Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Le Roux C, Astrup A, Fujioka K, Greenway F, Lau DCW, Van Gaal L, Ortiz RV, Wilding J, Skjøth TV, Shapiro Manning L, and Pi-Sunyer X.
3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial

Table of contents

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Supplemental methods

The 3-year trial population consisted of 2248 individuals with prediabetes, plus an additional 6 individuals with normoglycaemia who entered the 3-year arm. 37 individuals with prediabetes at screening who continued into the re-randomised period of the 56-week trial were not included in the analyses for the 3-year trial, but were included in the 56-week trial. The 43 individuals just described were incorrectly stratified in the 56-week trial, and are described in protocol deviations in the trial report.

Diet and exercise counselling

Standardised dietary and exercise counselling was provided, in individual or group sessions, up to week 172. Participants were advised to increase their physical activity to at least 150 minutes per week and to reduce their daily energy intake to 500 kcal below their individualised energy requirement based on World Health Organization estimates and an 'average' physical activity factor of 1·3.[1] The recommended macronutrient distribution was 30% of energy from fat, 20% from protein, and 50% from carbohydrate. To encourage adherence, pedometers were provided and a 3-day food diary was dispensed for completion every second month. Participants were also weighed at each visit and supported to maintain their lifestyle changes.

Clinical assessments and procedures

If an individual developed diabetes during the trial,[2] self-monitoring of plasma glucose on a regular basis was encouraged at the discretion of the investigator, using a glucose meter supplied by Novo Nordisk. A sufficient amount of test strips, lancets and calibration solutions and a diabetes diary were supplied together with the glucose meter. Furthermore, individuals were to receive the best possible care if they developed diabetes. They were not withdrawn from the trial, unless the investigator recommended use of insulin, a glucagon-like peptide-1 (GLP-1) receptor agonist or dipeptidyl peptidase-IV (DPP-IV) inhibitor for treatment, in which case the individual had to be withdrawn. No subsequent oral glucose-tolerance tests were performed for individuals diagnosed with diabetes.

Measures of insulin resistance (HOMA-IR, Matsuda index[3]) and beta-cell function (HOMA-B, disposition index) were derived from glucose, insulin, and C-peptide data collected in connection with the oral glucose-tolerance test. The insulin secretion ratio based on C-peptide was calculated as the ratio of the estimated insulin secreted during the first 120 minutes following glucose administration (using deconvolution[4]) and the corresponding glucose area under the concentration–time curve (AUC).[5] The disposition index was calculated as the product of the insulin secretion ratio based on C-peptide and the Matsuda index.[6]

Health-related quality of life was assessed using the 36-Item Short-Form Health Survey (SF-36),[7] the Impact of Weight on Quality of Life–Lite[8] and the Treatment Related Impact Measure–Weight[9] questionnaires. For these, higher scores indicated better health-related quality of life.

Specific attention was given to certain types of adverse events (AEs), including those with increased prevalence in the population with obesity, or side effects relevant to the GLP-1 drug class (table S2). Serum samples for anti-liraglutide antibodies were assessed at screening and at week 162 (week 160 for individuals who discontinued the trial prematurely).

All hypoglycaemic episodes were to be reported as AEs, and severity was rated according to the sponsor's standard definition (mild, moderate or severe). Hypoglycaemic episodes requiring the assistance of another person (i.e., 'severe hypoglycaemic episodes') qualified as an event of special interest. Participants were not routinely provided with blood glucose meters or diaries unless they developed diabetes; hence blood glucose was not measured in case of symptoms of hypoglycaemia unless it coincided with a clinic visit. There were three types of hypoglycaemia AEs reported:

- Those spontaneously reported, i.e., symptoms of hypoglycaemia (not biochemically confirmed) occurring outside of visits to the clinic
- Those registered by site personnel during visits to the clinic where FPG was assessed. All glucose values ≤3·9 mmol/L (70 mg/dL), per the ADA definition for individuals with diabetes,[2] were to be reported as AEs, irrespective of symptoms or diagnosis of diabetes
- Those registered during a visit to the clinic when an oral glucose-tolerance test was performed. No specific guidance was provided during the oral glucose-tolerance test on when to report a low glucose value as a hypoglycaemia AE.

Hypoglycaemia was not included in table 3 (Adverse events and serious adverse events) as the majority of 'hypoglycaemic events' comprised measurements of glucose below 3·9 mmol/L (70 mg/dL) captured during fasting visits or oral glucose-tolerance test procedures and recorded as hypoglycaemia per protocol, irrespective of symptoms.

Individuals were to be withdrawn if they became or intended to become pregnant. Women of childbearing age had a serum pregnancy test performed at screening, week 56 and at the end of treatment, using blood drawn for the biochemistry assessments. Urine pregnancy tests were also carried out for those women of childbearing age at any time during the trial if a menstrual period was missed or as required by local law.

Timing of assessments

Participants had body weight measured at scheduled visits after an overnight fast. Body weight, waist circumference and vital signs were assessed at every visit. Glycaemic control parameters (glycated haemoglobin and fasting plasma glucose, insulin and C-peptide) were measured at weeks 0, 4, 16, 28, 40, 56, 68, 80, 92, 104, 116, 128, 140, 152, 160, and 172. Fasting plasma glucose was additionally measured at screening and at weeks 2, 8, 20, 50, and 162; fasting insulin and C-peptide were additionally measured at week 162. Fasting lipids and cardiovascular biomarkers were measured at weeks 0, 28, 56, 68, 80, 104, 128, 152, 160, and 172.

Measures of insulin resistance (HOMA-IR, Matsuda index[3]) and beta-cell function (HOMA-B, disposition index) were derived from glucose, insulin, and C-peptide data collected in connection with the oral glucose-tolerance test, which was performed at screening and again at weeks 28, 56, 68, 80, 104, 128, 152, 160 and 172.

Additional statistical methodology

The primary objective was to evaluate the proportion of individuals with T2DM at 160 weeks, with time to onset of diabetes as the primary endpoint. An analysis of covariance (ANCOVA) model was used to analyse mean changes in continuous endpoints. The model included treatment, country, sex and baseline body-mass index (BMI) stratum as fixed effects, with the baseline value of the relevant variable as a covariate. Categorical changes for dichotomous endpoints were analysed with the use of logistic regression, with the same fixed effects and covariates as the respective analysis of covariance.

Prespecified subgroup analyses of body weight and HbA_{1c} endpoints were performed in individuals with different baseline BMI categories. BMI was calculated as the weight in kilograms divided by the square of the height in meters. The relative change from baseline in mean fasting body weight was analysed using an ANCOVA that included treatment, BMI category at baseline (27−29·9, 30−34·9, 35−39·9, or ≥40 kg/m^2), the interaction between baseline BMI subgroup and treatment, country and sex as fixed effects and the baseline value as a covariate. Categorical weight changes were analysed by logistic regression, using the same fixed effects and covariates as the ANCOVA analysis. Statistical interaction tests were performed to investigate possible differences in treatment effects between baseline BMI subgroups. Changes from baseline in HbA_{1c} were analysed in a similar manner, except that baseline HbA_{1c} level was included as a covariate in the model.

Endpoints assessed during the 12-week observational follow-up period

Efficacy: Glycaemic control parameters, body weight and waist circumference, vital signs, lipids, cardiovascular biomarkers, and quality of life questionnaires.

Safety: Adverse events, physical examination and electrocardiogram, binge eating, haematology and biochemistry, antibodies, and mental health.

Supplemental results

Efficacy

After being off-treatment for 12 weeks while continuing to receive counselling on diet and exercise, 31 individuals in the liraglutide 3·0 mg group and 47 in the placebo group had developed T2DM at week 172 (figure S3). The time to onset of T2DM from baseline to 172 weeks was one of the sensitivity analyses of the primary endpoint of the 3-year trial and results were consistent with those from week 160. An additional sensitivity analysis that included individuals with possible T2DM and those that the investigator reported had T2DM within the total 172-week period (see table S5) also showed consistent results with the primary analysis (figure S3).

Analysis of time to T2DM diagnosis over 160 weeks using Cox regression provided a hazard ratio of 0·20, 95% confidence interval (CI) 0·12 to 0·33.

Individuals in the study were diagnosed with prediabetes or T2DM based on screening assessments of HbA_{1c}, FPG and/or 2-hour post-challenge plasma glucose, according to ADA 2010 criteria.[2] An evaluation was made of the proportion of individuals in each screening category (see page 3) that had regressed to normoglycaemia at week 160 (overall 66% of individuals in the liraglutide 3·0 mg group and 36% of those in the placebo group). In general, the majority of individuals that regressed in both groups had been diagnosed based on one criterion, rather than any combination of the three criteria (figure S4), and so were less progressed at screening. Similarly, an evaluation was made of the proportion of individuals in each screening category that had been diagnosed with diabetes by week 160. The majority of those individuals in each group

had been diagnosed based on a combination of HbA_{1c} and one or two other criteria (impaired fasting glucose and/or impaired glucose tolerance), and so were at greater risk of disease progression at screening.

During an oral glucose-tolerance test at week 160, liraglutide was associated with lower plasma glucose and higher insulin and C-peptide concentrations than placebo; these effects had reverted approximately to placebo levels by week 172 (figure S5).

Significantly greater proportions of participants lost at least 5% and more than 10% or 15% of their body weight with liraglutide 3·0 mg as compared with placebo over the course of the trial (figure S7, Panels A-C). Overall, 85% *vs* 60% of individuals in the liraglutide 3·0 mg and placebo group, respectively, lost weight (Panel D). Individuals in the liraglutide 3·0 mg group had greater mean reductions in waist circumference and BMI than those in the placebo group (table 2); greater mean reductions in waist circumference were observed in women than in men in the liraglutide group (a test for interaction between treatment and sex showed a p value of 0·0125).

US Prescribing Information for liraglutide 3·0 mg states that those individuals who have not achieved ≥4% weight loss after 16 weeks of treatment should discontinue treatment. Post-hoc analysis of those individuals who received liraglutide, achieved ≥4% weight loss at week 16 and completed 160 weeks of treatment demonstrated 8·2% weight loss at 160 weeks *vs* 1·4% in individuals who met this discontinuation criterion.

After treatment cessation at week 160, a mean weight regain of 1·9% occurred in the liraglutide 3·0 mg group by week 172 in those individuals who completed the trial and entered the follow-up period (table S8). This was from a mean weight loss of 7·1% at week 160. However, mean weight loss remained greater than that achieved with placebo at week 172. FPG reverted to placebo levels within 2 weeks of treatment cessation (figure 2C), but at week 172 it remained significantly lower in the liraglutide 3·0 mg group than in the placebo group (table S8). Systolic and diastolic blood pressure increased in the liraglutide 3·0 mg group and the placebo group after treatment cessation (figure S15), with no significant difference between treatments at week 172 (table S8).

More than 90% of the individuals in each treatment group who were diagnosed with T2DM while on treatment had lost less body weight at the time of diagnosis than the treatment group mean (figure S9). In fact, a median weight gain of 0·3% of baseline body weight in the liraglutide 3·0 mg group and 1·7% in the placebo group was observed.

Liraglutide 3·0 mg was associated with a higher average score than placebo on the 36-item Short-Form health status survey for the physical component summary score (table S9), indicating better quality of life, driven by significant improvements in the physical function and general health domains (figure S10). There was no significant difference in the mental component summary score between treatments (p=0·08), but significant improvements in mental health and vitality domains were observed with liraglutide 3·0 mg. A higher mean total score on the Impact of Weight on Quality of Life–Lite questionnaire and higher scores for each of the five individual domains were also observed in the liraglutide 3·0 mg group as compared to the placebo group. The scores for weight management and treatment burden on the Treatment Related Impact Measure–Weight questionnaire were also higher in the liraglutide 3·0 mg group than in the placebo group, although the liraglutide group had a lower mean score for daily life and the experience of side effects.

Analyses of the proportion of participants that had a decrease from baseline to week 160 in the use of anti-hypertensive, lipid-lowering and oral anti-diabetic medications were not done because a simple algorithm for evaluating this change could not be established for all individuals in a blinded manner. The use of anti-hypertensive, lipid-lowering and oral anti-diabetic medications was unchanged for the majority of participants (table S10).

Safety

As reported previously,[10] nausea (figure S12) and vomiting occurred primarily within the first 4 to 8 weeks after liraglutide treatment started.

In the liraglutide 3·0 mg group, increases from baseline to week 160 in mean lipase and amylase activity (12·3 and 4·2 U/L, respectively) were observed, as compared to increases of 1·5 and 1·0 U/L, respectively, in the placebo group. However, few individuals had a lipase or amylase value that was 3 or more times the upper limit of the normal range at any time during the trial: 78 of 1501 individuals [5·2%] in the liraglutide 3·0 mg group and 11 of 747 individuals [1·5%] in the placebo group for lipase; 2 of 1501 individuals [0·1%] in the liraglutide group and 0 of 747 individuals [0%] in the placebo group for amylase. The isolated enzyme elevations did not seem to be predictive of a pancreatitis diagnosis, as previously described.[10]

Mean heart rate reverted to baseline levels in the liraglutide 3·0 mg group after treatment cessation, from an approximately 2 beats per minute increase observed during treatment (figure S15). Three non-fatal myocardial infarctions, two non-fatal strokes and one cardiovascular death occurred in five individuals in the liraglutide 3·0 mg group, as compared with one non-fatal myocardial infarction and two non-fatal strokes in three individuals in the placebo group. The rates of cardiac arrhythmia were also similar in the two study groups, although the event rate for tachycardia was higher in the liraglutide

3·0 mg group than in the placebo group (0·4 *vs* 0·1 events per 100 person-years of observation (PYO); all but one event in the liraglutide group were non-serious).

Adverse event rates for pancreatitis (table S11) and neoplasms covered the total 172-week trial period from the start of treatment until the final contact with the individual (including events that occurred 15 days or more after treatment ended or during the observational follow-up period).

The incidence of adjudicated and confirmed colorectal neoplasms was similar in the liraglutide 3·0 mg group as compared to the placebo group over the 3-year period. A numerical imbalance was observed for malignant and pre-malignant breast neoplasms in females over the 172-week trial period: 10 events in the liraglutide 3·0 mg group (7 of them malignant) *vs* no events in the placebo group (figure S13). Most of the events (7 of the 10) occurred in the 56-week trial period, as described previously.[10] This pattern does not support a relationship between liraglutide exposure and the development of breast neoplasms.

Based on several factors, it is considered likely that the observed event imbalance is not causally related to liraglutide treatment, but a chance finding or resulting from enhanced ascertainment. These factors include the low number of events, the short interval between study entry and diagnosis of breast cancer with nodal involvement in most cases, and the fact that obesity *per se* is associated with oestrogen and progesterone receptor positive postmenopausal breast cancer. Most of the breast neoplasm cases occurred in postmenopausal women in the current trial (table S13). Furthermore, weight loss in women with breast neoplasms was greater than the overall treatment group mean (table S13.) Women with obesity often have reduced compliance with mammographic screening and breast examination compared to women of normal weight,[11, 12] and significant weight loss could have led to increased mammography/breast examination uptake and/or accuracy and therefore increased diagnosis.

Based on tissue samples from thyroidectomies for other indications, three thyroid disease events, reported by three individuals in the liraglutide 3·0 mg group, were confirmed by adjudication as thyroid neoplasms, all of papillary origin (two events of thyroid neoplasm and one non treatment-emergent event of autoimmune thyroiditis). One of the thyroid neoplasm cases was malignant; the other two cases were pre-malignant.

Rates for events potentially related to acute renal failure (Medical Dictionary for Regulatory Activities [MedDRA] search term) were similar with liraglutide 3·0 mg and placebo (0·8 and 1·0 events per 100 PYO). The majority of these events were increased blood creatinine. There was no difference in seriousness or severity between treatments. Overall, five cases of acute renal failure were observed, two in the liraglutide 3·0 mg group and three in the placebo group.

Injection site reaction rates were 10·1 and 7·3 events per 100 PYO with liraglutide 3·0 mg and placebo, respectively, with similar allergic reaction rates between treatments (2·3 and 2·9 events per 100 PYO).

Overall rates of psychiatric disorder-related AEs were 13·0 and 14·3 events per 100 PYO in the liraglutide 3·0 mg and placebo group, respectively. Assessments of depression using the Patient Health Questionnaire-9 (PHQ-9) (tables S12 and S13), or of suicidal behaviour and suicidal ideation using the Columbia Suicidality Severity Rating Scale (C-SSRS) (table S16), did not demonstrate differences to suggest an effect of liraglutide on the severity of depression symptoms or an increase in suicidal thinking. However, there was a numerical imbalance in reported AEs related to suicidal ideation or behaviour: seven individuals treated with liraglutide 3·0 mg (versus none treated with placebo) reported eight suicidal ideation AEs, and one individual in the placebo group (versus none in the liraglutide group) reported suicidal depression. One of the seven individuals in the liraglutide group reported a suicide attempt together with one of the suicide ideation events, and an additional individual in the placebo group attempted suicide, thus there was one attempted suicide in each treatment group. Of the nine individuals reporting suicidal ideation or behaviour, all except one in each treatment group (liraglutide, suicidal ideation event; placebo, suicide attempt) reported past history of psychiatric disorders (including major depression, depression and anxiety) or life stressors related to the events. Furthermore, only one of the seven individuals in the liraglutide group had reported ideation at baseline on the C-SSRS; none of those in the placebo group had done so, and no individuals in either treatment group reported suicidal behaviour on the C-SSRS at baseline. The individual who reported ideation at baseline on the C-SSRS was not excluded as this did not occur in the month before randomisation. PHQ-9 total scores at baseline or screening indicated no or mild depression for all nine individuals.

Narratives for the nine individuals mentioned above are presented here by treatment group:

<u>Liraglutide 3·0 mg</u>

- A 42-year-old female with a medical history of depression reported a suicide attempt on day 113 of treatment. This individual also reported suicidal ideation on day 13, lasting 29 days. She was hospitalised after taking an overdose of an unknown medication with suicidal ideation following an argument with her mother. The individual reported situational depression (family issues and work-related stress) and that she had made a poor choice. By report, she was grateful that

her suicide attempt did not succeed. She continued to receive psychological counselling for her suicidal ideations. Eight months later, the individual experienced depression, which was not considered a separate event by the investigator. She was on leave from work due to mental health issues. At that time the individual denied suicidal thoughts or plans and was reportedly better away from work stress. She was treated with aripiprazole, clonazepam, and bupropion. Four months later, the individual discontinued trial product due to the psychiatrist's recommendation and 5 months later reportedly recovered from her suicidal ideations, although major depressive disorder was ongoing and considered a chronic condition.

- A 42-year-old female with no reported history of mental illness had a one-day AE of suicidal ideation on day 16 of treatment. The AE was reported as mild and 'possibly' related to study drug. On the C-SSRS, the individual reported 'wish to be dead' and 'active suicidal ideation with any methods (not plan) without intent to act' (type 3), at week 4. She recovered and remained in the trial with no change to her dose. No further psychiatric AEs were reported.
- A 41-year-old female with a history of situational depression had a one-day AE of suicidal ideation on day 327 of treatment. The AE was reported as mild and 'unlikely' to be related to study drug. A separate suicidal ideation event was reported on day 701, and lasted 49 days. On the C-SSRS the individual reported 'wish to be dead' at screening and at week 50. She recovered from both events and remained in the trial with no change to her dose. She also had an AE of mild worsening depression reported on day 327 and moderate chronic anxiety reported on day 388, neither of which she had recovered from by report.
- A 44-year-old female with a medical history of borderline personality and depression, associated with suicidal ideation at the time of diagnosis, reported suicidal ideation on day 416 of treatment; the event lasted for 34 days. The individual experienced death wish; she described feeling lonely and was not looking forward to the holiday season. The individual said she wished she would fall asleep and not wake up. On the C-SSRS, question 1 was answered with 'yes', all other questions answered with 'no'. The individual was not hospitalised due to the event and did not receive any treatment. The individual was referred to a mental health practitioner (psychiatrist and general practitioner) and confirmed as diagnosed with borderline personality disorder, as previously reported in medical history. Approximately one month after the diagnostic test, the individual recovered, with no change to trial drug.
- A 60-year-old female with no reported history of mental illness had a one-day AE of suicidal ideation on day 616 of treatment. The individual stated that the suicidal ideation was due to her sister's recent diagnosis of cancer. She did not plan or intend to act on her thoughts. The individual was referred to a mental health practitioner, but refused to go for an appointment. There were no concomitant medications relevant to the event. The individual did not receive any treatment for the event, and she recovered from the event the same day with no change to trial drug.
- A 45-year-old male with a history of depression and attention deficit hyperactivity disorder had an event of single transient suicidal ideation lasting one day on day 689 of treatment. Worsening of personal stressors (employment, financial) preceded the event. The individual recovered from the event without change in trial drug and continued in the trial.
- A 47-year-old male with no reported history of mental illness reported suicidal ideation on day 697 of treatment; the event lasted for 48 days. The individual presented with suicidal ideation following the death of his father. He expressed guilt, sadness, remorse and experienced insomnia since that day. The individual was referred to and was treated by a psychiatrist for the events of suicidal ideation and major depressive disorder, both of which he recovered from, with no change to trial drug.

<u>Placebo</u>

- A 33-year-old male with no reported history of mental illness reported a suicide attempt on day 728 of treatment. The individual was admitted to hospital several hours after a suicide attempt. On the same day, after follow-up and psychiatric evaluation, the individual was discharged from hospital in good condition, with no change to trial drug.
- A 60-year-old male with medical history of mild depressive complaints and prior hospitalisation for a psychiatric disorder reported suicidal depression on day 742 of treatment; the event lasted for 15 days. The individual presented with a major depressive episode with contemplation about suicide. The individual had the same event within the previous two months, and was on an organ (heart) transplant waiting list, which was reportedly hard for him. The individual was not hospitalised and did not receive any treatment for this event but was already being treated and on medication for moderate depressive disorder and depressive complaints and was seen by a psychologist weekly. The individual had a heart transplant performed and approximately two weeks later the individual had recovered from "major depressive episode with contemplation about suicide". The individual withdrew from the trial.

For a full list of hypoglycaemia AEs in individuals who did not develop T2DM see table S17. No events were serious or required third-party assistance.[13] The majority (90·6%) of the events for individuals in the liraglutide 3·0 mg group were registered at visits when an oral glucose-tolerance test was performed (78·1%; primarily at 90 or 120 minutes) or when FPG was measured (12·5%). A similar pattern was seen in the placebo group, where most (67·3%) of the events were registered at oral glucose-tolerance test visits (55·1%) or when fasting glucose was measured (12·2%). Most of the events reported in both groups were associated with plasma glucose values ≤3·9 mmol/L (70 mg/dL), the ADA cut-off alert value for hypoglycaemia in people with T2DM,[2] but were ≥3·1 mmol/L (56 mg/dL) and perhaps not so clinically relevant in this population without diabetes.

With regard to anti-liraglutide antibodies, 5 of 1180 (0·4%) exposed individuals in the liraglutide 3·0 mg group who had a post-baseline antibody measurement developed anti-liraglutide antibodies; 1 (0·1%) had antibodies that cross-reacted with native GLP-1 and 3 (0·3%) had antibodies with *in vitro* neutralising capability (none had both neutralising and cross-reacting antibodies).

In total, 39 women became pregnant (27 [2·4%] in the liraglutide 3·0 mg group *vs* 12 [2·1%] in the placebo group). In the liraglutide 3·0 mg group, 8 (30%) of the pregnancies resulted in spontaneous abortions, although it was unknown whether one of the cases was spontaneous or elective. In the placebo group, there was one spontaneous abortion, corresponding to 8% of pregnancies. A similar proportion of pregnant women in each group gave birth to healthy children (52% in the liraglutide 3·0 mg group *vs* 50% in the placebo group).

No specific types of adverse events related to potential withdrawal or rebound effects were identified during the 12-week off-drug follow-up period.

Supplemental figures

Figure S1. Trial design

This was a 3-year randomised, double-blind, placebo-controlled, multi-centre, multinational trial. Individuals were stratified at screening according to whether or not they had prediabetes (according to American Diabetes Association 2010 criteria).[2] Individuals with prediabetes continued on randomised treatment (liraglutide 3·0 mg or placebo) for160 weeks, including the 56-week trial period reported previously,[10] plus a 12-week observational off-drug follow-up period.

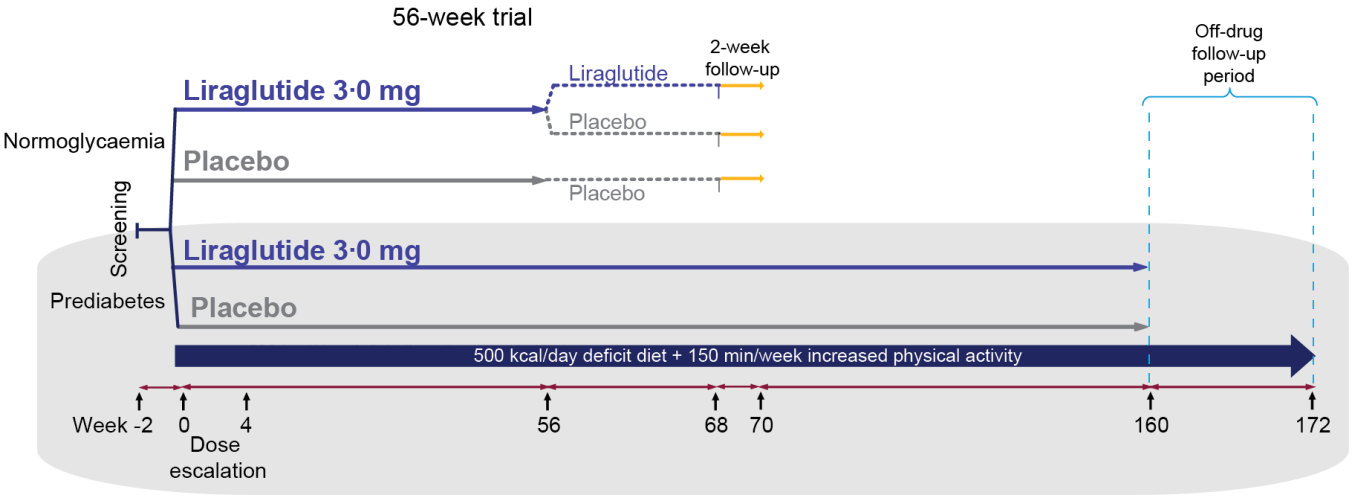


Figure S2. Liraglutide 3·0 mg and development of type 2 diabetes

The figure shows the estimated survival time based on an analysis of the time to onset of type 2 diabetes mellitus (T2DM) up to 160 weeks of treatment from a Weibull model for individuals in the full-analysis set. The full-analysis set included all randomised participants who received treatment and had at least one assessment after baseline. The Weibull model included treatment, sex and body-mass index (BMI) stratification factor as fixed factors and baseline fasting plasma glucose as a covariate. The estimated time-to-event ratio indicates that the time to onset of T2DM for individuals treated with liraglutide 3·0 mg is 2·7 times longer than for those treated with placebo during the 3-year period. The estimated number of individuals needed to be treated for 3 years was calculated as 100 × 1/(98-91), or 14 individuals.

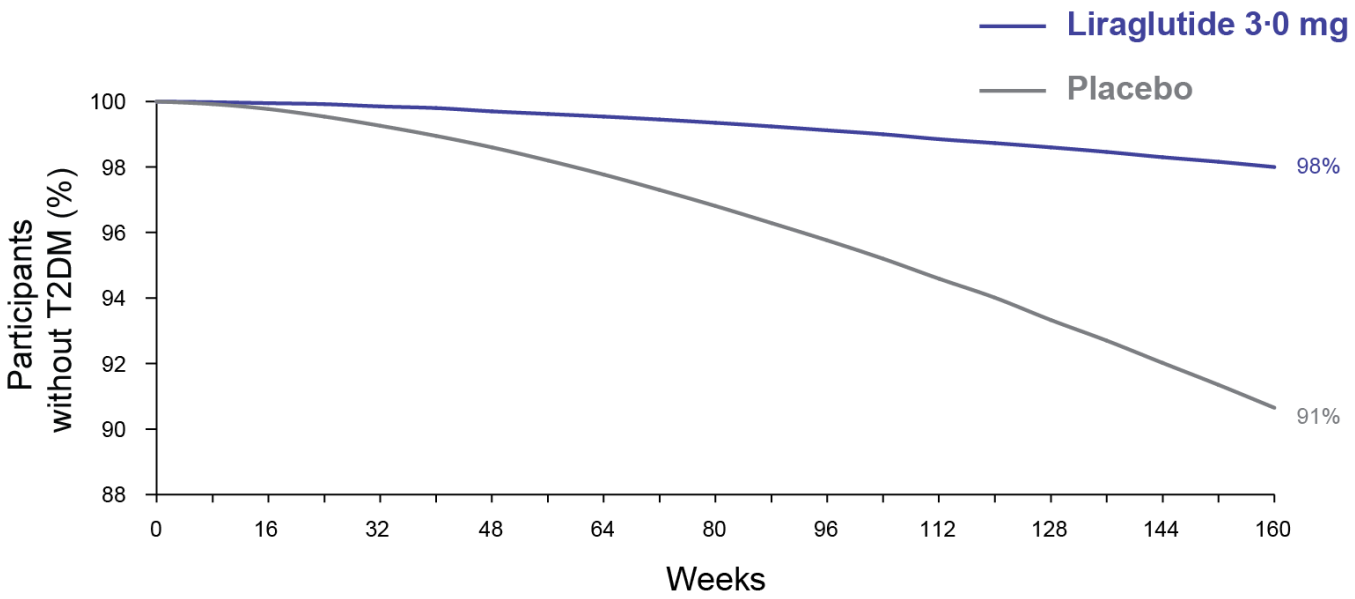
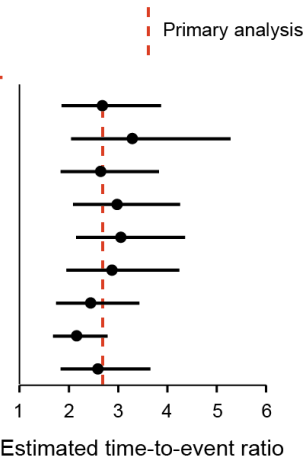


Figure S3. Sensitivity analyses of the time to onset of type 2 diabetes

A forest plot of the various Weibull sensitivity analyses performed for the primary endpoint is shown. The analyses were done at 160 weeks, unless stated. The panel at the right illustrates the estimated treatment effect and the 95% confidence interval. All of the associated p values were <0·0001. Findings were similar across the analyses, and showed consistent results with the primary analysis. See table S5 for more details of the individual sensitivity analyses.

Number of events of T2DM		Number of individuals in the analysis				
Liraglutide 3·0 mg	Placebo	Liraglutide 3·0 mg / Placebo	Type of analysis	Estimated time-to-event ratio	LCL	UCL
26	46	1472 / 738	Primary analysis	2·681	1·856	3·872
19	40	791 / 337	Completer population	3·290	2·050	5·281
26	45	1495 / 746	Individuals with screening prediabetes diagnosis	2·649	1·833	3·828
40	63	1472 / 738	Including individuals with possible T2DM	2·980	2·089	4·252
40	67	1472 / 738	Including individuals with possible T2DM†	3·058	2·147	4·354
24	46	1450 / 735	Excluding potentially unblinded individuals	2·874	1·948	4·241
31	47	1472 / 738	At week 172	2·444	1·741	3·431
60	73	1472 / 738	At week 172 incl. individuals with possible T2DM†	2·161	1·677	2·785
26	47	2437 / 1225	Full-analysis set from 56-week trial	2·590	1·836	3·654

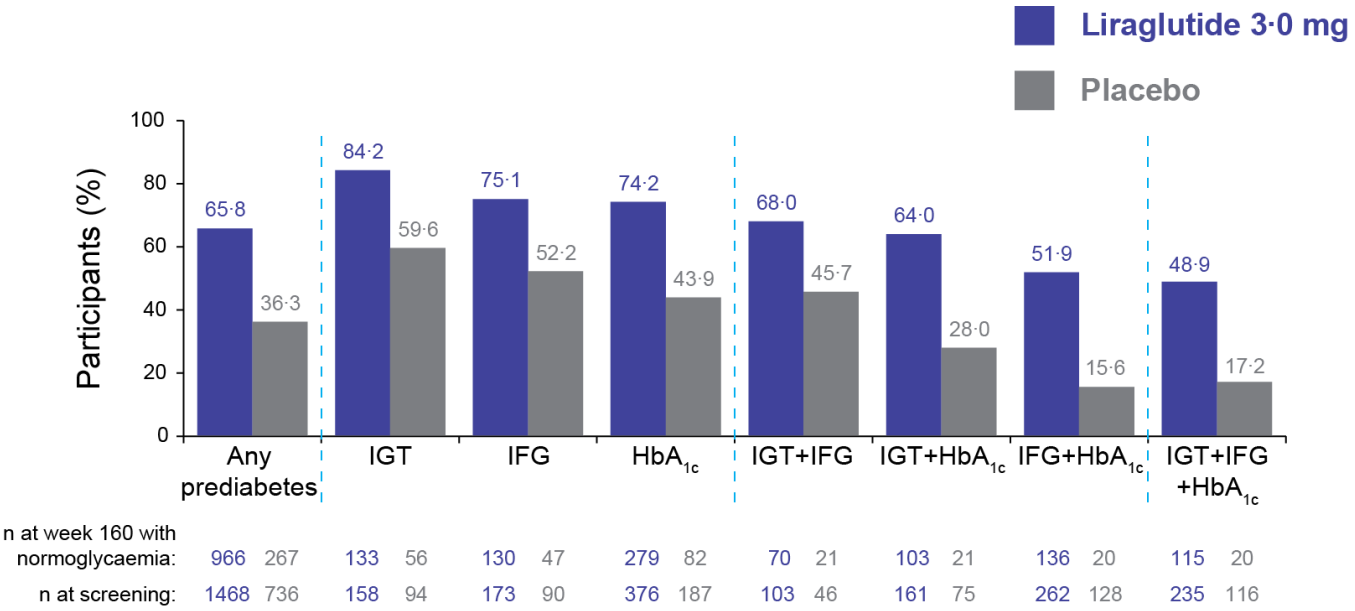


†Including those individuals that the investigator assessed as having T2DM
LCL=lower confidence limit. T2DM=type 2 diabetes mellitus. UCL=upper confidence limit.

Figure S4. Participants with normoglycaemia or type 2 diabetes at week 160, based on prediabetes category at screening

Panel A shows the proportion of participants with normoglycaemia at week 160, according to the types of screening assessments for glycated haemoglobin, fasting plasma glucose and 2-hour post-challenge plasma glucose that made up the original diagnosis of prediabetes, according to American Diabetes Association 2010 criteria.[2] Panel B shows the proportion of participants with type 2 diabetes, according to the same criteria.
HbA_{1c}=glycated haemoglobin. IFG=impaired fasting glucose. IGT=impaired glucose tolerance.

A



B

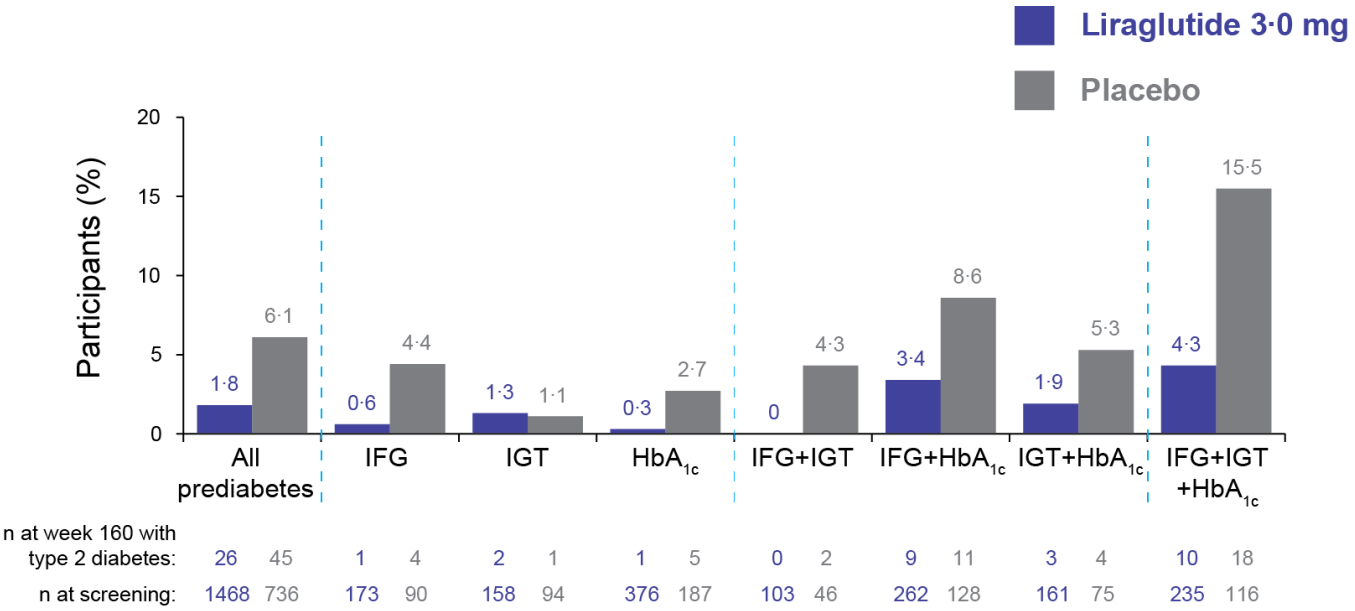
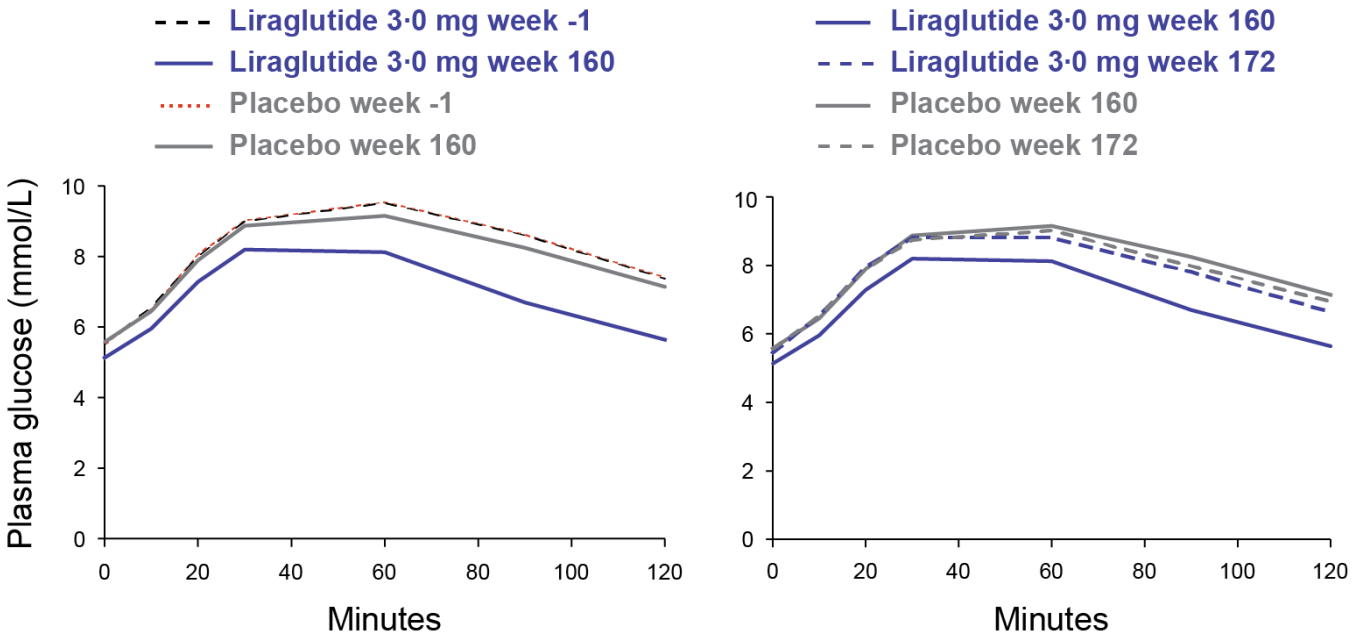


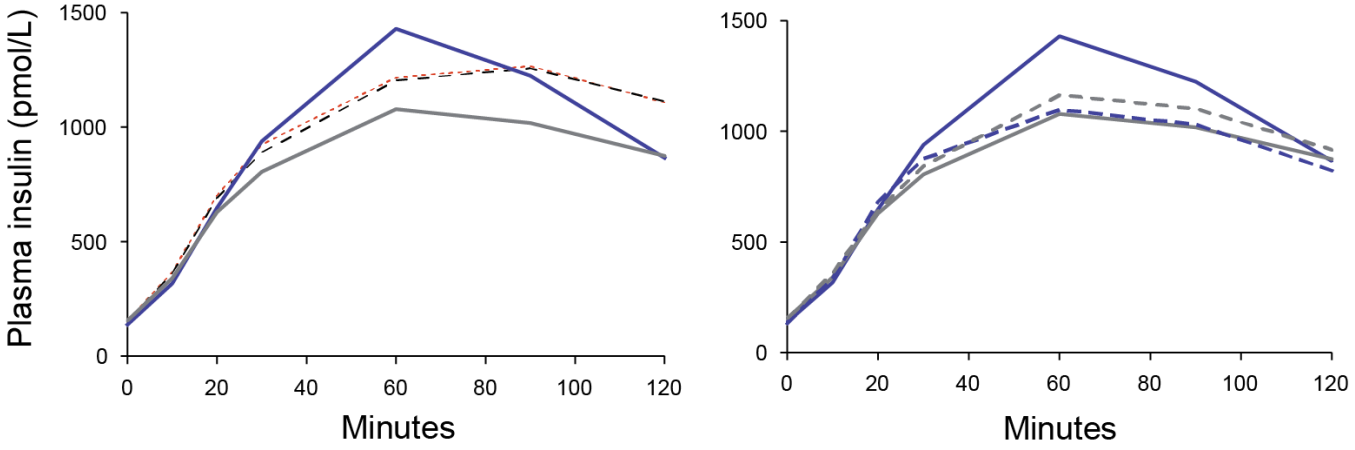
Figure S5. Plasma glucose, insulin and C-peptide during oral glucose-tolerance test

Mean plots of plasma glucose (Panel A), insulin (Panel B) and C-peptide (Panel C) during a 75-g oral glucose-tolerance test (OGTT) are shown. For each panel, OGTTs performed at screening (week -1) and after 160 weeks of treatment are shown on the left, and OGTTs performed after 172 weeks of treatment compared with 160 weeks are shown on the right. The OGTT was done at screening for the purpose of diagnosis of prediabetes (see the Supplemental Methods).

A



B



C

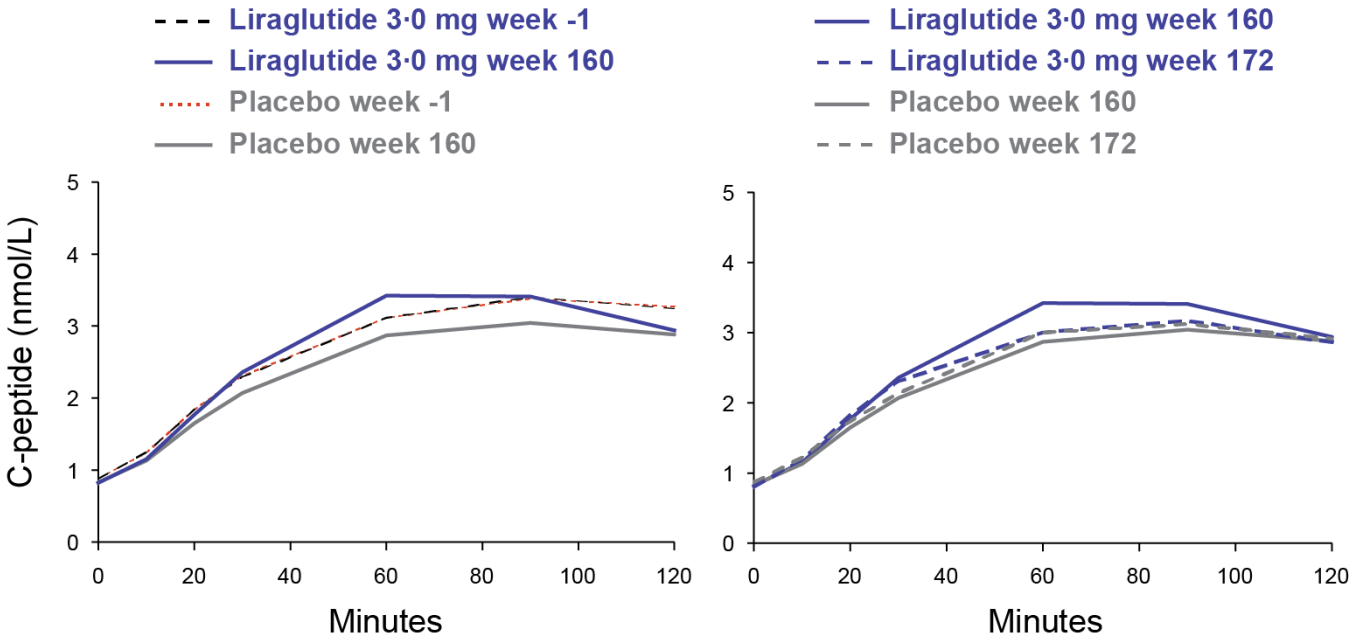

Liraglutide 3·0 mg week -1
Liraglutide 3·0 mg week 160
Placebo week -1
Placebo week 160
Liraglutide 3·0 mg week 160
Liraglutide 3·0 mg week 172
Placebo week 160
Placebo week 172
C-peptide (nmol/L)
0
1
2
3
4
5
0
20
40
60
80
100
120
Minutes
Minutes

Figure S6. Relative changes in fasting glucose (%) over the course of the trial

Data shown are the observed means with 95% confidence intervals, and the separate symbols represent the 160-week changes using last-observation-carried-forward (LOCF) imputation.

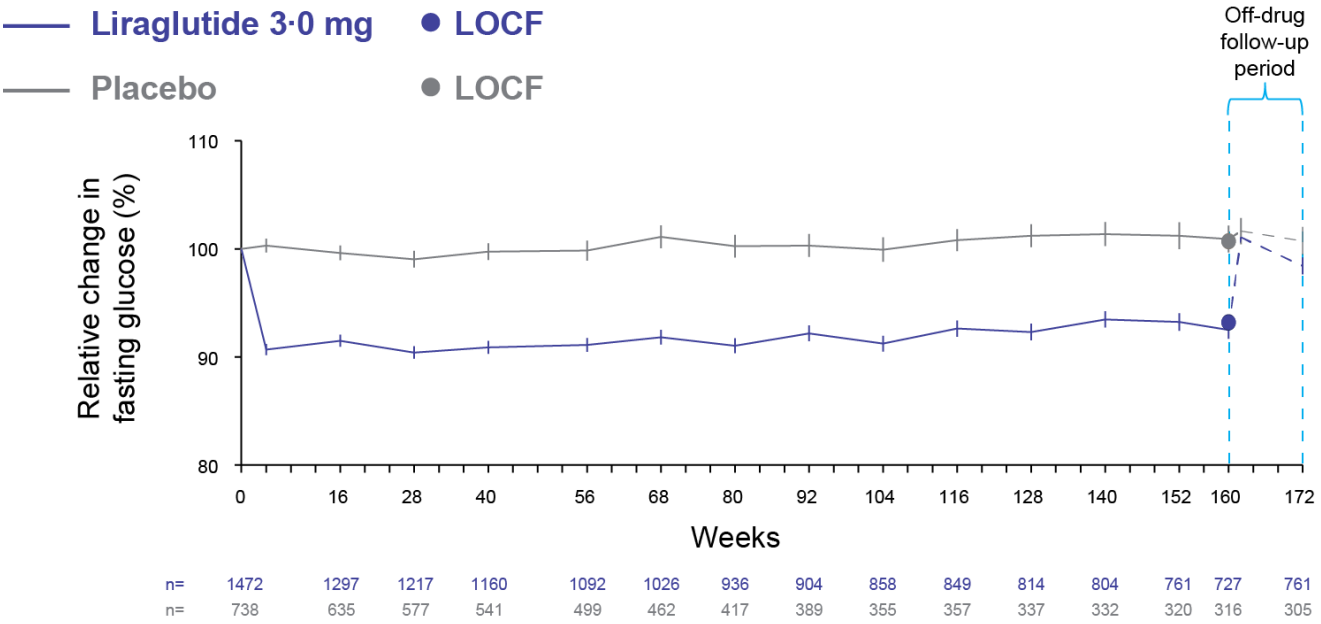
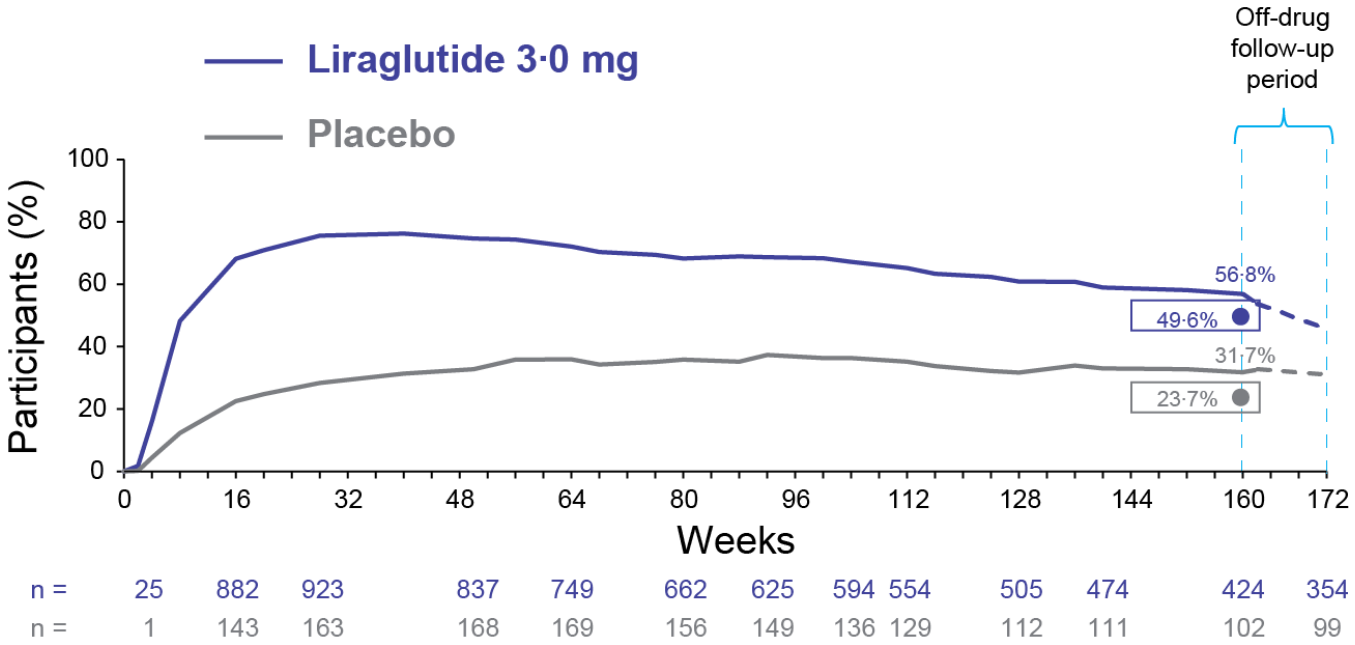


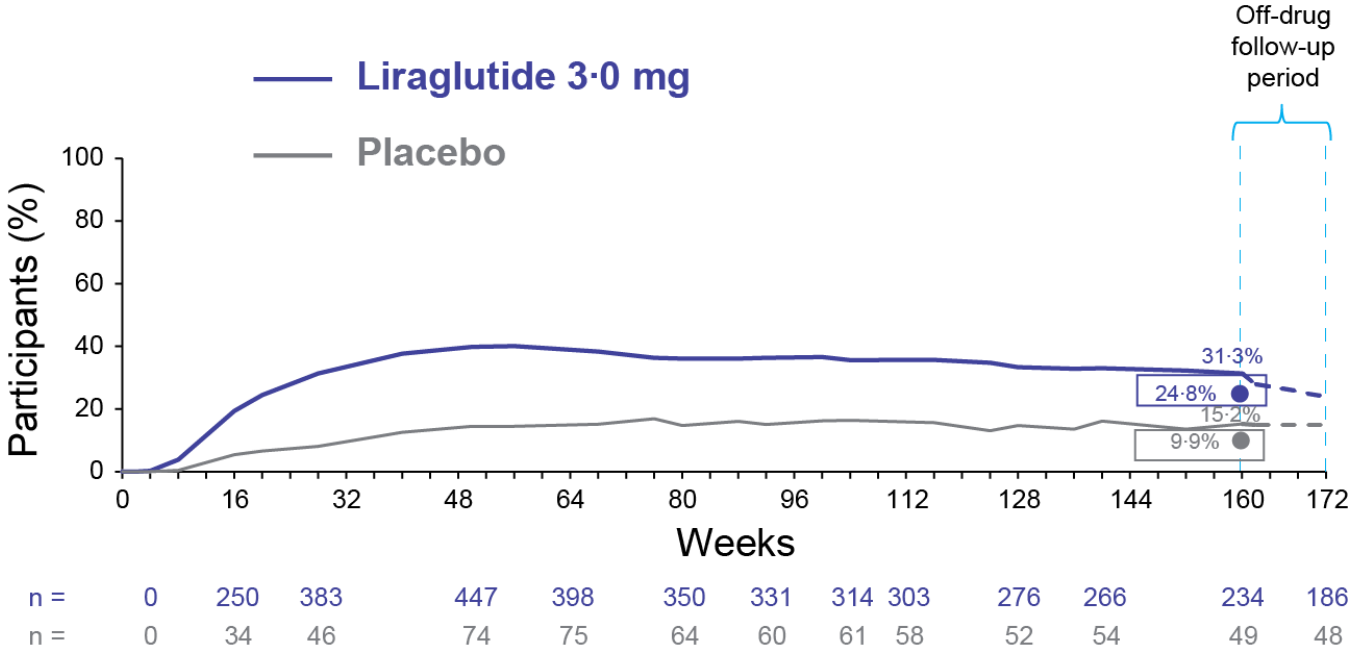
Figure S7. Liraglutide 3·0 mg and body weight over the course of the trial

The proportions of participants who had lost at least 5% (Panel A), more than 10% (Panel B) or more than 15% (Panel C) of their body weight over the course of the trial are shown. Data shown are the observed means, and the separate symbols represent the 160-week proportions using last-observation-carried-forward (LOCF) imputation. Individuals were off treatment during the 12-week observational follow-up period, but still on diet and exercise. Panel D shows the cumulative percentage of individuals with changes in body weight (%) after 160 weeks of treatment.

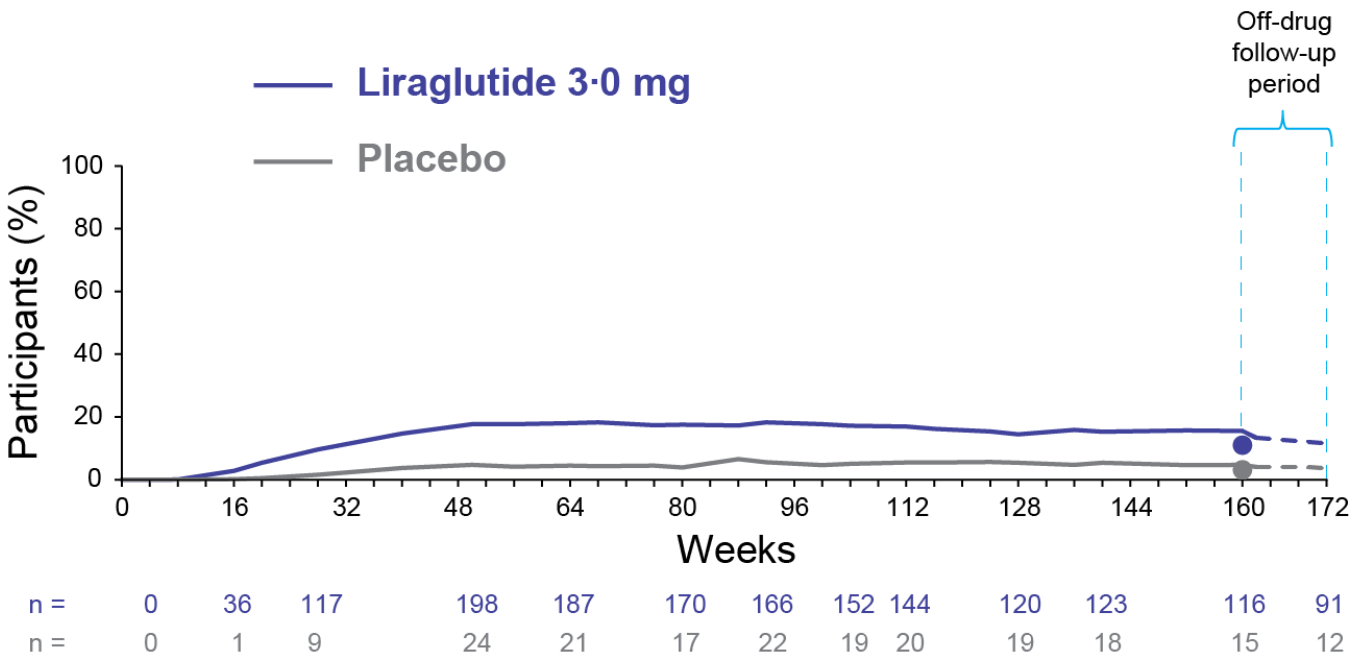
A



B



C


Off-drug follow-up period
Liraglutide 3·0 mg
Placebo
Participants (%)
100
80
60
40
20
0
0
16
32
48
64
80
96
112
128
144
160
172
Weeks
n = 0 36 117 198 187 170 166 152 144 120 123 116 91
n = 0 1 9 24 21 17 22 19 20 19 18 15 12

D

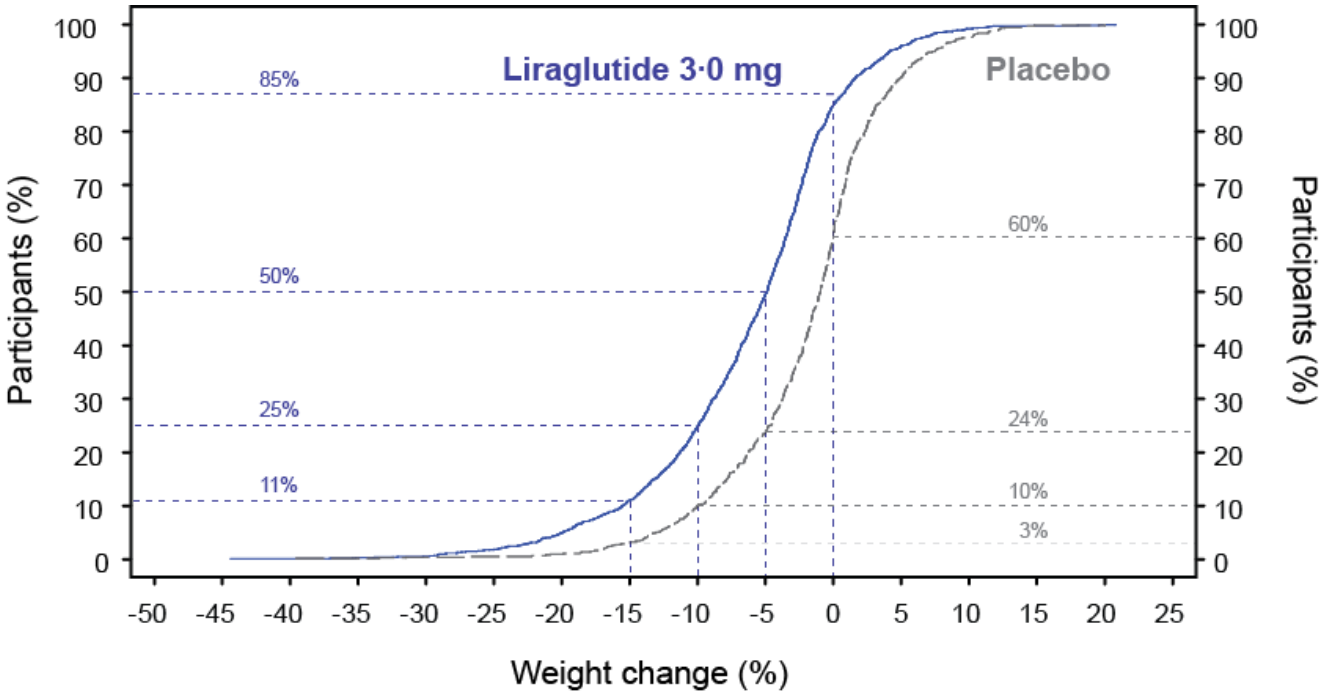
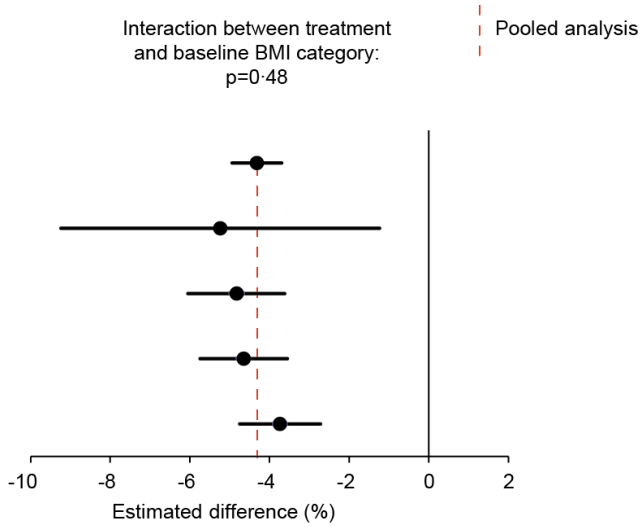

Liraglutide 3·0 mg
Placebo
85%
50%
25%
11%
60%
24%
10%
3%
Participants (%)
Participants (%)
100
90
80
70
60
50
40
30
20
10
0
-50
-45
-40
-35
-30
-25
-20
-15
-10
-5
0
5
10
15
20
25
Weight change (%)

Figure S8. Changes in body weight and glycated haemoglobin after 160 weeks by baseline BMI categories

For mean weight loss (%) in Panel A, 5% weight loss in Panel B, 10% weight loss in Panel C and glycated haemoglobin in Panel D, the right-hand panel illustrates the estimated treatment effect together with 95% confidence interval. P values for tests of no interaction between treatment and baseline BMI category are shown and were all non-significant, illustrating a consistent treatment effect across BMI subgroups.
BMI=body-mass index in kg/m^2. n=the number of individuals contributing to the analysis.

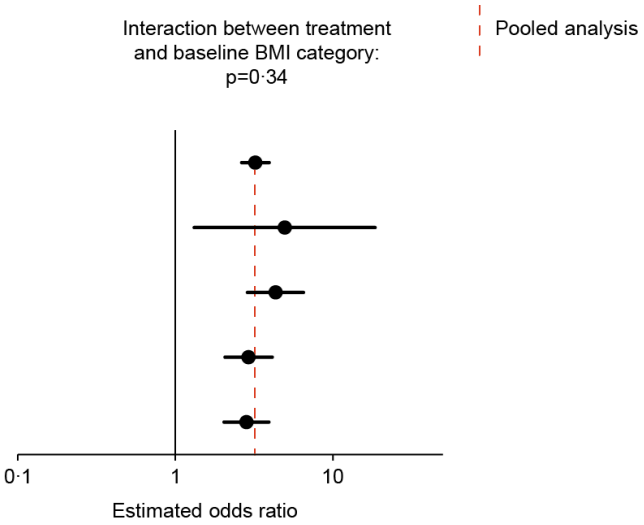
A

	Estimated means and treatment differences (%)		
	Liraglutide 3·0 mg Mean (n)	**Placebo** Mean (n)	Treatment Difference
Pooled analysis	-6·2 (1467)	-1·8 (734)	-4·3
BMI 27·0–29·9	-5·7 (39)	-1·8 (23)	-5·2
BMI 30·0–34·9	-6·5 (415)	-1·7 (192)	-4·8
BMI 35·0–39·9	-6·2 (478)	-1·8 (241)	-4·7
BMI ≥40	-5·9 (535)	-2·1 (278)	-3·7



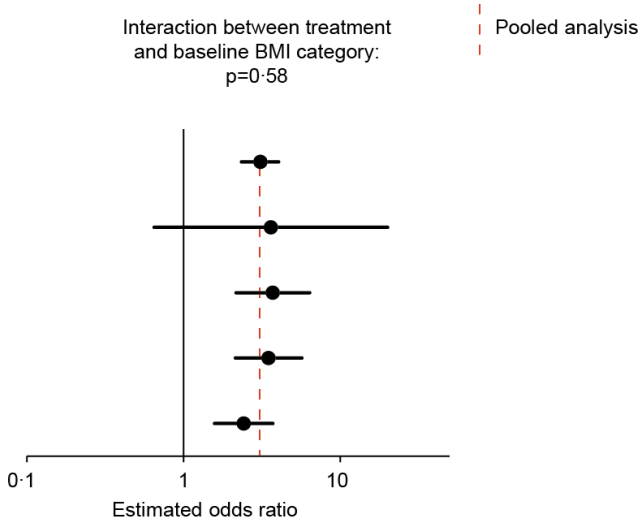
B

	Estimated proportions (%) and odds ratios		
	Liraglutide 3·0 mg Mean (n)	**Placebo** Mean (n)	Odds Ratio
Pooled analysis	49·6% (1467)	23·4% (734)	3·2
BMI 27·0–29·9	12·2% (39)	2·7% (23)	5·0
BMI 30·0–34·9	46·0% (415)	16·4% (192)	4·3
BMI 35·0–39·9	50·3% (478)	25·7% (241)	2·9
BMI ≥40	50·8% (535)	26·7% (278)	2·8



C

	Estimated proportions (%) and odds ratios		
	Liraglutide 3·0 mg Mean (n)	**Placebo** Mean (n)	Odds Ratio
Pooled analysis	24·4% (1467)	9·5% (734)	3·1
BMI 27·0–29·9	5·4% (39)	1·6% (23)	3·6
BMI 30·0–34·9	24·0% (415)	7·8% (192)	3·7
BMI 35·0–39·9	25·9% (478)	9·1% (241)	3·5
BMI ≥40	23·9% (535)	11·5% (278)	2·4



D

	Estimated means and treatment differences (%)		
	Liraglutide 3·0 mg Mean (n)	**Placebo** Mean (n)	Treatment Difference
Pooled analysis	-0·35 (1439)	-0·14 (730)	-0·21
BMI 27·0–29·9	-0·29 (35)	-0·28 (23)	0·01
BMI 30·0–34·9	-0·34 (407)	-0·14 (189)	-0·19
BMI 35·0–39·9	-0·36 (468)	-0·13 (240)	-0·24
BMI ≥40	-0·36 (529)	-0·14 (278)	-0·21

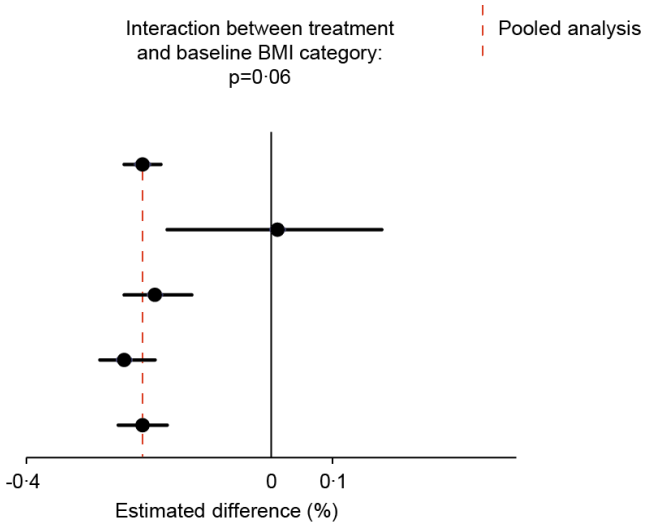


Figure S9. Relative change in body weight for individuals diagnosed with type 2 diabetes over the course of the trial

The mean relative change in body weight for individuals in each treatment group who completed each scheduled visit is represented by the solid lines. Weight change at the time of diagnosis for individuals who were diagnosed with type 2 diabetes during the trial is represented by the circles.

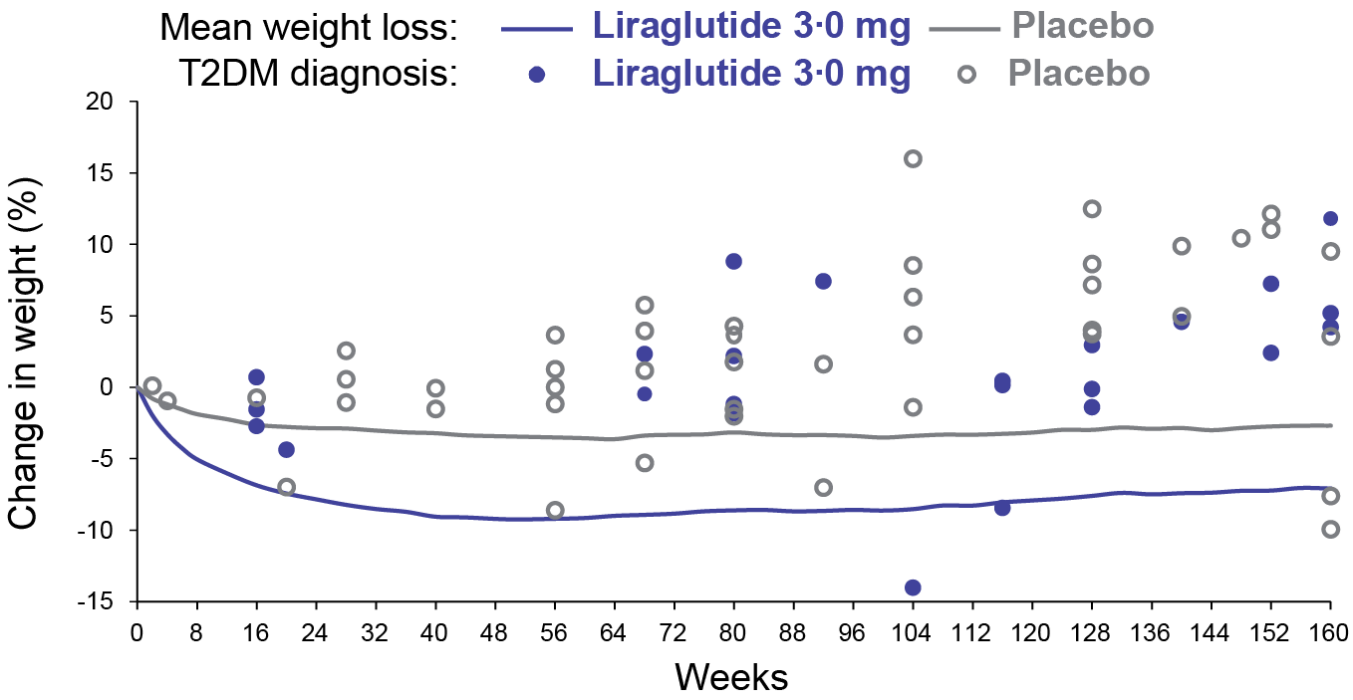
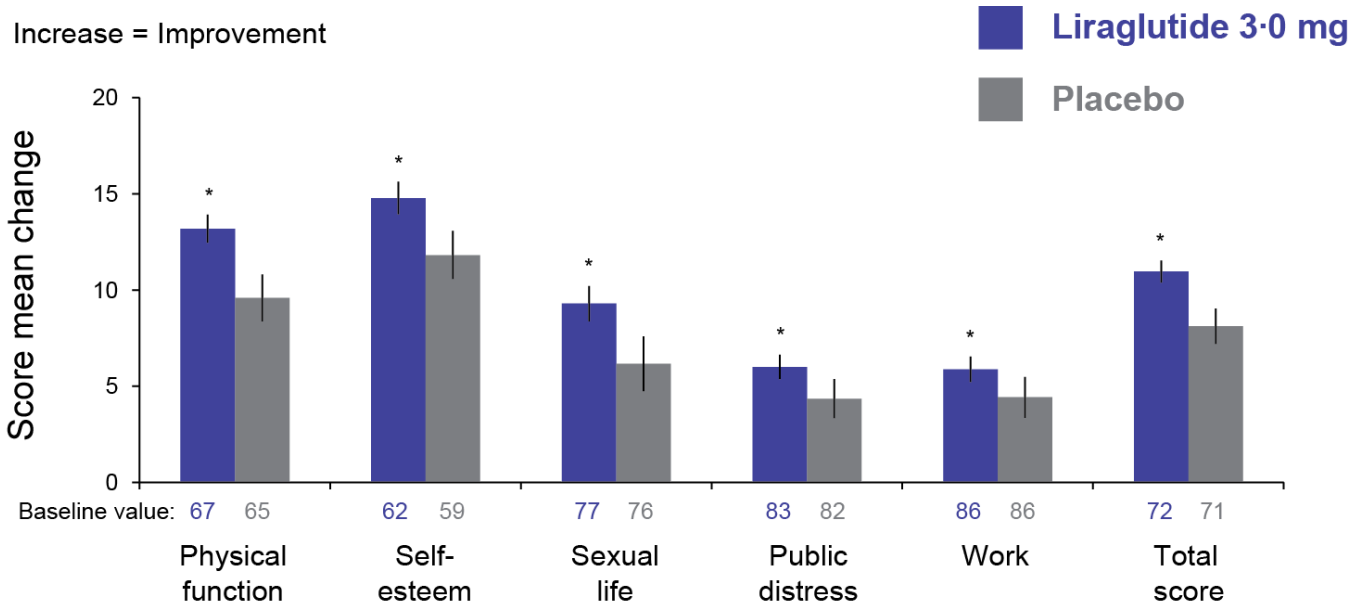


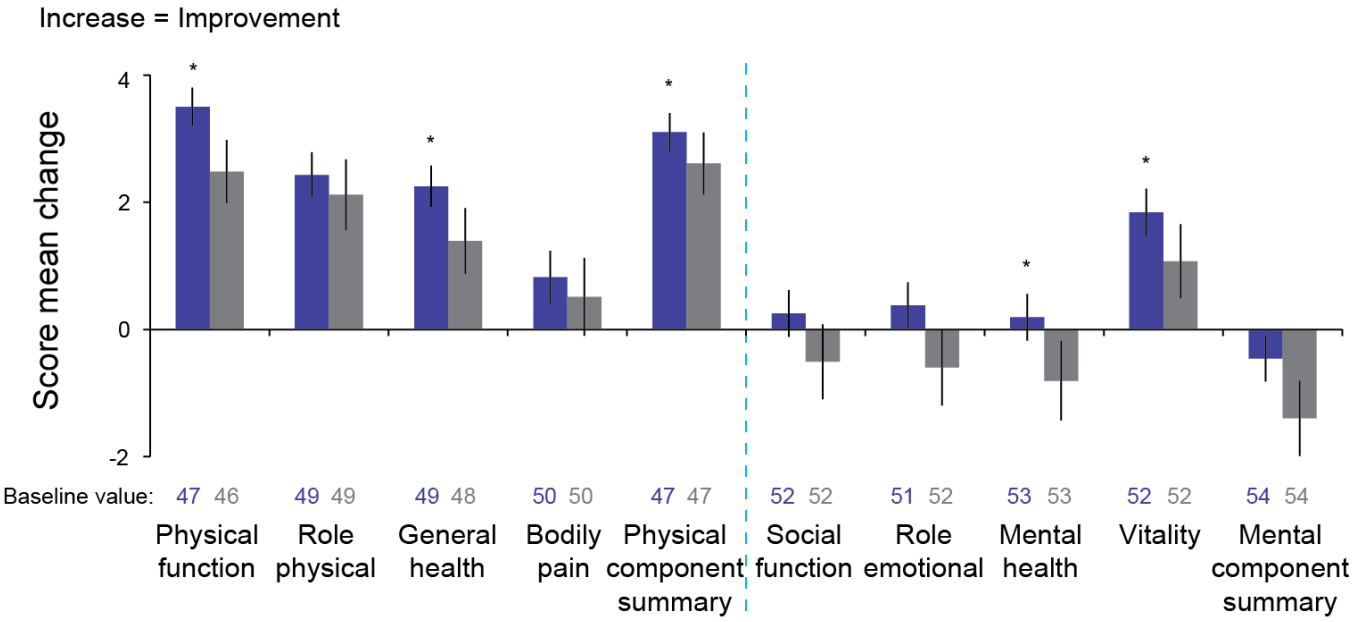
Figure S10. Liraglutide 3·0 mg and health-related quality of life

Observed mean changes in scores for Panel A (IWQoL-Lite) and Panel B (SF-36) are shown at week 160 with last-observation-carried-forward (LOCF) imputation; both questionnaires have a 100-point scale with an increase indicating improvement. The minimal important difference for the IWQoL-Lite total score is between 7·7 and 12.[14] The minimal important difference for any domain of the SF-36 is between 2 and 4.[15] For Panel C, TRIM–Weight (also on a 100-point scale), mean scores at week 160 are shown, with LOCF imputation, as the questionnaire was not completed at baseline. IWQoL-Lite=the Impact of Weight on Quality of Life-Lite version questionnaire. SF-36=the 36-item Short-Form health status survey. TRIM-Weight=the Treatment Related Impact Measure-Weight. *p<0·05.

A



B



C

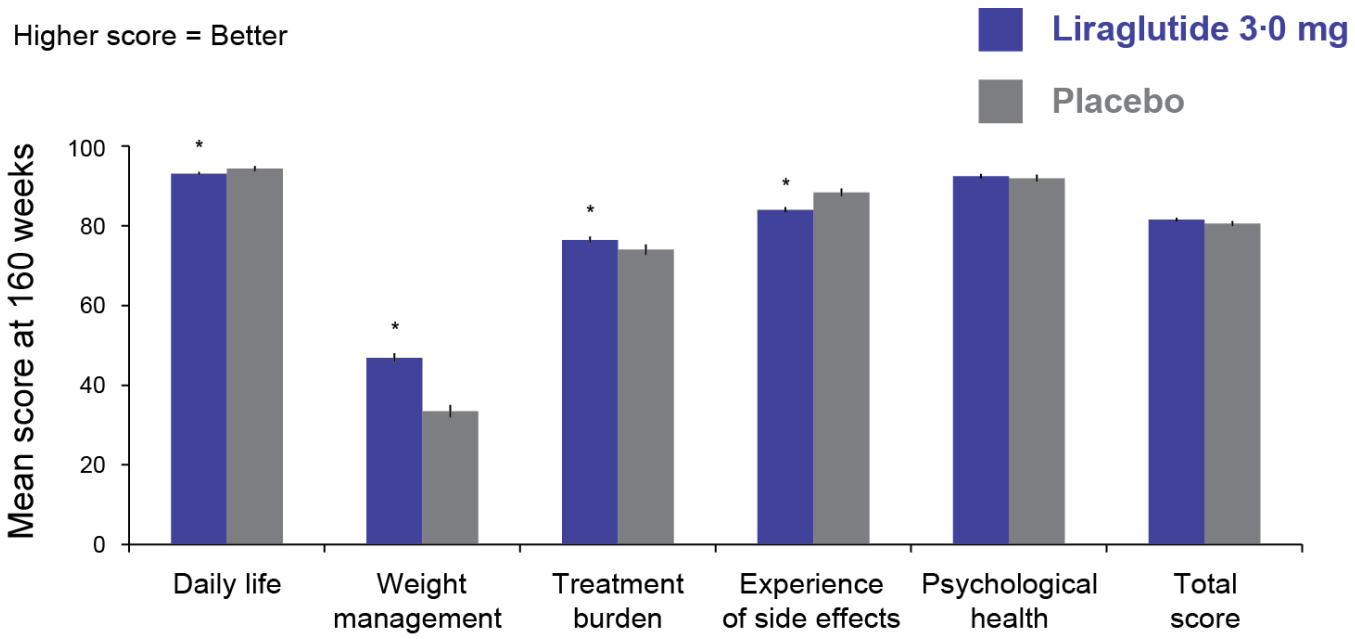

Higher score = Better
Liraglutide 3·0 mg
Placebo
Mean score at 160 weeks
100
80
60
40
20
0
*
*
*
*
Daily life
Weight management
Treatment burden
Experience of side effects
Psychological health
Total score

Figure S11. Adverse events leading to discontinuation of 0·2% or more individuals in either group, by treatment group and up to week 162

Adverse events are presented by preferred term and are observed mean data for the safety-analysis set (liraglutide 3·0 mg N=1501; placebo N=747). Adverse events are treatment-emergent, defined as an event that has onset date on or after the first day of randomised treatment and no later than 14 days after the last day of randomised treatment. Individuals were randomised 2:1 to liraglutide 3·0 mg and placebo.
R denotes the event rate per 100 years of observation time and % the proportion of individuals reporting the adverse event.

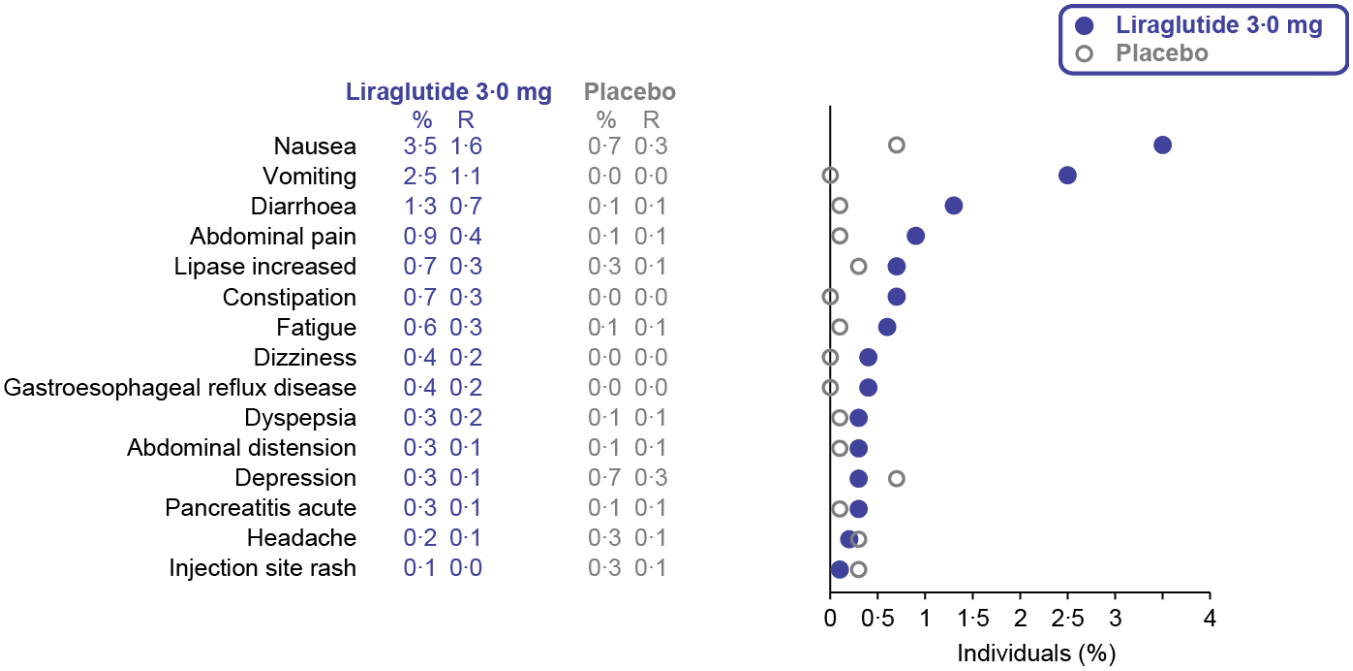


Figure S12. Percentage of participants with ongoing nausea by week and treatment

Observed mean data for the safety-analysis set (liraglutide 3·0 mg N=1501; placebo N=747). A similar pattern was observed for individuals who experienced diarrhoea, constipation and vomiting, although with lower percentages of participants experiencing the events. Overall, 52 individuals in the liraglutide 3·0 mg group withdrew owing to nausea compared with 5 in the placebo group. Individuals were randomised 2:1 to liraglutide 3·0 mg and placebo.

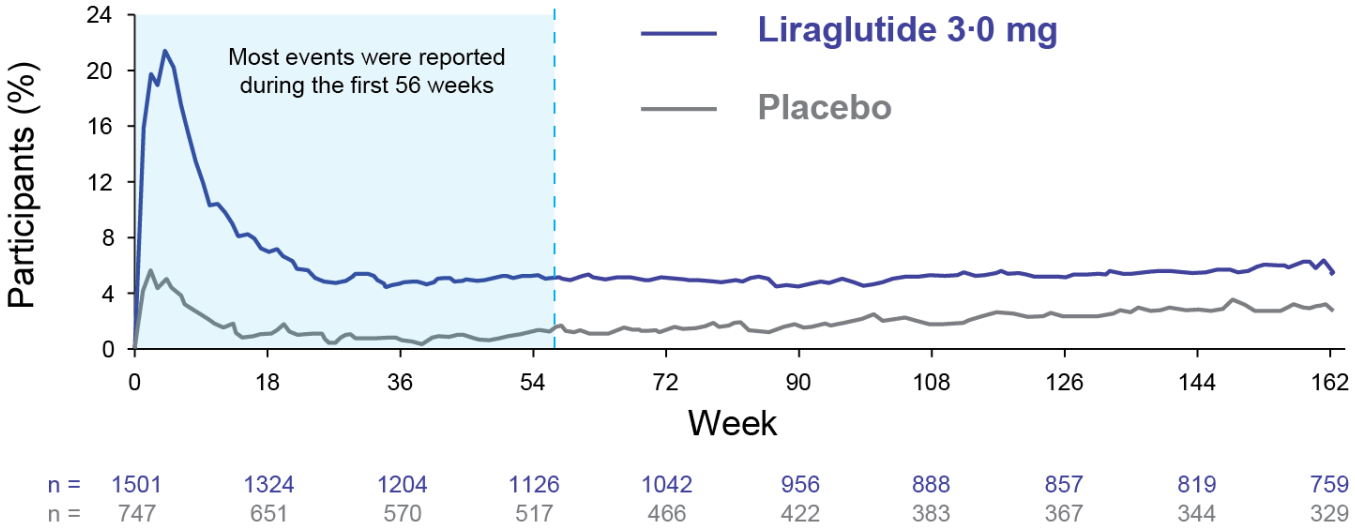
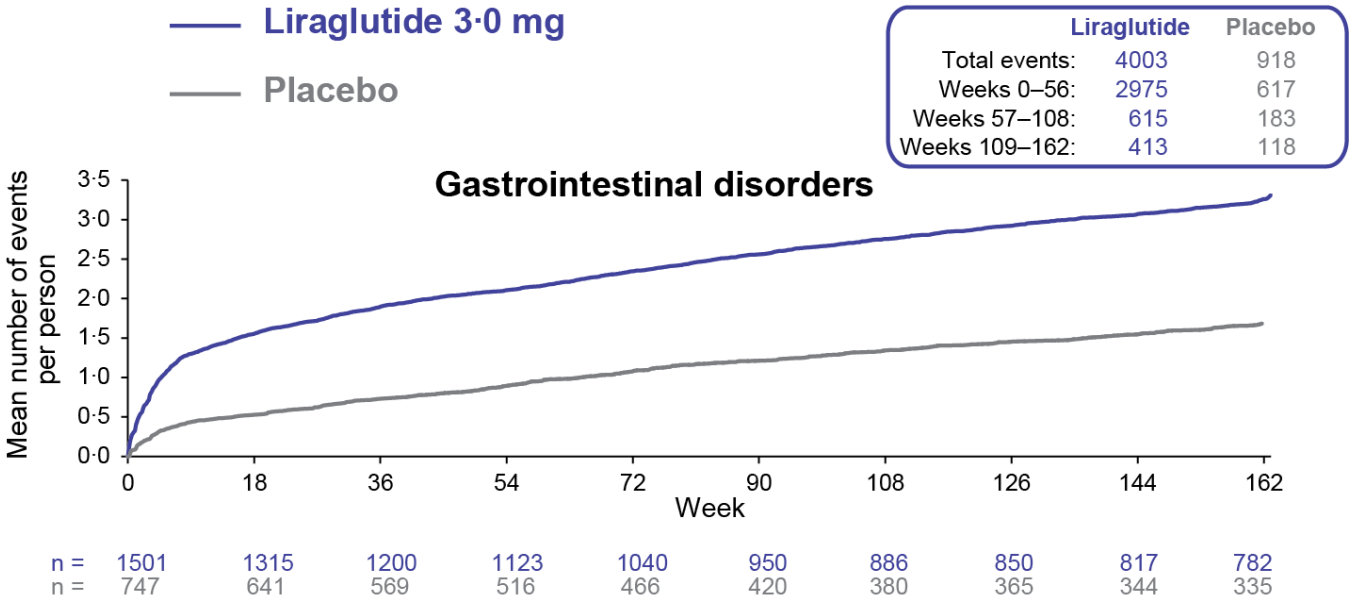


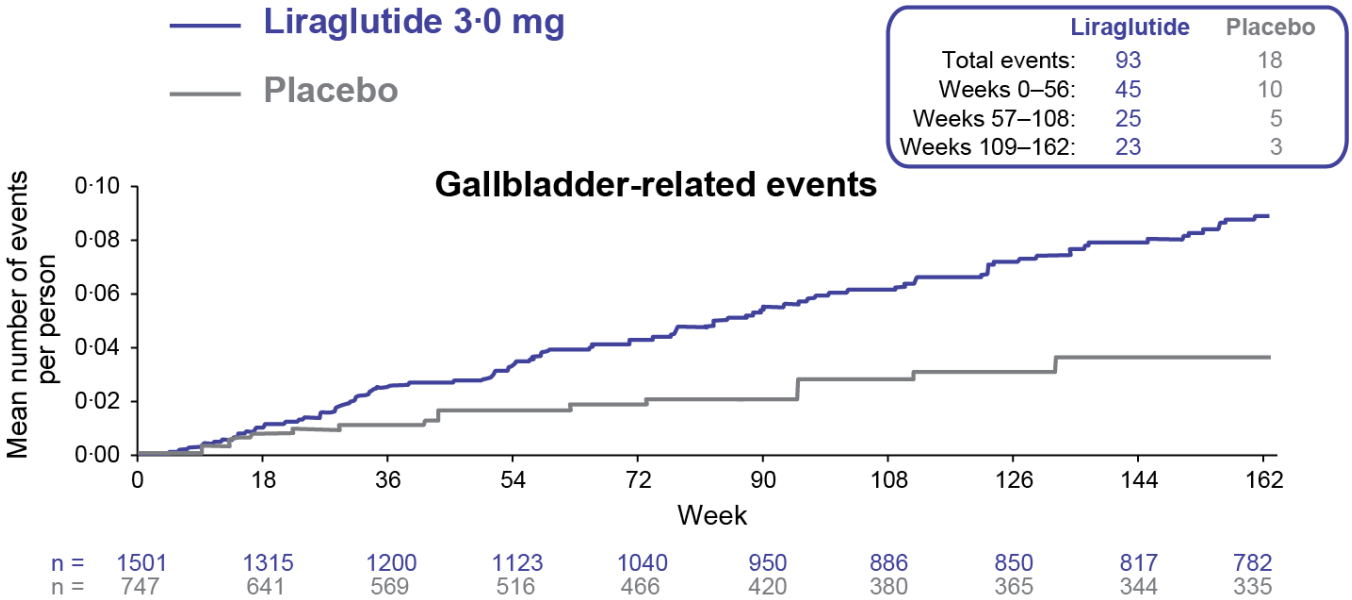
Figure S13. Development of specific adverse events over the course of the trial

The cumulative number of treatment-emergent events of gastrointestinal disorders (Panel A), gallbladder-related events (Panel B), and hypoglycaemic episodes reported as adverse events (Panel C) is shown over the course of the trial. Treatment emergent events are those that occurred up to and including week 162 among individuals in the safety-analysis set. For pancreatitis (Panel D) and malignant and pre-malignant breast neoplasms (Panel E), events that occurred during the full 172-week trial period are shown, including non-treatment emergent events (non-TEAEs). Non-TEAEs are events that occurred after the first 2 weeks of the 12-week observational follow-up period or during the 160-week treatment period in individuals who had withdrawn. Individuals were randomised 2:1 to liraglutide 3·0 mg and placebo.

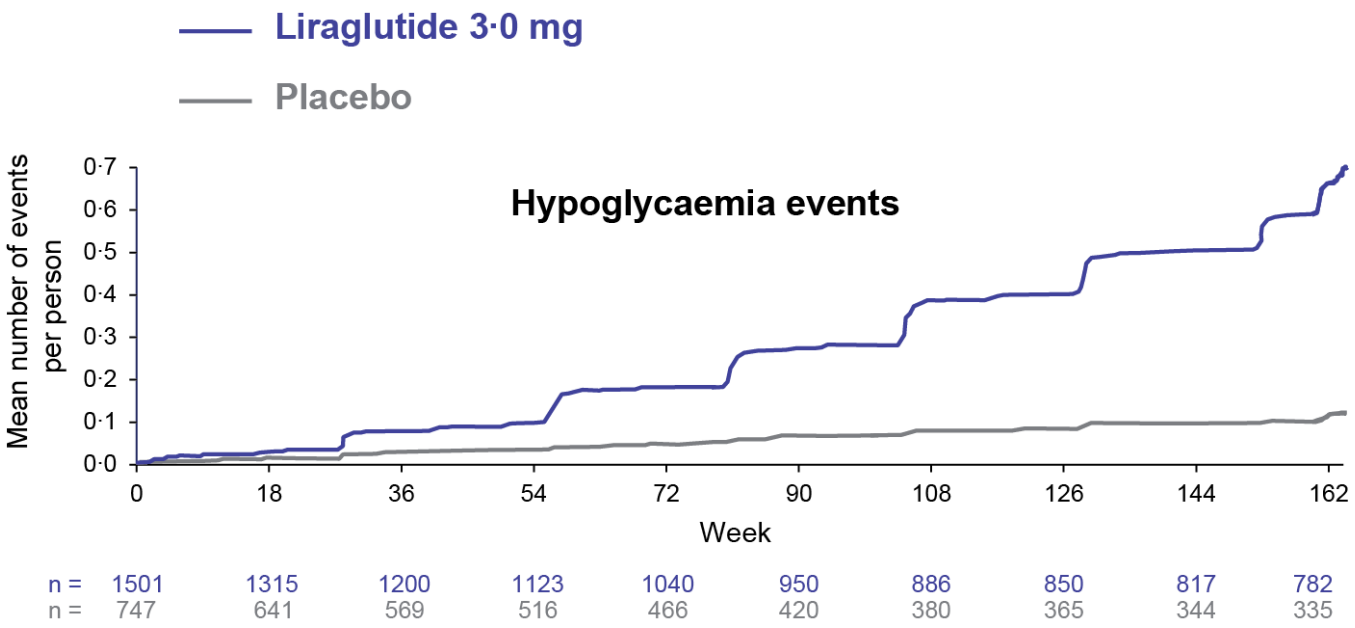
A



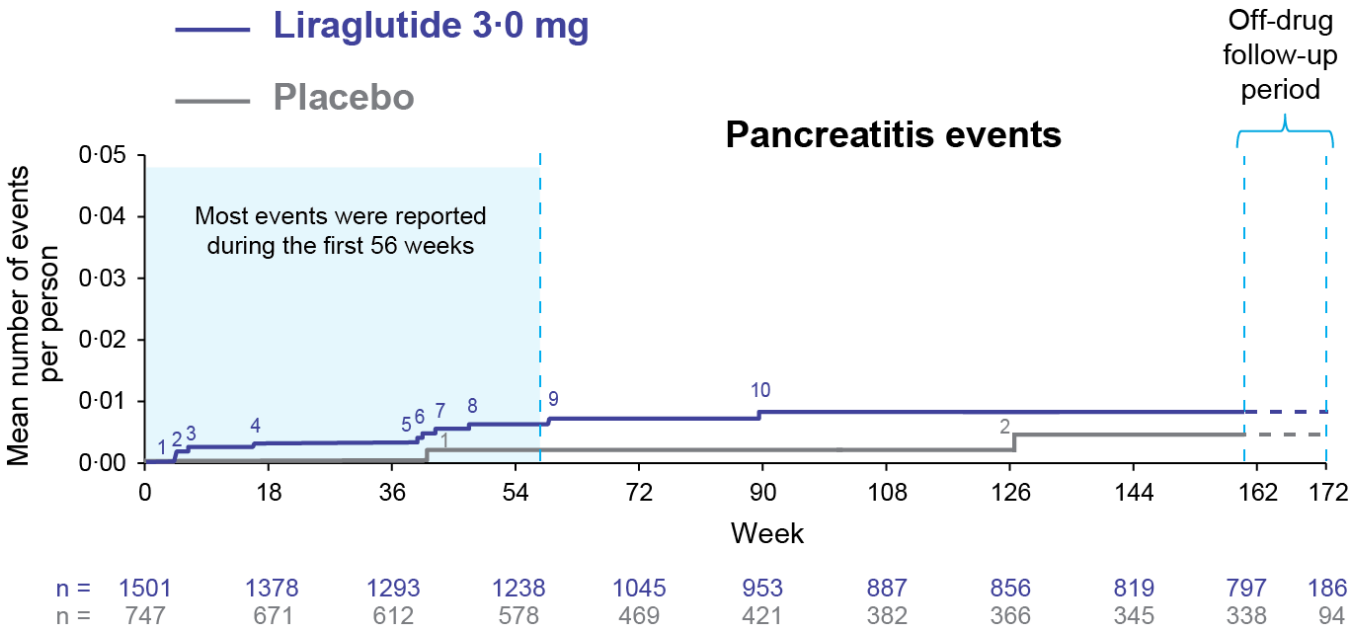
B



C


Liraglutide 3·0 mg
Placebo
Hypoglycaemia events
Mean number of events per person
0·7
0·6
0·5
0·4
0·3
0·2
0·1
0·0
0
18
36
54
72
90
108
126
144
162
Week
n = 1501 1315 1200 1123 1040 950 886 850 817 782
n = 747 641 569 516 466 420 380 365 344 335

D


Liraglutide 3·0 mg
Placebo
Off-drug follow-up period
Pancreatitis events
Most events were reported during the first 56 weeks
Mean number of events per person
0·05
0·04
0·03
0·02
0·01
0·00
1 2 3 4 5 6 7 8 9 10
1
2
0
18
36
54
72
90
108
126
144
162
172
Week
n = 1501 1378 1293 1238 1045 953 887 856 819 797 186
n = 747 671 612 578 469 421 382 366 345 338 94

E

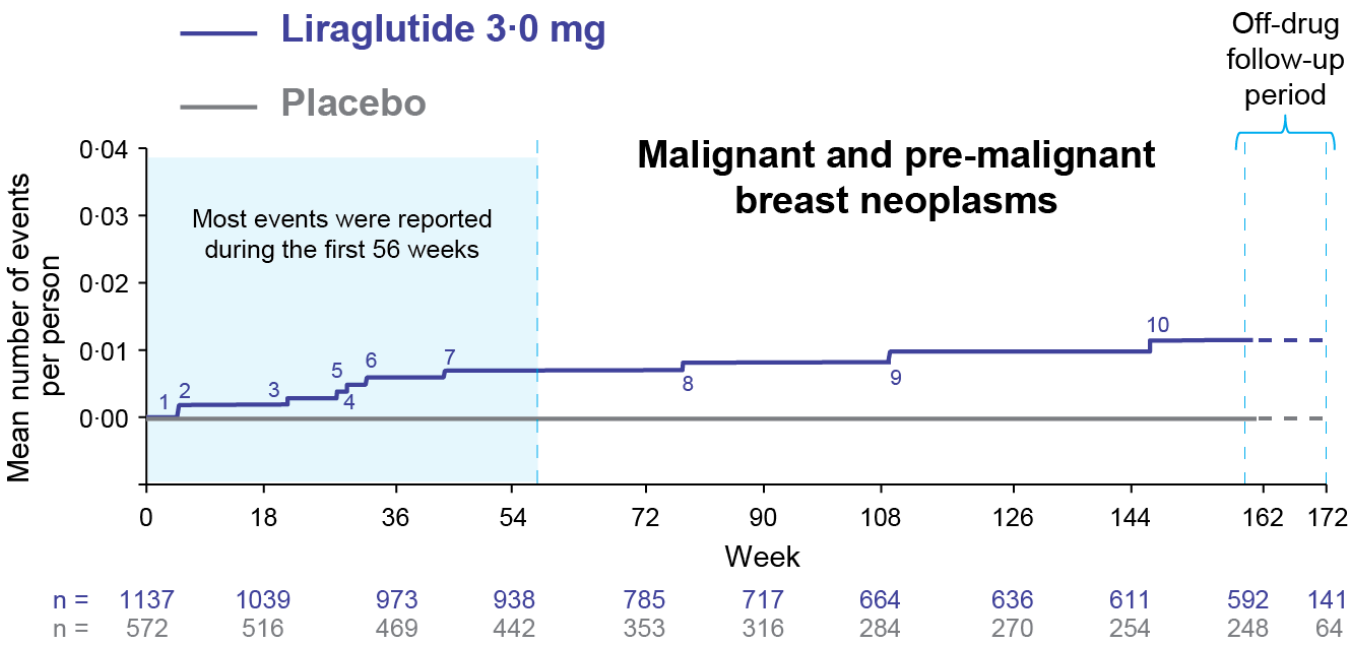

Liraglutide 3·0 mg
Placebo
Off-drug follow-up period
Malignant and pre-malignant breast neoplasms
Most events were reported during the first 56 weeks
Mean number of events per person
0·04
0·03
0·02
0·01
0·00
1
2
3
4
5
6
7
8
9
10
0
18
36
54
72
90
108
126
144
162
172
Week
n = 1137 1039 973 938 785 717 664 636 611 592 141
n = 572 516 469 442 353 316 284 270 254 248 64

Figure S14. Gallbladder-related events by weight loss

The onset of gallbladder-related events by weight loss at the time of onset of the event is shown over 162 weeks of the trial. Data are from the full-analysis set (% weight loss) and safety analysis set. The lines represent the mean weight loss achieved by individuals treated with liraglutide 3·0 mg or placebo in the analysis; each event is plotted by time of event and the weight change experienced by the individual at the time of the event. Individuals were randomised 2:1 to liraglutide 3·0 mg and placebo. MedDRA denotes Medical Dictionary for Regulatory Activities.

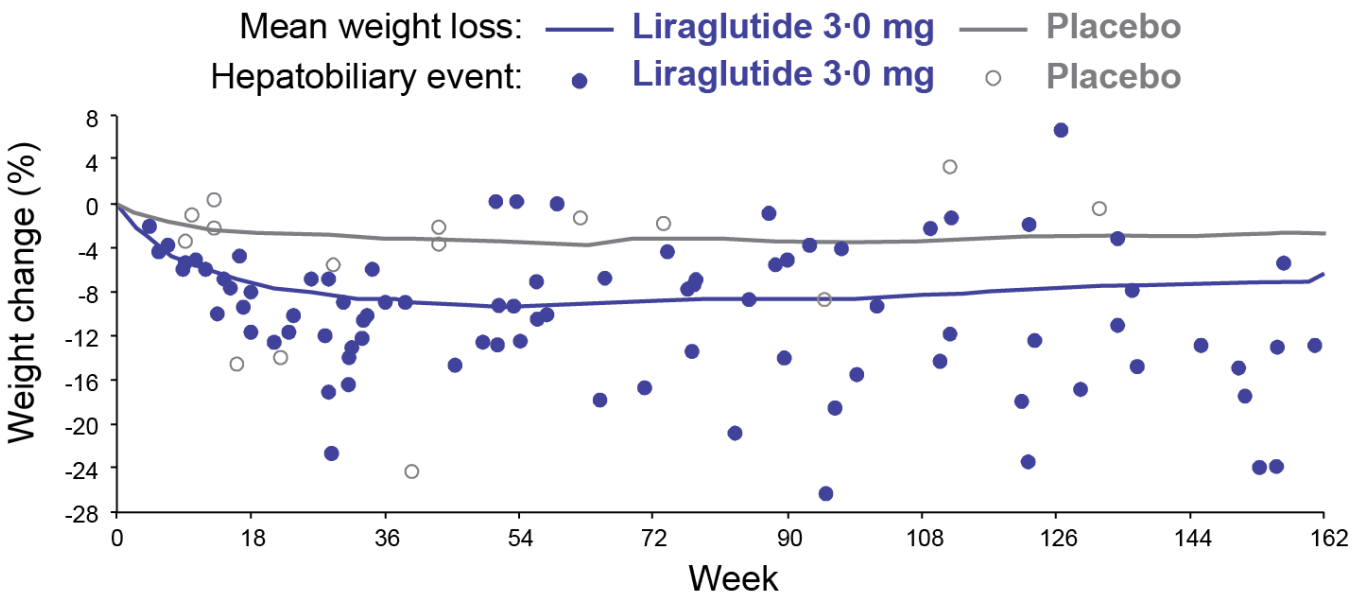
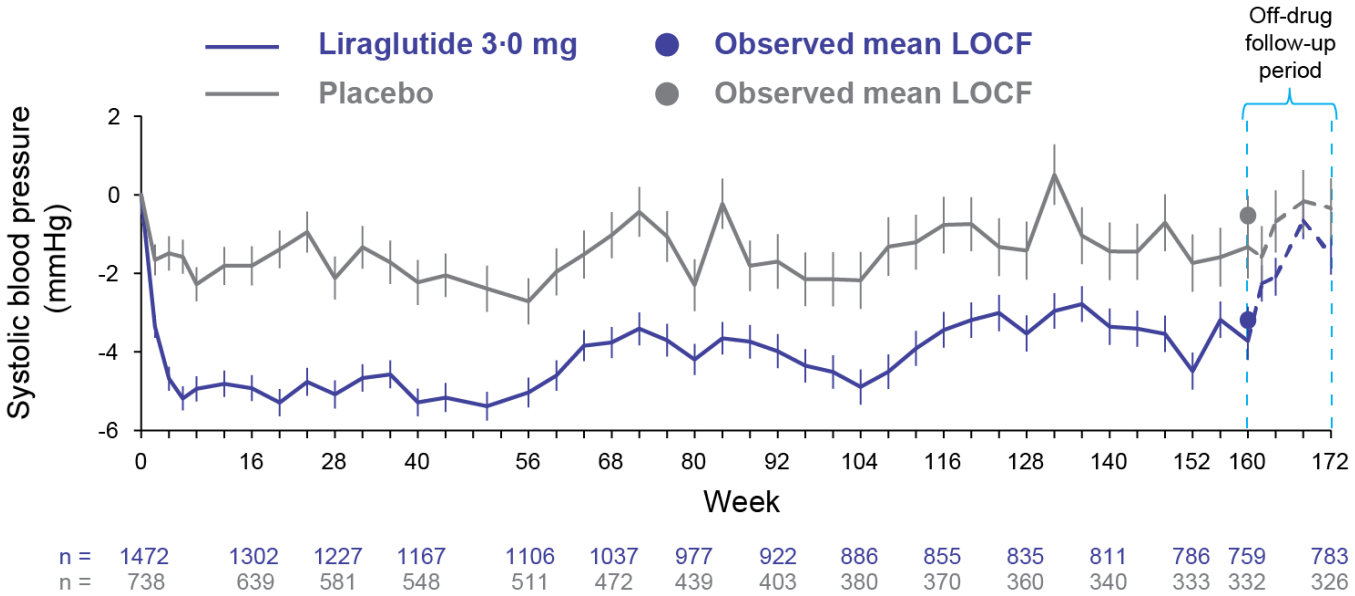


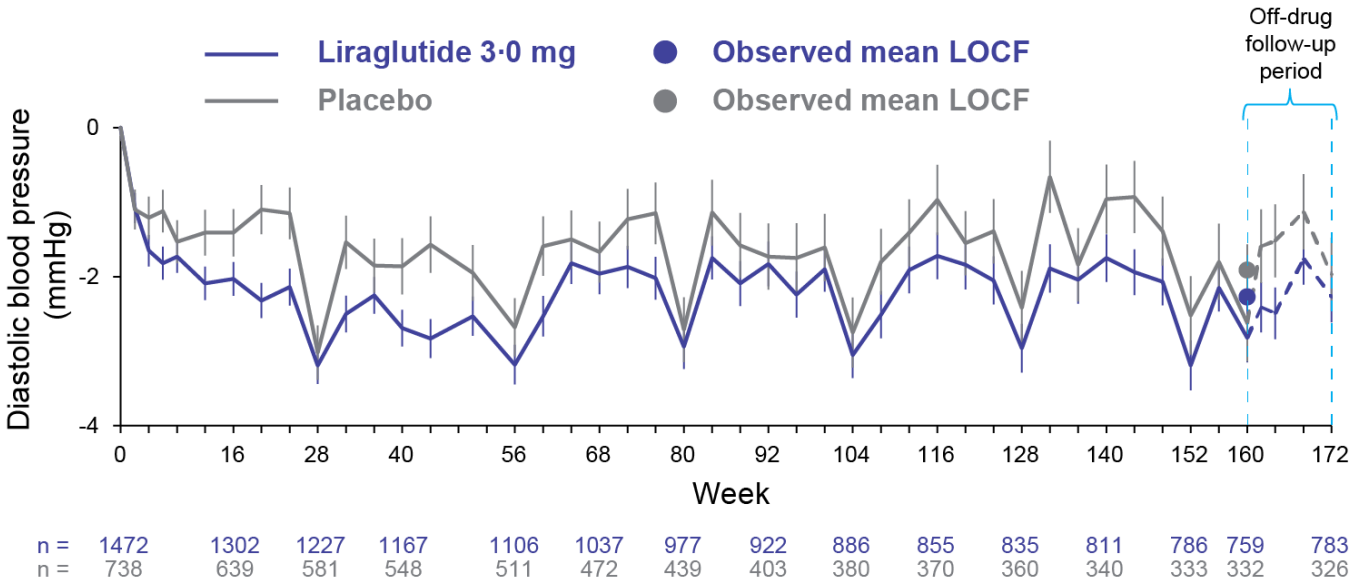
Figure S15. Blood pressure and heart rate changes over the course of the trial

Mean changes in systolic blood pressure (Panel A), diastolic blood pressure (Panel B), and heart rate (Panel C) are shown. Data are observed means with standard error bars for the full-analysis set (blood pressure) or safety analysis set (heart rate), with last-observation-carried-forward (LOCF) imputation at week 160 shown as a separate symbol. Treatment was discontinued at week 160, but diet and exercise continued until week 172.

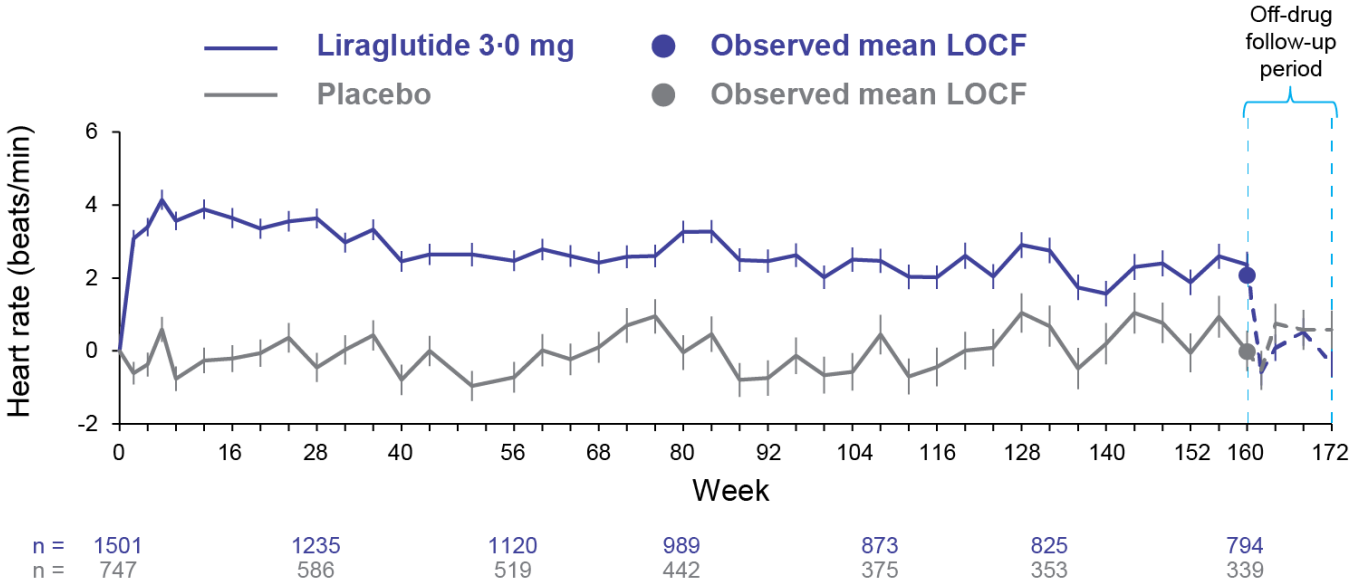
A



B



C


Liraglutide 3·0 mg
Placebo
Observed mean LOCF
Observed mean LOCF
Off-drug follow-up period
Heart rate (beats/min)
6
4
2
0
-2
0
16
28
40
56
68
80
92
104
116
128
140
152
160
172
Week
n = 1501 1235 1120 989 873 825 794
n = 747 586 519 442 375 353 339

Supplemental tables

Table S1. Complete list of inclusion and exclusion criteria

Inclusion criteria
Informed consent obtained before any trial-related activity takes place
Obesity (BMI ≥30·0 kg/m^2); or overweight (BMI ≥27·0 kg/m^2) with treated or untreated co-morbid dyslipidaemia[†] and/or hypertension[‡]
Stable body weight (less than 5 kg self-reported change during the previous 3 months)
Preceding failed dietary effort
Age ≥18 years
Exclusion criteria
Diagnosis of type 1 or type 2 diabetes per the judgment of the investigator
HbA_{1c} ≥6·5% or fasting plasma glucose ≥7·0 mmol/L (126 mg/dL) or 2-hour post-challenge plasma glucose ≥11·1 mmol/L (200 mg/dL) (at screening)
Previous treatment with GLP-1 receptor agonists (including liraglutide or exenatide) within the last 3 months
Untreated or uncontrolled hypothyroidism/hyperthyroidism defined as thyroid-stimulating hormone >6 mIU/L or <0·4 mIU/L
Screening calcitonin ≥50 ng/L
Family or personal history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma (FMTC)
Personal history of non-familial medullary thyroid carcinoma
History of chronic pancreatitis or idiopathic acute pancreatitis
Obesity induced by other endocrinologic disorders (e.g. Cushing's Syndrome)
Current or history of treatment with medications that may cause significant weight gain, within 3 months prior to screening, including systemic corticosteroids (except for a short course of treatment, i.e. 7−10 days), tri-cyclic antidepressants, atypical antipsychotic and mood stabilizers (e.g. imipramine, amitriptiline, mirtazapin, paroxetine, phenelzine, clorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium)
Diet attempts using herbal supplements or over-the-counter medications within 3 months before screening
Current participation (or within the last 3 months) in an organised weight reduction programme or currently using or used within 3 months before screening: pramlintide, sibutramine, orlistat, zonisamide, topiramate, phenteremine, or metformin (either by prescription or as part of a clinical trial)
Participation in a clinical trial within the last 3 months prior to screening
Simultaneous participation in any other clinical trial of an investigational drug
Previous surgical treatment for obesity (excluding liposuction if performed >1 year before trial entry)
History of major depressive disorder within the last 2 years
History of other severe psychiatric disorders, e.g. schizophrenia, bipolar disorder
A Patient Health Questionnaire-9 (PHQ-9) score of ≥15
Any lifetime history of a suicidal attempt
A history of any suicidal behaviour in the last month prior to randomisation
Any suicidal ideation of type 4 (active suicidal ideation with some intent to act without specific plan) or 5 (active suicidal ideation with specific plan and intent) on the Columbia Suicidality Severity Rating Scale (C-SSRS) in the last month prior to randomisation
Surgery scheduled for the trial duration period, except for minor surgical procedures, at the discretion of the investigator
Uncontrolled treated/untreated hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥100 mm Hg). If white-coat hypertension is suspected at screening, a repeated measurement prior to other trial related activities is allowed.
Cancer (past or present, except basal cell skin cancer or squamous cell skin cancer), which in the investigator's opinion could interfere with the results of the trial
Known or suspected hypersensitivity to trial product or related products
Previous participation in the randomised phase of this trial. Re-screening is allowed once within the limit of the recruitment period.
Known or suspected abuse of alcohol or narcotics
Language barrier, mental incapacity, unwillingness or inability to understand and be able to complete the mental health questionnaire in the provided language
Individuals from the same household participating in the trial
Females of child-bearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods (adequate contraceptive measures as required by local law or practice). US: abstinence and the following methods: diaphragm with spermicide, condom with spermicide (by male partner), intrauterine device, sponge, spermicide, Norplant, Depo-Provera or oral contraceptives. Germany: adequate contraceptive measures are implants, injectables, combined oral contraceptives, hormonal Intra-Uterine Device (IUD), sexual abstinence or vasectomised partner. UK: adequate contraceptive measures are defined as sterilisation, intra-uterine device, oral contraceptives, consistent use of

barrier methods, male sterilisation or true abstinence.
The receipt of any investigational drug within 4 weeks prior to screening for this trial (Brazil: The receipt of any investigational drug within 1 year prior to screening for this trial, unless there is direct benefit to the individual at the investigator discretion).
France: Abnormality of the thyroid identified during the physical exam at screening

[†]Low-density lipoprotein ≥160 mg/dl, or triglycerides ≥150 mg/dl, or high-density lipoprotein <40 mg/dl for males and <50 mg/dl for females.[16, 17]

[‡]Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.[18]

BMI=body-mass index. GLP-1=glucagon-like peptide-1. HbA_{1c},=glycated haemoglobin.

Table S2. Adverse events of special interest

Pre-defined, broad searches based on standard MedDRA queries (SMQ), high-level group terms (HLGT), high-level terms (HLT) and/or preferred terms (PT) for adverse events (AEs) in the categories below were performed among all AEs in order to identify relevant events. All AEs in the below categories (except death) were evaluated based on the above-mentioned search results (those marked 'Pre-defined MedDRA search based' below). Some types of AEs were also evaluated via a blinded adjudication process by an independent, external adjudication committee of medical experts (those marked 'Adjudicated' below). Based on predefined diagnostic criteria, the adjudication committee could either confirm or not confirm the AE classification/diagnosis.

Event type	Evaluation	
	Pre-defined MedDRA search based	Adjudicated
Death	No	Yes
Cardiovascular events[a]		
Acute coronary syndrome	Yes	Yes
Cerebrovascular	Yes	Yes
Heart failure	Yes	Yes
Stent thrombosis	Yes	Yes
Revascularisation procedure	Yes	Yes
Hospitalisation for cardiac arrhythmia	Yes	No
Pancreatitis/suspicion of pancreatitis[b]	Yes	Yes
Gallbladder-related events[c]	Yes	No
Neoplasms[d]	Yes	Yes
Thyroid disease[e]	Yes	AEs requiring thyroidectomy and thyroid neoplasms only
Acute renal failure[f]	Yes	No
Severe hypoglycaemic episodes[g]	Not applicable	No
Immunogenicity events[h]		
Allergic reactions	Yes	No
Immune-complex disease	Yes	No
Injection-site reactions	Yes	No
Psychiatric disorders[i]	Yes	No

MedDRA=Medical Dictionary for Regulatory Activities.

[a]Cerebrovascular disorders (SMQ), Cardiac failure (SMQ), Embolic and thrombotic events (SMQ), Torsade de pointes/QT prolongation (SMQ), Cardiac arrhythmias (SMQ), Arrhythmia related investigations (signs and symptoms) (SMQ), Bradyarrhythmia terms (nonspecific) (SMQ), Conduction defects (SMQ), Disorders of sinus node function (SMQ), Cardiac arrhythmia terms (nonspecific) (SMQ), Supraventricular tachyarrhythmias (SMQ), Tachyarrhythmia terms (nonspecific) (SMQ), Ventricular tachyarrhythmias (SMQ).

[b]Acute pancreatitis (narrow scope) (SMQ) and Acute and chronic pancreatitis (HLT).

[c]Bile duct related disorders (SMQ), Biliary system related disorders and investigations (signs and symptoms) (SMQ), Gallstone related disorders (SMQ), Infectious biliary disorders (SMQ), Site unspecified biliary disorders (SMQ), Gallbladder related disorders (SMQ).

[d]Biliary neoplasms malignant and unspecified (SMQ), Biliary malignant tumours (SMQ), Biliary tumours of unspecified malignancy (SMQ), Breast neoplasms - malignant and unspecified (SMQ), Breast malignant tumours (SMQ), Breast tumours of unspecified malignancy (SMQ), Liver neoplasms - malignant and unspecified (SMQ), Liver malignant tumours (SMQ), Liver tumours of unspecified malignancy (SMQ), Malignant or unspecified tumours (SMQ), Malignant tumours (SMQ), Tumours of unspecified malignancy (SMQ), Ovarian neoplasms - malignant and unspecified (SMQ), Ovarian malignant tumours (SMQ), Ovarian tumours of unspecified malignancy (SMQ), Oropharyngeal neoplasms (SMQ), Premalignant disorders (SMQ), Blood premalignant disorders (SMQ), Gastrointestinal premalignant disorders (SMQ), Premalignant disorders - general conditions and other site specific disorders (SMQ), Reproductive premalignant disorders (SMQ), Skin premalignant disorders (SMQ), Prostate neoplasms - malignant and unspecified (SMQ), Prostate malignant tumours (SMQ), Prostate tumours of unspecified malignancy (SMQ), Skin neoplasms - malignant and unspecified (SMQ), Skin malignant tumours (SMQ), Skin tumours of unspecified malignancy (SMQ), Uterine and fallopian tube neoplasms - malignant and unspecified (SMQ), Uterine and fallopian tube malignant tumours (SMQ), Uterine and fallopian tube tumours of unspecified malignancy (SMQ), Tumour markers (SMQ).

[e]Hyperthyroidism (SMQ), Hypothyroidism (SMQ) and Thyroid gland disorders (HLGT) and Calcitonin secretion disorder (PT), Ectopic calcitonin production (PT), Hypercalcitoninaemia (PT), Blood calcitonin abnormal (PT), Blood calcitonin increased (PT).

[f]Acute renal failure (SMQ).

[g]American Diabetes Association Workgroup on Hypoglycaemia.[13]

[h]Anaphylactic reaction (narrow scope) (SMQ), Anaphylactic/anaphylactoid shock conditions (narrow scope) (SMQ), Angioedema (narrow scope) (SMQ), Severe cutaneous adverse reactions (narrow scope) (SMQ), Asthma/bronchospasm (narrow scope) (SMQ), Documented hypersensitivity to administered drug (PT), Type II hypersensitivity (PT), Type IV hypersensitivity reaction (PT), Systemic lupus erythematous (narrow scope) (SMQ), Vasculitis (narrow scope) (SMQ), Guillain-Barre syndrome (narrow scope) (SMQ) and Serum sickness (PT), Serum sickness-like reaction (PT), Cryoglobulin urine present (PT), Cryoglobulins (PT), Cryoglobulinuria (PT), Acute interstitial pneumonitis (PT), Granulomatous pneumonitis (PT), Pneumonitis (PT), Fibrillary glomerulonephritis (PT), Glomerulonephritis (PT), Glomerulonephritis acute (PT), Glomerulonephritis chronic (PT), Glomerulonephritis membranoproliferative (PT), Glomerulonephritis membranous (PT), Glomerulonephritis minimal lesion (PT), Glomerulonephritis proliferative (PT), Glomerulonephritis rapidly progressive (PT), Immunotactoid glomerulonephritis (PT), Mesangioproliferative glomerulonephritis (PT), Immune complex level increased (PT), Type III immune complex mediated reaction (PT), Administration site reactions (HLT), Application and instillation site reactions (HLT), Infusion site reactions (HLT), Lipodystrophies (HLT), Injection site reactions (HLT).

[i]Search results were all reported AEs included in the system organ class of ‘psychiatric disorders’ (including primary and secondary preferred terms).

Table S3. Additional baseline characteristics of all randomised individuals.*

Characteristic	Liraglutide 3·0 mg (N=1505)	Placebo (N=749)
Cardiovascular disease – n (%)†	191 (12·7)	99 (13·2)
Gallbladder disease – n (%)‡	208 (13·8)	112 (15·0)
Treated with anti-hypertensive drugs – n (%)	586 (38·9)	293 (39·1)
Treated with lipid-lowering drugs – n (%)	294 (19·5)	136 (18·2)
HOMA-IR	4·4±96·8	4·4±87·4
Matsuda index (insulin sensitivity)#	1·5±1·1	1·5±0·7
HOMA-B	192·4±67·4	192·3±106·5
Disposition index#	1·6±0·7	1·6±0·6
hsCRP – mg/L	4·2±125·3	4·2±103·7
PAI-1 – ng/mL	17·7±99·3	17·7±91·4
Adiponectin – µg/ml	7·1±46·3	7·1±45·6
Fibrinogen – g/L	4·4±22·8	4·4±21·8
Urinary albumin:creatinine ratio (mg/g)	3·8±321·6	3·9±625·1
IWQoL-Lite total score	71·9±18·8	70·7±18·9
SF-36 overall physical health score	47·2±8·7	46·6±9·0
SF-36 overall mental health score	53·8±8·2	54·0±8·0

*Data are observed means ± SD or number (%), except for HOMA-related parameters and cardiovascular biomarkers, where data are geometric means and CV%. Scores on the IWQoL-Lite questionnaire and the SF-36 can range from 0 to 100, with higher scores indicating a better quality of life.
CV=coefficient of variation. HOMA=homeostasis model assessment. hsCRP=high-sensitivity C-reactive protein. IWQoL-Lite=Impact of Weight on Quality of Life–Lite version. MedDRA=Medical Dictionary for Regulatory Activities. N=number of individuals. OGTT=oral glucose tolerance test. PAI-1=plasminogen activator inhibitor-1. SD=standard deviation. SF-36=Short-Form (36-item) health status survey.
†Based on standardised MedDRA queries ischaemic heart disease, cardiac failure, central nervous system haemorrhages, cerebrovascular conditions, embolic and thrombotic events.
‡Includes individuals previously diagnosed with gallbladder disease, gallstones or cholecystitis.
Beta-cell function and insulin resistance in the fasting state were derived from fasting plasma glucose and fasting insulin data using the HOMA method and were for the full-analysis set of individuals (1427 in the liraglutide group and 706 in the placebo group).[19] HOMA-B is a measure of beta-cell function in the fasting state. HOMA-IR is a measure of insulin resistance in the fasting state, mainly at the site of the liver.
#The Matsuda index was derived from data obtained during a 75 g OGTT.[3] The disposition index was estimated as the product of the insulin secretion ratio and the Matsuda index during the OGTT. The disposition index is a measure of dynamic insulin secretion adjusted for the ambient degree of insulin resistance.[6]

Table S4. Baseline characteristics of randomised individuals by withdrawal status.*

Characteristic	Individuals who completed the trial		Individuals who withdrew from the trial	
	Liraglutide 3·0 mg (N=791)	Placebo (N=337)	Liraglutide 3·0 mg (N=714)	Placebo (N=412)
Sex – n (%)				
Female	588 (74·3)	247 (73·3)	553 (77·5)	326 (79·1)
Male	203 (25·7)	90 (26·7)	161 (22·5)	86 (20·9)
Age - years	49·6±11·0	49·3±11·0	45·3±12·0	45·7±12·2
White race – n (%)†	667 (84·3)	288 (85·5)	589 (82·5)	340 (82·5)
Hispanic or Latino ethnic group – n (%)†	61 (7·7)	32 (9·5)	82 (11·5)	38 (9·2)
Weight - kg	107·3±21·8	108·5±22·8	107·8±21·4	107·3±20·9
Body-mass index – kg/m^2	38.7±6.6	38.9±6.5	38.9±6.2	39.0±6.2
Body-mass index categories – n (%)				
27-29·9 – overweight	26 (3·3)	13 (3·9)	13 (1·8)	10 (2·4)
30-34·9 – obesity class I	226 (28·6)	94 (27·9)	201 (28·2)	103 (25·0)
35-39·9 – obesity class II	259 (32·7)	106 (31·5)	233 (32·6)	139 (33·7)
≥40 – obesity class III	280 (35·4)	124 (36·8)	267 (37·4)	160 (38·8)
Glycated haemoglobin – %	5·8±0·3	5·8±0·3	5·7±0·3	5·7±0·3
Fasting glucose – mmol/L	5·5±0·6	5·5±0·5	5·5±0·7	5·4±0·5
Dyslipidaemia – n (%)‡	290 (36·7)	120 (35·6)	209 (29·3)	129 (31·3)
Hypertension – n (%)‡	373 (47·2)	152 (45·1)	262 (36·7)	160 (38·8)
Dyslipidaemia and hypertension – n (%)‡	191 (24·1)	79 (23·4)	126 (17·6)	77 (18·7)
Cardiovascular disease – n (%)#	107 (13·5)	51 (15·1)	84 (11·8)	48 (11·7)

*Data are observed means ± SD or number (%).
MedDRA=Medical Dictionary for Regulatory Activities. N=number of individuals. SD=standard deviation.
†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.
#Based on standardised MedDRA queries ischaemic heart disease, cardiac failure, central nervous system haemorrhages, cerebrovascular conditions, embolic and thrombotic events.

Table S5. Sensitivity analyses performed for primary endpoints

Endpoint	Type of analysis	Description
Time to onset of T2DM	Completer population	Same analysis as the primary Weibull applied to completers in the full-analysis set with a valid non-imputed measurement at week 160.
	Only individuals with a diagnosis of prediabetes at screening	Same analysis as the primary Weibull applied to individuals who had a diagnosis of prediabetes at screening (i.e., including the 37 individuals with prediabetes from the 56-week trial who entered the re-randomised treatment period and excluding the 6 without prediabetes who continued into the 3-year trial.)
	Including individuals with possible T2DM†	Same analysis as the primary Weibull including individuals with possible T2DM, who either had a blood test indicating diabetes and were withdrawn from the trial, or were put on anti-diabetic medication prior to confirmation by a subsequent test.
	Including individuals with possible T2DM and those assessed as having T2DM by the investigator†	Same analysis as above but also including individuals indicated as having T2DM by the investigator in the electronic data capture system.
	Excluding potentially unblinded individuals†	Same analysis as the primary Weibull but excluding individuals who were potentially unblinded: 1) 16 individuals who were potentially unblinded because the central laboratory released the pharmacokinetic profile reports to the sites during the 56-week part of the trial; 2) 9 individuals who were potentially unblinded at site 469 because the investigator at that site was signatory investigator for the 56-week part of the trial and therefore received the 56-week clinical study report for review.
	Up to week 172	Same analysis as the primary Weibull but up to 72 weeks.
	Up to week 172 and including individuals with possible T2DM and those assessed as having T2DM by the investigator†	Same analysis as the primary Weibull up to weeks 72 including individuals with possible T2DM, who either had a blood test indicating diabetes and were withdrawn from the trial, or were put on anti-diabetic medication prior to confirmation by a subsequent test. Also including individuals indicated as having T2DM by the investigator in the electronic data capture system.
	Full-analysis set from 56-week trial	Same analysis as the primary Weibull applied to all individuals from the full-analysis set from the 56-week trial (i.e., including individuals with prediabetes and those with normoglycaemia.) Prediabetes status was excluded from the model due to convergence issues.
Change in % body weight	Completer population	Same analysis as the primary ANCOVA applied to completers in the full-analysis set with a valid non-imputed measurement at week 160.
	Multiple imputation	Same analysis as the primary ANCOVA but missing values post-baseline were imputed using a regression model.
	Multiple imputation with copy from placebo†	Same analysis as the primary ANCOVA but based on the assumption that individuals immediately after withdrawal lose any treatment effect beyond what can be expected from placebo treatment.
	Adding 0·3 kg for each month of trial missed	Same analysis as the primary ANCOVA but missing values post-baseline were imputed by adding 0·3 kg to the last observed body weight measurement for each additional month the individual should have remained in the trial. If the imputed weight measurement exceeded the baseline body weight, then that was used instead.

The full-analysis set included all randomised individuals who received treatment and had at least one assessment after baseline.
ANCOVA=analysis of covariance. T2DM=type 2 diabetes mellitus.
†Sensitivity analyses defined post-hoc.

Table S6. Results of prespecified sensitivity analyses for body weight

Estimated mean change in body weight from baseline to week 160 (%)	Liraglutide 3·0 mg	Placebo	Estimated treatment difference (95% CI)	p value
Primary ANCOVA analysis	N=1467	N=734		
	-6·2	-1·8	-4·3 (-4·9 to -3·7)	<0·0001
Completer population	N=747	N=322		
	-7·1	-2·7	-4·4 (-5·5 to -3·4)	<0·0001
Multiple imputation	N=1472	N=738		
	-6·0	-1·5	-4·5 (-5·4 to -3·5)	<0·0001
Multiple imputation with copy from placebo†	N=1467	N=734		
	-4·8	-2·6	-2·2 (-3·1 to -1·3]	<0·0001
Adding 0·3 kg for each month of	N=1472	N=738		
trial missed	-4·5	-0·9	-3·6 (-4·2 to -3·0)	<0·0001

ANCOVA=analysis of covariance. N=the number of individuals included in the analysis.
†This multiple imputation method is known as 'copy from placebo' or 'jump to reference', and is based on the assumption that individuals immediately after withdrawal lose any treatment effect beyond what can be expected from placebo treatment.[20] For this analysis, a non-sequential approach was used based on estimated parameters at week 160 from the placebo completer group.

Table S7. Measures of insulin resistance and beta-cell function between baseline and week 160

Endpoint	Liraglutide 3·0 mg (N=1472)	Placebo (N=738)	Relative difference for liraglutide *vs* placebo (95% CI)*	p value
HOMA-IR (%)	-14·5	3·0	-17 (-21 to -12)	<0·0001
Matsuda index (insulin sensitivity) (%)†	20	10	11 (5 to 17)	<0·001
HOMA-B (%)	15·9	0·6	15 (9 to 20)	<0·0001
Disposition index (%)‡	38	1	39 (31 to 47)	<0·001

*Data are relative changes from baseline and % relative treatment differences (ANCOVA on a log scale) for the full-analysis set with the last observation carried forward.
Measures of beta-cell function and insulin resistance in the fasting state were derived from fasting plasma glucose and fasting insulin data using the homeostasis model assessment (HOMA) method.[19]
†Completer exploratory analysis, based on estimation of the Matsuda index during a 75 g oral glucose-tolerance test (OGTT).[3]
‡Completer exploratory analysis, estimated as the product of the insulin secretion ratio and the Matsuda index during the OGTT. The disposition index is a measure of dynamic insulin secretion adjusted for the ambient degree of insulin resistance.[6] HOMA-B is a measure of beta-cell function in the fasting state. HOMA-IR is a measure of insulin resistance in the fasting state, mainly at the site of the liver.

Table S8. Mean changes in efficacy endpoints between baseline and week 172, after a 12-week observational follow-up period

Endpoint	Liraglutide 3·0 mg (N=783)	Placebo (N=326)	Estimated treatment difference, liraglutide *vs* placebo (95% CI) at week 172	p value
Body weight (% and kg)				
Week 160 (%)	-7·1±8·4	-2·7±7·2		
Week 172 (%)	-5·2±8·3	-2·1±7·3	-3·2 (-4·3 to -2·2)	<0·0001
Week 160 (kg)	-7·5±9·3	-2·8±8·4		
Week 172 (kg)	-5·6±9·2	-2·2±8·4	-3·5 (-4·7 to -2·4)	<0·0001
Waist circumference (cm)				
Week 160	-8·0±9·1	-3·9±8·6		
Week 172	-6·7±9·0	-3·4±8·7	-3·2 (-4·4 to -2·1)	<0·0001
Fasting plasma glucose (mmol/L)				
Week 160	-0·41±0·67	0·07±0·65		
Week 172	-0·08±0·66	0·06±0·67	-0·13 (-0·21 to -0·05)	0·0019
Systolic blood pressure (mm Hg)				
Week 160	-3·7±13·2	-1·3±14·6		
Week 172	-1·6±13·5	-0·35±13·9	-1·5 (-3·0 to 0·05)	0·06
Diastolic blood pressure (mm Hg)				
Week 160	-2·8±9·1	-2·6±9·4		
Week 172	-2·3±9·6	-2·0±8·9	-0·74 (-1·8 to 0·3)	0·15

Data are observed means±SD for individuals in the full-analysis set who entered the follow-up period and had a valid measurement at week 172. CI=confidence interval. N=number of individuals. SD=standard deviation.

Table S9. Observed mean changes in lipids, cardiovascular biomarkers and health-related quality of life 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
Fasting lipid profile				
Total cholesterol (%)	-2·6	-1·6	-2 (-3 to 0)	0·0274
LDL-cholesterol (%)	-4·2	-3·3	-2 (-4 to 0)	0·10
HDL-cholesterol (All) (%)	4·9	4·0	1 (-1 to 3)	0·23
Females (n=1110 *vs* 565)	5·7	4·0	2 (0 to 4)	0·0547
Males (n=362 *vs* 173)	2·5	4·2	-2 (-5 to 2)	0·34
VLDL-cholesterol (%)	-11·1	-6·4	-6 (-9 to -3)	0·0002
Non-HDL cholesterol (%)	-5·4	-3·9	-3 (-5 to -1)	0·0097
Triglycerides (%)	-11·3	-6·8	-6 (-9 to -3)	0·0003
Free fatty acids (%)	0·2	2·6	-5 (-9 to -1)	0·0252
Cardiovascular biomarkers				
hsCRP (%)	-36·9	-11·0	-29 (-34 to -23)	<0·0001
PAI-1 (%)‡	–	–	-13 (-18 to -7)	<0·0001
Adiponectin (%)	29·3	24·1	4 (0 to 9)	0·0450
Fibrinogen (%)	-9·1	-6·5	-3 (-5 to -1)	0·0134
Urinary albumin:creatinine ratio (%)	10·1	11·2	-2 (-11 to 8)	0·72
Health-related quality of life				
IWQoL-Lite total score	11·0±14·2	8·1±14·7	3·4 (2·0 to 4·7)	<0·0001
SF-36 physical component summary	3·1±7·3	2·6±7·6	0·9 (0·2 to 1·6)	0·0156
SF-36 mental component summary	-0·5±8·7	-1·4±9·2	0·8 (-0·1 to 1·6)	0·08
TRIM-Weight total score#	–	–	1·0 (-0·2 to 2·1)	0·11

*Data for quality of life are observed means ± SD; for lipids and cardiovascular biomarkers, data were log-transformed for analysis and presented as the relative changes from baseline and relative treatment differences.
†Estimated treatment differences or relative differences are from an analysis of covariance using the full-analysis set with last-observation-carried-forward (LOCF) imputation. Changes in HDL-cholesterol are presented for all individuals (All), and for females and males separately. All health-related quality of life questionnaires have a 100-point scale with an increase indicating improvement. Post-hoc analysis was performed for HDL-cholesterol by sex and for non-HDL cholesterol.
‡PAI-1 was analysed using different methods at baseline and week 56, therefore changes between baseline and week 56 cannot be calculated. The analysis adjusted for individual baseline values.
#Changes from baseline are not available as the TRIM-Weight questionnaire was not completed at baseline.
HDL= high-density lipoprotein. hsCRP=high-sensitivity C-reactive protein. IWQoL-Lite=Impact of Weight on Quality of Life–Lite version. LDL=low-density lipoprotein. N=number of individuals. PAI-1=plasminogen activator inhibitor-1. SD=standard deviation. SF-36=Short-Form (36-item) health status survey. TRIM-Weight=Treatment Related Impact Measure-Weight. VLDL=very low density lipoprotein.

Table S10. Summary of changes in the use of concomitant medications between baseline and week 160

Type of medication	Liraglutide 3·0 mg (N=1472)	Placebo (N=738)
Anti-hypertensive medications		
Taken at baseline	577 (39·2)	291 (39·4)
Not taken at baseline	895 (60·8)	447 (60·6)
Change at week 160 (LOCF)		
Increase	75 (5·1)	64 (8·7)
No change	1194 (81·1)	602 (81·6)
Decrease	101 (6·9)	28 (3·8)
Unknown	102 (6·9)	44 (6·0)
Lipid-lowering medications		
Taken at baseline	288 (19·6)	134 (18·2)
Not taken at baseline	1184 (80·4)	604 (81·8)
Change at week 160 (LOCF)		
Increase	77 (5·2)	47 (6·4)
No change	1329 (90·3)	659 (89·3)
Decrease	35 (2·4)	14 (1·9)
Unknown	31 (2·1)	18 (2·4)
Oral-antidiabetic medications		
Taken at baseline	1 (0·1)	0 (0·0)
Not taken at baseline	1471 (99·9)	738 (100·0)
Change at week 160 (LOCF)		
Increase	9 (0·6)	19 (2·6)
No change	1463 (99·4)	719 (97·4)
Decrease	0 (0·0)	0 (0·0)
Unknown	0 (0·0)	0 (0·0)

Data are observed numbers (%) using the full-analysis set and changes from baseline are with last-observation-carried-forward (LOCF) imputation.
N=number of individuals.

Table S11. Pancreatitis events confirmed by external adjudication committee of medical experts

Over 172 weeks, 12 pancreatitis cases were confirmed by independent adjudication: 10 in the liraglutide 3.0 mg group and 2 in the placebo group. Most events were mild according to the Atlanta classification[21] and were of short duration (2–15 days). All individuals recovered following treatment discontinuation. Two of the pancreatitis cases were judged to be non-treatment emergent, occurring 74 and 125 days after discontinuation of liraglutide treatment. Gallstone-related pancreatitis was defined as indicated by gallstones on imaging and/or enzyme levels 3 or more times the upper limit of the normal range.[22]

Treatment	Preferred term	Exposure at onset / duration (days)	Diagnostic criteria fulfilled	Severity (Revised Atlanta criteria*)	Gallstones on imaging (Y/N)	Elevated ALT (Y/N)
Treatment emergent events						
Liraglutide 3·0 mg	Pancreatitis acute	29 / 5	Abdominal pain, enzymes (imaging not done)	Mild	N	N
	Pancreatitis acute	31 / 4	Abdominal pain, enzymes	Mild	N	Y ALT 4×ULN
	Pancreatitis acute	43 / 2	Abdominal pain, imaging	Mild	N	N
	Lipase increased	277 / 15	Abdominal pain, enzymes	Mild	N	N
	Pancreatitis	283 / 9	Abdominal pain, enzymes, imaging	Mild	Y	Y ALT 8×ULN
	Pancreatitis acute	330 / 92	Abdominal pain, imaging	Mild	N	Y ALT <1·5×ULN
	Gastroenteritis	410 / 29	Abdominal pain, enzymes	Mild	N	N
	Pancreatitis	625 / 9	Abdominal pain, imaging	Mild	N	N
Placebo	Pancreatic disorder	287 / 105	Abdominal pain, imaging	Mild	Y	Y ALT 2·5×ULN
	Pancreatitis acute	886 / 5	Enzymes, imaging	Mild	N	N
Non-treatment emergent events reported by withdrawn individuals						
Liraglutide 3·0 mg	Pancreatitis	35[†] / 5	Abdominal pain, enzymes, imaging	Mild	N	Y ALT 3×ULN
	Pancreatic pseudocyst	170[‡] / 92	Abdominal pain, enzymes, imaging	Moderately severe	Y	Unknown; AST 24×ULN

Data are from the safety analysis set.
ALT=alanine aminotransferase. AST=aspartate aminotransferase. N=no. ULN=the upper limit of the normal range. Y=yes.
*Post-hoc assessment by Dr Vikesh Singh, Pancreatitis Center, Division of Gastroenterology, Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, MD 21287, USA, according to the Revised Atlanta Criteria.[21]
[†]Event onset 74 days after last dose of liraglutide. [‡]Event onset 124 days after last dose of liraglutide.

Table S12. Mean changes in resting heart rate, by treatment

Heart rate category	Liraglutide 3·0 mg (N=1501) N (%)	Placebo (N=747) N (%)
Change in heart rate >5 bpm at ≥2 consecutive visits	991 (66·0)	385 (51·5)
Change in heart rate >10 bpm at ≥2 consecutive visits	622 (41·4)	203 (27·2)
Change in heart rate >20 bpm at ≥2 consecutive visits	113 (7·5)	27 (3·6)

Bpm=beats per minute. N=number of individuals. %=percentage of individuals experiencing at least one episode.

Table S13. Malignant and pre-malignant breast neoplasms in women confirmed by independent medical experts

Treatment	Diagnosis trial day	Age (years)/ BMI (kg/m^2)	Screen detected	Grade	Stage				E/P/HER 2 status	Weight loss, %
					T	N	M	AJCC[1] / EAC		
Malignant neoplasms										
Liraglutide 3·0 mg	30	51 / 53·2	Y	2	pT2	pN1a	M0	IIB / Stage 3: advanced	+/+/-	-6·4
	142/224*	60 / 29·6	N	2	pT1c	pN1	M0	IIA / Stage 1: localised	+/+/-	-10·0
	193	43 / 37·0	N	3	cT3	pN1	M0	IIIA / Stage 3:advanced	-/-/-	-8·0
	222	62 / 51·0	Y	2	pT1c	pN1a		IIA / Stage 2: locally advanced	U	-12·0
	546	53 / 36·6	Y	1	pT1a	pN0	M0	I / Stage 1: localised	+/+/-	-3·2
	757	58 / 38·2	Y	2	pT1c	N1		IIA / Stage 2: locally advanced	+/+/-	-11·1
Pre-malignant neoplasms										
Liraglutide 3·0 mg	31	54 / 44·2	Y	3	pTis	Nx	Mx	0 / Stage 0: *in situ*	+/+/U	-2·6
	302	59 / 44·5	Y	2	pTis	Nx	Mx	0 / Stage 0: *in situ*	+/-/U	-9·4
	1021	57 / 36·3	Y	2 to 3	U	U	U	U / Stage 0: *in situ*	U	-13·9

Age was at randomisation. *Individual had 2 events; weight loss at the time of the first event is shown.
AJCC=American Joint Committee on Cancer. BMI=body-mass index. EAC=Event adjudication Committee. E/P/HER 2=oestrogen/progesterone/human epidermal growth factor receptor 2. U=unknown.
The AJCC has designated staging by tumour, node, and metastasis (TNM) classification to define breast cancer.[23]

Table S14. Overview of PHQ-9 scores at baseline, end of treatment and categorical increases by treatment

PHQ-9 Mean Scores	Liraglutide 3·0 mg (N=1501)	Placebo (N=747)
Mean PHQ-9 total score at baseline	2·9	3·1
Mean PHQ-9 total score at week 160 (LOCF)	1·9	1·9
Percentage of individuals with total score above cut-off		
≥10 at week 160 (LOCF)	2·4	2·3
≥10 at any time during trial	10·7	11·7
≥15 at week 160 (LOCF)	0·7	0·8
≥15 at any time during trial	2·7	3·4
≥20 at week 160 (LOCF)	0·1	0·1
≥20 at any time during trial	0·7	0·9

The PHQ-9 has a 27-point maximum score with a decrease indicating improvement. No depression: PHQ-9 total score of 0–4; mild depression: total score of 5-9; moderate depression: total score of 10-14; moderate severe depression: total score of 15–19; severe depression: total score of ≥20.
LOCF=last-observation-carried-forward imputation. N=number of individuals. PHQ-9=Patient Health Questionnaire-9.

Table S15. PHQ-9 total scores: change in PHQ-9 classification group during treatment

	Liraglutide 3·0 mg		Placebo	
	N	(%)	N	(%)
Number of individuals	1501		747	
Total number of individuals improving from baseline to highest score	121	(8·1)	61	(8·2)
Mild to none	84	(5·6)	40	(5·4)
Moderate to none	12	(0·8)	5	(0·7)
Moderate to mild	25	(1·7)	14	(1·9)
Moderately severe to moderate	0	(0·0)	0	(0·0)
Moderately severe to mild	0	(0·0)	1	(0·1)
Moderately severe to none	0	(0·0)	1	(0·1)
Severe to moderately severe	0	(0·0)	0	(0·0)
Severe to moderate	0	(0·0)	0	(0·0)
Severe to mild	0	(0·0)	0	(0·0)
Severe to none	0	(0·0)	0	(0·0)
Total number of individuals worsening from baseline to highest score	421	(28·0)	201	(26·9)
None to mild	279	(18·6)	127	(17·0)
None to moderate	53	(3·5)	24	(3·2)
None to moderately severe	11	(0·7)	11	(1·5)
None to severe	3	(0·2)	4	(0·5)
Mild to moderate	51	(3·4)	25	(3·3)
Mild to moderately severe	14	(0·9)	4	(0·5)
Mild to severe	5	(0·3)	2	(0·3)
Moderate to moderately severe	3	(0·2)	3	(0·4)
Moderate to severe	2	(0·1)	1	(0·1)
Moderately severe to severe	0	(0·0)	0	(0·0)
No change	946	(63·0)	478	(64·0)
Missing	13	(0·9)	7	(0·9)

No depression: PHQ-9 total score of 0–4; mild depression: total score of 5–9; moderate depression: total score of 10–14; moderate severe depression: total score of 15–19; severe depression: total score of ≥20.
N=number of individuals. %=percentage of individuals. PHQ-9=Patient Health Questionnaire-9.

Table S16. Post-baseline C-SSRS (any time during the treatment period) - suicidal behaviour and suicidal ideation

	Liraglutide 3·0 mg			Placebo		
	N	**n**	**(%)**	**N**	**n**	**(%)**
Number of individuals	1501			747		
Number of individuals answering the C-SSRS	1488			744		
Years of exposure	3466			1576		
Individuals with suicidal behaviour and/or ideation		19	(1·3)		12	(1·6)
Individuals with suicidal ideation on the C-SSRS		19	(1·3)		12	(1·6)
1. Wish to be dead		18	(1·2)		11	(1·5)
2. Active suicidal ideation, non-specific thoughts		8	(0·5)		4	(0·5)
3. Active suicidal ideation with any methods (no plan) without intent		6	(0·4)		1	(0·1)
4. Active suicidal ideation with some intent to act, without specific plan		1	(0·1)		0	(0·0)
5. Active suicidal ideation with specific plan and intent		1	(0·1)		1	(0·1)
Individuals with suicidal behaviour on the C-SSRS		0	(0·0)		0	(0·0)
1. Completed Suicide		0	(0·0)		0	(0·0)
2. Actual suicide attempt		0	(0·0)		0	(0·0)
3. Interrupted attempt		0	(0·0)		0	(0·0)
4. Aborted suicide attempt		0	(0·0)		0	(0·0)
5. Preparatory acts towards imminent suicidal behaviour		0	(0·0)		0	(0·0)
Suicidal behaviour (item)		0	(0·0)		0	(0·0)
Non-suicidal self-injurious behaviour		0	(0·0)		0	(0·0)

C-SSRS=Columbia Suicide Severity Rating Scale. N=number of individuals. n=number of individuals answering yes. %=percentage based on the total N.

Table S17. Overview of hypoglycaemic events from baseline to week 162 in individuals who did not develop type 2 diabetes during the trial

Visit type	Liraglutide 3·0 mg (N=1470)			Placebo (N=700)		
	N	%	E	N	%	E
All hypoglycaemic events	**293**	**19·9**	**634**	**33**	**4·7**	**49**
Spontaneously reported	50	3·4	60	12	1·7	16
Reported at FPG visits	62	4·2	79	6	0·9	6
Reported at OGTT visits	235	16·0	495	18	2·6	27
≤3·9 mmol/L (70 mg/dL) at 120 minutes	190	12·9	388	15	2·1	23
<3·1 mmol/L (56 mg/dL) at 120 minutes	66	4·5	104	3	0·4	6

E=number of hypoglycaemic events. FPG=fasting plasma glucose. N=number of individuals. OGTT=oral glucose-tolerance test. %=percentage of individuals reporting the event.

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