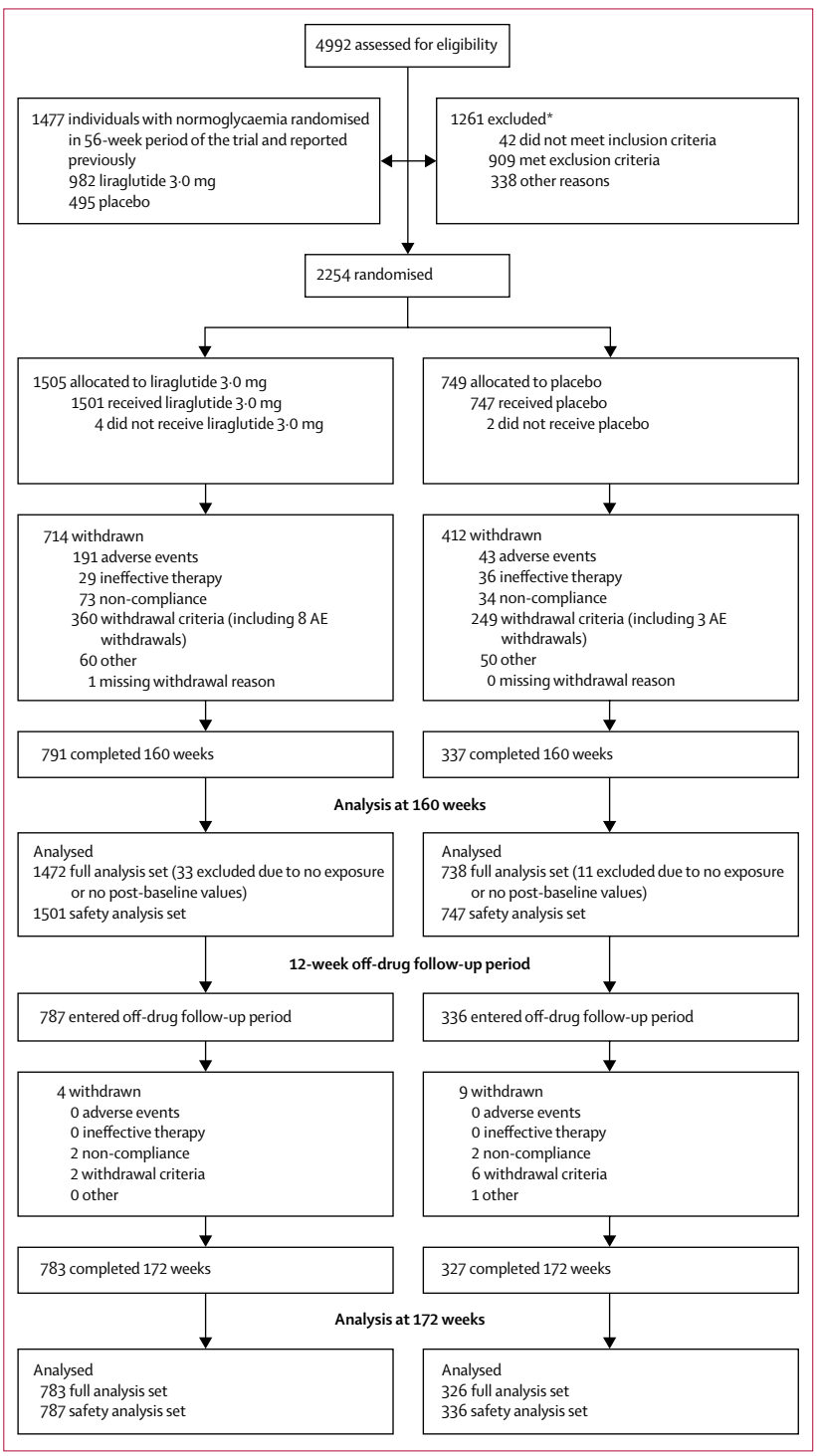

***Figure 1*: Trial profile**

AE=adverse event. *Individuals could be excluded for more than one criterion. 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,[11] and are not included, and six with normoglycaemia entered the 3-year part of the trial and are included.

	Liraglutide 3·0 mg (n=1505)	Placebo (n=749)
Sex		
Female	1141 (76%)	573 (77%)
Male	364 (24%)	176 (23%)
Age (years)	47·5 (11·7)	47·3 (11·8)
Race*		
White	1256 (83%)	628 (84%)
Black or African-American	146 (10%)	71 (9%)
Asian	75 (5%)	39 (5%)
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*	143 (10%)	70 (9%)
Weight (kg)	107·5 (21·6)	107·9 (21·8)
BMI (kg/m^2)	38·8 (6·4)	39·0 (6·3)
BMI category		
27–29·9, overweight	39 (3%)	23 (3%)
30–34·9, obesity class 1	427 (28%)	197 (26%)
35–39·9, obesity class 2	492 (33%)	245 (33%)
≥40, obesity class 3	547 (36%)	284 (38%)
Waist circumference (cm)		
Overall	116·5 (14·4)	116·7 (13·9)
Women	113·9 (13·0)	113·8 (12·7)
Men	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-h 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		
Overall	1·3 (26·1)	1·3 (26·4)
Women (n=1139 *vs* 572)	1·4 (25·3)	1·4 (25·1)
Men (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†	499 (33%)	249 (33%)
Hypertension†	635 (42%)	312 (42%)
Dyslipidaemia and hypertension†	317 (21%)	156 (21%)

Data are observed n (%) or mean (SD). For fasting insulin and lipids, data are geometric means and coefficients of variation. BMI=body-mass index. HDL=high-density lipoprotein. LDL=low-density lipoprotein. OGTT=oral glucose-tolerance test. 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 1*: Baseline characteristics of all randomised individuals**

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. We imputed missing values 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. We analysed mean changes in continuous endpoints using an analysis of covariance and categorical changes for dichotomous endpoints with logistic regression. We did sensitivity analyses 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 we specified additional post-hoc analyses to further address the issue. We did a post-hoc Cox regression analysis at week 172, in which we imputed diabetes status for all withdrawn individuals. We 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 we assumed that none of those withdrawn in the placebo group did so. We 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.

We did five prespecified subgroup analyses to investigate whether baseline BMI (four categories) had any effect on weight or glycated haemoglobin level (appendix p 4). For all statistical analyses in the trial we used SAS software, version 9.3. Additional statistical analysis details are included in the appendix. The trial is registered with ClinicalTrials.gov, number NCT01272219.

Role of the funding source

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

Results

The study was done between June 1, 2011, and March 2, 2015. 2254 individuals with prediabetes, based on ADA 2010 criteria,[17] were randomised to 3 years of lifestyle intervention plus treatment with liraglutide

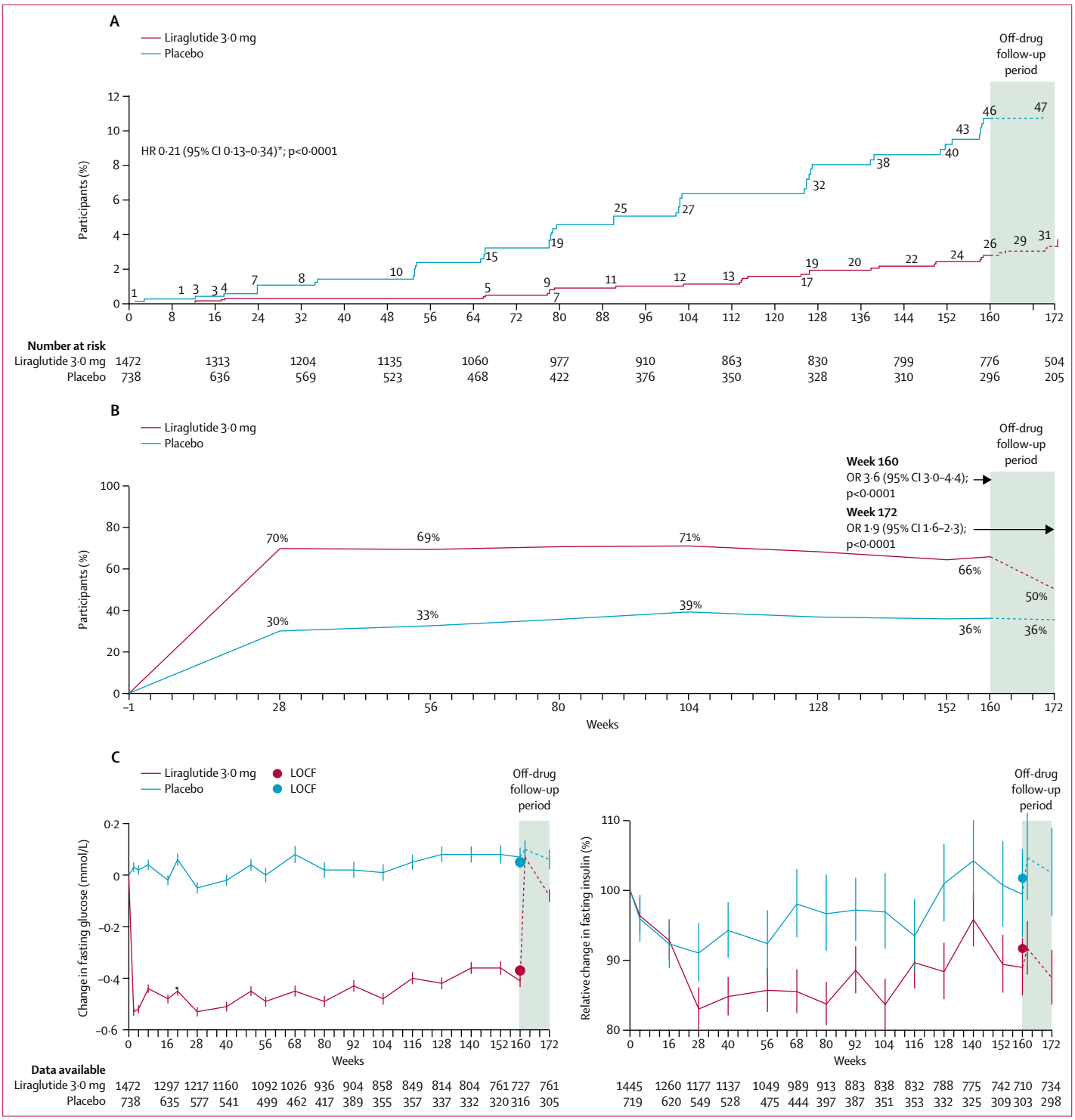

***Figure 2*: Liraglutide 3·0 mg and glycaemic status**

LOCF=last-observation-carried-forward. OR=odds ratio. *Derived from the primary Weibull analysis. (A) 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.[17] 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. (B) Proportion of participants with prediabetes at screening who regressed to having normoglycaemia during the 172 weeks. (C) Changes in fasting plasma glucose and fasting serum insulin during the 172 weeks. 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. Relative changes in fasting glucose (%) are shown in the appendix p 15. Data shown are the observed means with SE (fasting glucose) or with 95% CI (fasting insulin).

	Liraglutide 3·0 mg (n=1472)	Placebo (n=738)	Estimated treatment difference, liraglutide *vs* placebo (95% CI)*	p value
Change in bodyweight				
Percentage of bodyweight	−6·1% (7·3)	−1·9% (6·3)	−4·3 (−4·9 to −3·7)	<0·0001
Kg of bodyweight	−6·5 (8·1)	−2·0 (7·3)	−4·6 (−5·3 to −3·9)	<0·0001
Loss of ≥5% bodyweight (%)†	49·6%	23·7%	3·2 (2·6 to 3·9)	<0·0001
Loss of >10% bodyweight (%)†	24·8%	9·9%	3·1 (2·3 to 4·1)	<0·0001
Loss of >15% bodyweight (%)†	11·0%	3·1%	4·0 (2·6 to 6·3)	<0·0001
Bodyweight-related endpoints				
BMI (kg/m²)	−2·4 (2·9)	−0·7 (2·6)	−1·7 (−1·9 to −1·4)	<0·0001
Waist circumference (cm)	−6·9 (8·3)	−3·4 (7·5)	−3·5 (−4·2 to −2·8)	<0·0001
Women (n=1110 *vs* 565)	−7·2 (8·3)	−3·1 (7·3)	−4·0 (−4·8 to −3·2)	<0·0001
Men (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-h 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
Heart rate (beats per min)	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 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. BMI=body-mass index. AUC=area under the curve. LOCF=last-observation-carried-forward. OGTT=oral glucose-tolerance test. PG=plasma glucose. *Estimated treatment differences for all endpoints, except heart rate, 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 for heart rate 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% (post-hoc) of bodyweight 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 2*: Changes in bodyweight and cardiometabolic risk factors between baseline and week 160**

3·0 mg (n=1505) or placebo (n=749; figure 1). In the liraglutide group, 791 (53%) of 1505 participants completed 160 weeks of treatment, as did 337 (45%) of 749 participants in the placebo group. A greater proportion of participants in the liraglutide group withdrew owing to adverse events (199 [13%] of 1501 participants) than did in the placebo group (46 [6%] of 747). A smaller proportion of participants in the liraglutide group withdrew owing to ineffective therapy (29 [2%] of 1505 participants) than did in the placebo group (36 [5%] of 749) or withdrew their consent to remain in the trial (324 [22%] of 1505 participants for liraglutide *vs* 233 [31%] of 749 for placebo). Individuals who withdrew were slightly younger than the average trial population; otherwise, we observed no noteworthy differences in baseline characteristics or medical history (table 1; appendix p 5). The full-analysis set comprised 1472 participants in the liraglutide group and 738 participants in the placebo group (figure 1).

By week 160, 26 (2%) of 1472 individuals in the liraglutide group were diagnosed with diabetes while on treatment compared with 46 (6%) of 738 in the placebo group. We calculated the cumulative probability of a diagnosis of diabetes taking censoring into account: 3% of individuals in the liraglutide group were diagnosed with diabetes by week 160, compared with 11% in the placebo group (figure 2).

For the 26 individuals in the liraglutide group, the mean time from randomisation to diagnosis was about 99 (SD 47) weeks compared with 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% CI 1·9–3·9, p<0·0001; appendix p 10), corresponding with a hazard ratio (HR) of 0·21 (95% CI 0·13–0·34; p<0·0001).

Results were consistent across sensitivity analyses, and the treatment difference remained statistically significant after the 12-week off-treatment follow-up period, with five additional individuals being diagnosed with diabetes with liraglutide, compared with one individual with placebo (appendix p 11). We did an additional post-hoc analysis at week 172 to address 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 (HR 0·34, 95% CI 0·22–0·53, p<0·0001).

While on treatment, more individuals in the liraglutide 3·0 mg group (970 [66%] of 1472) had regressed from prediabetes to normoglycaemia by week 160 than had individuals in the placebo group (268 [36%] of 738; odds ratio [OR] 3·6, 95% CI 3·0–4·4, p<0·0001, figure 2), corresponding with a number needed to treat of three. After a 12-week treatment cessation, some individuals in the liraglutide group reverted to prediabetes but 740 (50%) of 1472 randomised and exposed individuals still had normoglycaemia at week 172 compared with 263 (36%) of 738 of those individuals in the placebo group (1·9, 1·6–2·3, p<0·0001).

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

Liraglutide induced greater weight loss than placebo at week 160 while on treatment (–6·1% [SD 7·3] for

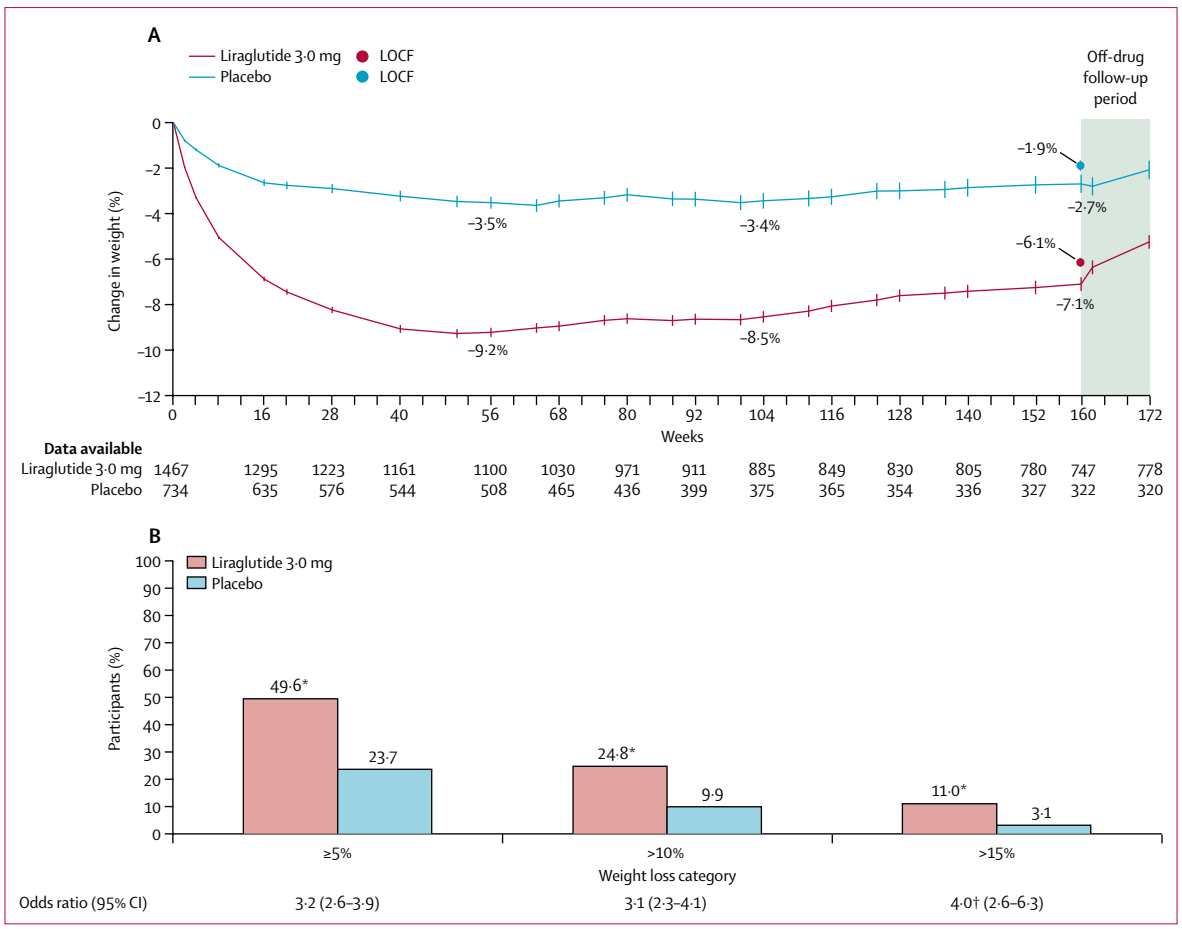

***Figure 3*: Liraglutide 3·0 mg and bodyweight**

Data shown are the observed means for the full-analysis set, with LOCF. LOCF=last-observation-carried-forward. OR=odds ratio. *p<0·0001. †Analysis for >15% weight loss was done post hoc. (A) Mean relative change in bodyweight for individuals in the full-analysis set who completed each scheduled visit. Data shown are the observed means with SE. (B) The proportion of participants who lost at least 5%, more than 10%, and more than 15% of their baseline bodyweight at week 160.

liraglutide *vs* –1·9% [6·3] for placebo; 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 3). Greater mean and categorical weight loss were achieved in the liraglutide group than in the placebo group (table 2, 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).

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

More than 90% of individuals in each treatment group who were diagnosed with diabetes lost less bodyweight than the treatment group mean at the time of diagnosis (appendix p 20).

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

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

Gastrointestinal disorders, 93% of which were mild or moderate in severity, were the most common side-effects in the liraglutide 3·0 mg group (table 3), and also the most common cause of withdrawal (118 [8%] of 1501 individuals in the liraglutide group *vs* 11 [2%] of 747 in the placebo group; adverse events leading to discontinuation of ≥0·2% individuals in either group are in the appendix p 23). More serious adverse events were reported in the liraglutide group than in the placebo group (table 3).

	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 (95%)	15759	489·6	668 (89%)	6350	431·9
Adverse events in ≥5% of individuals	1322 (88%)	8240	256·0	579 (78%)	2837	193·0
Gastrointestinal disorders						
Nausea	614 (41%)	961	29·9	125 (17%)	166	11·3
Diarrhoea	379 (25%)	610	19·0	107 (14%)	145	9·9
Constipation	331 (22%)	419	13·0	85 (11%)	100	6·8
Vomiting	295 (20%)	472	14·7	40 (5%)	53	3·6
Dyspepsia	154 (10%)	192	6·0	35 (5%)	40	2·7
Abdominal pain	114 (8%)	152	4·7	38 (5%)	50	3·4
Upper abdominal pain	112 (8%)	139	4·3	39 (5%)	47	3·2
Gastro-oesophageal reflux disease	98 (7%)	110	3·4	18 (2%)	20	1·4
Eructation	85 (6%)	95	3·0	4 (<1%)	4	0·3
Flatulence	81 (5%)	94	2·9	20 (3%)	23	1·6
General disorders and administration site conditions						
Fatigue	152 (10%)	188	5·8	57 (8%)	66	4·5
Injection site haematoma	91 (6%)	102	3·2	60 (8%)	68	4·6
Oedema peripheral	53 (4%)	60	1·9	47 (6%)	58	3·9
Infections and infestations						
Nasopharyngitis	396 (26%)	755	23·5	209 (28%)	405	27·5
Upper respiratory tract infection	235 (16%)	388	12·1	119 (16%)	212	14·4
Influenza	181 (12%)	252	7·8	79 (11%)	122	8·3
Gastroenteritis	142 (9%)	173	5·4	46 (6%)	53	3·6
Sinusitis	128 (9%)	173	5·4	65 (9%)	111	7·6
Urinary tract infection	121 (8%)	176	5·5	43 (6%)	62	4·2
Bronchitis	114 (8%)	139	4·3	62 (8%)	82	5·6
Investigations						
Lipase increased	146 (10%)	208	6·5	23 (3%)	25	1·7
Metabolism and nutrition disorders						
Decreased appetite	164 (11%)	176	5·5	26 (4%)	27	1·8

(Table 3 continues on next page)

Adverse event incidence generally declined during the trial (appendix p 25). Four individuals died—two in the liraglutide group (due to cardiac arrest and metastatic cholangiocarcinoma) and two in the placebo group (pulmonary failure and cancer, primary tumour unknown).

As previously reported,[11] gallbladder-related events were more common with liraglutide than with placebo (occurring in 74 [5%] of 1501 individuals for liraglutide *vs* 13 of [2%] 747 individuals for placebo and 2·9 events per 100 person-years of observation [PYO] for liraglutide and 1·2 events per 100 PYO for placebo). 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 (appendix p 5). Overall, 12 pancreatitis cases (eleven graded as mild, one as moderately severe),[22] were confirmed by adjudication, occurring in ten (0·7%) of 1501 individuals in the liraglutide group (0·3 events per 100 PYO), and in two (0·3%) of 747 placebo-group individuals (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 concentrations at least 3 times the upper limit of the normal range or gallstones on imaging (appendix p 41).[23]

The incidence of adjudicated and confirmed neoplasms was similar in both treatment groups (2·2 events per 100 PYO for liraglutide *vs* 2·4 for placebo). As seen in the 56-week period of the trial,[11] more cases of malignant and premalignant breast neoplasms were reported with liraglutide: ten malignant and pre-malignant breast neoplasms were observed 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 neoplasms had above-average weight loss (appendix p 42). We observed no cases of medullary thyroid carcinoma or C-cell hyperplasia. Liraglutide treatment did not increase median serum calcitonin concentrations.

Resting heart rate increased in the liraglutide group at week 160 by about 2 beats per min (table 2). Increases of more than 5, 10, and 20 beats per min on at least two consecutive visits are shown in the appendix p 42. Prespecified cardiovascular events (appendix p 33) occurred in 242 (16%) of 1501 individuals in the liraglutide group (12·1 events per 100 PYO) compared with 142 (19%) of 747 individuals in the placebo group (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 events per 100 PYO for liraglutide *vs* 0·20 for placebo).

We observed no between-group differences 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. One suicide attempt occurred in each 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 reduce relative risk of diabetes by 40–70%, and enhance insulin sensitivity and β-cell function in individuals with prediabetes at high-risk of developing type 2 diabetes.[4] In both the Diabetes Prevention Program (DPP)[6] and Finnish Diabetes Prevention Study (DPS),[7] lifestyle intervention compared with placebo was associated with a 58% reduction in the risk of diabetes after 3 years. 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, 4 years of treatment with orlistat was associated with a 37% reduced risk of diabetes, concomitant with a mean 5·8 kg weight loss compared with 3·0 kg with placebo.[8] Additionally, 2 years of treatment with phentermine/topiramate provided a reduction versus placebo in the annualised incident rate of type 2 diabetes of 71% or 79%, depending on the dose, in individuals with prediabetes, or metabolic syndrome, or both.[9] Mean weight loss was 10·9% and 12·1% for the two phentermine/topiramate doses versus 2·5% with placebo. Pioglitazone reduced the conversion of impaired glucose tolerance to type 2 diabetes by 72% compared with placebo after a median follow-up period of 2·4 years, although it was associated with significant weight gain.[24] In this study, we address 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 a risk reduction of about 80% relative to placebo (HR 0·21, 95% CI 0·13–0·34) in the onset of type 2 diabetes. However, our primary analysis did not take into account the lack of follow-up information for withdrawn individuals. Therefore, we did a post-hoc analysis that made assumptions about those withdrawn individuals, which provided a risk reduction of about 66% relative to placebo (HR 0·34, 95% CI 0·22–0·53).

Whether the lack of a response to treatment for some individuals in the current trial was a result of individual participant characteristics, or due to other factors, is unclear. Most individuals who were diagnosed with diabetes lost less bodyweight 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 for 160 weeks, and was associated with a lower risk of diabetes.[5] Similar results have been observed previously with liraglutide and other GLP-1 receptor agonists.[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 show 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 with the DPP, which recruited individuals with impaired fasting glucose and impaired glucose tolerance, we enrolled a lower-risk, less progressed population because we allowed for fulfilment of any one of three ADA 2010 diagnostic criteria[17] at enrolment. This difference, together with the weight loss achieved, might partly explain the lower diabetes incidence of 11% observed in our lifestyle placebo group, compared with 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 bodyweight, 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

	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
(Continued from previous page)						
Musculoskeletal and connective tissue disorders						
Back pain	200 (13%)	287	8·9	120 (16%)	162	11·0
Arthralgia	184 (12%)	229	7·1	97 (13%)	135	9·2
Pain in extremity	108 (7%)	127	3·9	54 (7%)	64	4·4
Nervous system disorders						
Headache	270 (18%)	427	13·3	122 (16%)	219	14·9
Dizziness	146 (10%)	195	6·1	54 (7%)	72	4·9
Respiratory, thoracic, and mediastinal disorders						
Cough	111 (7%)	132	4·1	59 (8%)	85	5·8
Oropharyngeal pain	74 (5%)	81	2·5	44 (6%)	52	3·5
Vascular disorders						
Hypertension	75 (5%)	87	2·7	47 (6%)	57	3·9
Total number of serious adverse events	227 (15%)	350	10·9	96 (13%)	143	9·7
Serious adverse events in ≥0·4% of individuals						
Cholelithiasis	20 (1%)	21	0·7	6 (1%)	6	0·4
Cholecystitis acute	9 (1%)	9	0·3	1 (<1%)	1	<0·1
Cholecystitis	6 (<1%)	6	0·2	0	0	0
Osteoarthritis	12 (1%)	14	0·4	5 (1%)	6	0·4
Intervertebral disc protrusion	6 (<1%)	6	0·2	1 (<1%)	1	<0·1
Back pain	4 (<1%)	4	0·1	3 (<1%)	3	0·2
Fall	0	0	0	4 (1%)	4	0·3
Cellulitis	3 (<1%)	3	0·1	3 (<1%)	3	0·2
Obesity	1 (<1%)	1	<0·1	3 (<1%)	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 the study drug was administered and no later than 14 days after the last day the study drug was administered.

Table 3: **Adverse events and serious adverse events**

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. Because the participants lost more weight with liraglutide than placebo, future studies should quantify the relative contributions of weight loss versus the direct effects of liraglutide on glucose homoeostasis 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 during the 3 years in the liraglutide group, is 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 with 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 could have increased detection. The underlying mechanism for the increased resting heart rate with liraglutide is also unknown; a direct chronotropic effect of liraglutide on the sinoatrial node has been suggested.[32]

The prevalence of obesity and type 2 diabetes and their associated major comorbidities and health-care costs highlight the need for effective treatments. Adverse events in our trial were mostly predictable on the basis of the known effects of GLP-1 receptor agonists, including more gastrointestinal disorders with liraglutide than with placebo, notably nausea, diarrhoea, constipation, and vomiting. The increased heart rate associated with liraglutide, as observed with other GLP-1 receptor agonists, did not lead to an increased cardiovascular risk in a large cardiovascular-outcomes trial with liraglutide doses up to 1·8 mg.[33] Generally, liraglutide has a well-documented safety profile.[11–14,26,33] Although 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 this trial indicate 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 we provide in this trial 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 is comparable with 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 showed that the risk of diabetes was about 66% lower with liraglutide compared with placebo, the magnitude of which compares with the 58% lower risk observed in the DPP[6] and DPP Outcomes Study,[28] with higher retention and longer follow-up.

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 receptor agonist, 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 (Larix, Copenhagen, Denmark 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

CWlR 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 licensed patents for Neuroquest, as well as other patents issued or pending. DCWL 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. LG has received research grants from the EU (Hepadip + Resolve consortium), been an advisory board member or consultant for and received speaker's fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Johnson & Johnson, Merck, Novartis, Novo Nordisk, and Sanofi, and he has received speaker's fees from Servier. RVO has been an advisory board member for Boehringer Ingelheim, Eli Lilly, Janssen-Cilag,

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