Supplementary Appendix

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

Supplement to: Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015;373:11-22. DOI: 10.1056/NEJMoa1411892

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Supplement to: Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau D, le Roux C, Ortiz RV, Jensen CB, and Wilding J. A Randomized Controlled Trial of 3.0 mg of Liraglutide in Weight Management

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Supplemental Methods

Diet and Exercise Counseling

Standardized dietary and exercise counseling was provided, in individual or group sessions, up to week 68. Patients 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 individualized energy requirements 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.

Clinical Assessments and Procedures

At screening, patients were defined as having prediabetes according to the American Diabetes Association (ADA) 2010 criteria,[2] that is, if they had the following:

- HbA_{1c} measurement of 5.7−6.4% both inclusive,[3] or
- fasting plasma glucose measurement ≥100 mg/dl (5.6 mmol/liter) and ≤125 mg/dl (6.9 mmol/liter), or
- 2-hour plasma glucose measurement post-challenge (oral glucose tolerance test) ≥140 mg/dl (7.8 mmol/liter) and ≤199 mg/dl (11.0 mmol/liter).

The oral glucose tolerance test was done at screening for the diagnosis of prediabetes. Furthermore, patients were diagnosed with type 2 diabetes based on the following criteria:

- HbA_{1c} measurement of ≥6.5%, or
- fasting plasma glucose measurement ≥126 mg/dl (7.0 mmol/liter), or
- 2-hour plasma glucose measurement post-challenge (oral glucose tolerance test) ≥200 mg/dl (11.1 mmol/liter).

The diagnosis was confirmed by a second repeated measurement.

If a patient developed diabetes during the trial, 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.

Body weight, waist circumference and vital signs were assessed at every visit. Glycemic control parameters were measured at weeks 0, 4, 16, 28, 40, 56 and 68 (fasting plasma glucose was additionally measured at weeks 2, 8, 20, 50, 58 and 70; fasting C-peptide was additionally measured at weeks 58 and 70; fasting insulin was only measured at screening and at weeks 28, 56 and 68). Fasting lipids and cardiovascular biomarkers were measured at weeks 0, 28, 56 and 68.

Measures of insulin resistance (HOMA-IR, Matsuda index[4]) 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[5]) and the corresponding glucose area under the concentration–time curve (AUC).[6] The disposition index was calculated as the product of the insulin secretion ratio based on C-peptide and the Matsuda index.[7]

Specific attention was given to certain types of adverse events, including those with increased prevalence in the obese population or side effects relevant to the drug class (Supplemental Table S2).

Serum samples for anti-liraglutide antibodies were assessed at screening, at the start of the re-randomized period and at follow-up.

All hypoglycemic episodes were to be reported as adverse events, and severity was rated according to the sponsor's standard definition (mild, moderate or severe). Hypoglycemic episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions (i.e., 'severe hypoglycemic episodes') qualified as an event of special interest. Patients were not routinely provided with blood glucose meters or diaries; hence blood glucose was not measured in case of symptoms of hypoglycemia unless it coincided with a clinic visit. There were three types of hypoglycemia events reported:

- those spontaneously reported, i.e., symptoms of hypoglycemia (not biochemically confirmed) occurring outside of visits to the clinic;
- those registered by site personnel during visits to the clinic where fasting plasma glucose was assessed. All glucose values ≤70 mg/dl (3.9 mmol/liter) were to be reported as adverse events, irrespective of symptoms;
- those registered during a visit to the clinic when an oral glucose tolerance test was performed. No specific guidance was provided on when to report a low glucose value as a hypoglycemia adverse event.

Hypoglycemia was not included in Table 3 (Adverse Events Occurring in 5% or More Patients) as the majority of 'hypoglycemic events' comprised measurements of glucose below 70 mg/dl (3.9 mmol/liter) captured during fasting visits or oral glucose tolerance test procedures and recorded as hypoglycemia per protocol irrespective of symptoms.

Sample Size Determination and Additional Statistical Methodology

A sample size of 3600 randomized patients, 2400 to liraglutide and 1200 to placebo, was chosen to provide a reasonable assessment of the safety and efficacy of liraglutide for weight management over 3 years. This provided enough power for the three co-primary efficacy end points of the main 56-week trial, as well as the primary end point of the 2-year extension, which was the long-term efficacy of 3.0 mg liraglutide in delaying onset of type 2 diabetes in patients with a diagnosis of prediabetes at screening.

The power for the primary weight change end point was calculated based on a two-sided *t*-test with a significance level of 5%. The power with regard to the co-primary dichotomous end points was calculated based on a two-sided Chi-square test. The trial was estimated to have more than 99% power to detect a difference between liraglutide and placebo in the three weight-loss end points. The large number of randomized patients also provided sufficient power for the primary end point of the 2-year extension, which was to be analyzed by a two-sided Chi-square test with a significance level of 5%.

Prespecified subgroup analyses were performed in patients with or without prediabetes at enrolment (all end points) and in those with different baseline BMI categories (body weight and HbA_{1c} end points). BMI was calculated as the weight in kilograms divided by the square of the height in meters.

For the prediabetes status subgroups, continuous end points were analyzed using an ANCOVA with treatment, prediabetes status at screening, interaction between treatment and prediabetes status at screening, and country, sex and BMI strata nested within prediabetes status at screening as fixed effects, and the baseline value nested within prediabetes status at screening as covariate. Categorical end points were analyzed by logistic regression, using the same fixed effects and covariates as the ANCOVA analysis.

For the subgroups of different BMI categories, the relative change from baseline in mean fasting body weight was analyzed using an ANCOVA that included treatment, BMI category at baseline (27-29.9, 30-34.9, 35-39.9 and ≥40), interaction between treatment and BMI at baseline, country, sex and prediabetes status at screening nested within BMI at baseline as fixed effects and the baseline value nested within BMI at baseline as covariate. Categorical weight changes were analyzed by logistic regression, using the same fixed effects and covariates as the ANCOVA analysis. Changes from baseline in HbA_{1c} were analyzed in a similar manner, except that baseline HbA_{1c} level was included as a covariate in the model.

All statistical analyses in the trial were performed with SAS software, version 9.3 (SAS Institute).

End Points during the 12-week Re-randomized Follow-up Period for Patients without Prediabetes

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

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

Following the 12-week re-randomization period, patients entered a 2-week follow-up observational period to assess for potential liraglutide antibodies.

Acknowledgments

All authors were involved in designing or executing the study and preparing the manuscript, including the decision to submit it for publication, and all attest to the accuracy and completeness of data and the data analyses. The sponsor, Novo Nordisk A/S, planned and performed the statistical analyses.

Supplemental Results

Efficacy

The beneficial effects on blood pressure and lipids observed during the trial occurred concomitantly with a reduction in net use of anti-hypertensive and lipid-lowering medications with liraglutide vs. placebo (Supplemental Table S8). Net use was defined as an increase or decrease in dose or number of medications.

Safety

Adverse Events

A numerical imbalance was observed for malignant and pre-malignant breast neoplasms: 10 events in the liraglutide group (8 in the main 56-week period, 1 in the re-randomized treatment period in a patient who was re-randomized to liraglutide 3.0 mg and 1 non-treatment emergent event) vs. three in the placebo group (2 in the main period and 1 in the re-randomized period). Of the overall 13 events, four were pre-malignant (three with liraglutide [0.12 events per 100 patient years at risk; PYR] and one with placebo [0.08 events per 100 PYR]) and nine were malignant (seven in the liraglutide group [0.27 events per 100 PYR] and two in the placebo group [0.16 events per 100 PYR]).

Based on the low number of events, the short interval between study entry and diagnosis of breast cancer with nodal involvement in most cases, receptor status consistent with distribution in a population of obese women who may not have participated regularly in a breast cancer screening program, and greater than the average weight loss in women with events (Supplemental Table S13.), it is likely that the event imbalance observed is not causally related to liraglutide, but a chance finding or resulting from enhanced ascertainment. Obese women often have reduced compliance with mammographic screening and breast

examination compared to women of normal weight,[8,9] and significant weight loss could have led to increased mammography/breast examination uptake and/or accuracy and therefore earlier diagnosis.

Four confirmed thyroid disease events were reported by three patients in the liraglutide group (three events of thyroid cancer and one non treatment-emergent event of autoimmune thyroiditis).

Rates for events potentially related to acute renal failure (MedDRA search term) were similar with liraglutide 3.0 mg and placebo (0.7 and 0.5 events per 100 patient years of exposure; PYE). The majority of these events were an increase in blood creatinine, blood urea, a decreased glomerular filtration rate or albuminuria. There was no difference in seriousness, severity or outcome between treatments. Only two cases of acute renal failure were observed, one in each group.

Injection site reaction rates were 22.4 and 14.9 events per 100 PYE with liraglutide and placebo, respectively, with similar allergic reaction rates between treatments (2.6 and 3.2 events per 100 PYE).

Mental Health Assessments

No clinically relevant differences for any assessments of mental health were observed between treatments. This included reported psychiatric disorder-related adverse events and assessments of depression using the patient health questionnaire-9 (PHQ-9) (Supplemental Tables S14 and S15) or suicidal behavior and suicidal ideation, using the Columbia suicidality severity rating scale (C-SSRS) (Supplemental Table S16). Although results from the depression and suicidality questionnaires did not suggest an effect of liraglutide on the severity of depression symptoms or an increase in suicidal thinking, four patients treated with liraglutide (versus none treated with placebo) reported adverse events (AEs) of suicidality in the trial. The narratives for the four patients follow.

- The first patient was a 28-year-old female with no prior history of psychiatric disorder. Approximately 6 months into the treatment, the patient presented with depression. The patient's family reported that the depression had been evident for the last couple of months, whereas she felt it only over the last few weeks. The patient was not interested in daily activities and was emotionally labile. She had misused Vicodin to "take away the pain". Three weeks later, the patient reported that she had had two fleeting suicidal thoughts. No action was taken towards making a suicide attempt. The patient's PHQ-9 score at that time was 17 (moderately severe depression). The drug was discontinued. The investigator was unsure if the patient had recovered after treatment discontinuation. Two months later, the site contacted the patient for a post-study follow-up and she stated that she was diagnosed with mild depression and the depressed mood continued intermittently.
- The second patient was a 42-year-old female with no reported history of mental illness who had a 1-day AE of suicidal ideation on day 16 of the trial. The AE was reported as mild and ‘possibly’ related to study drug. On the C-SSRS, the patient 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.
- The third patient was a 41-year-old female with a history of situational depression who had a 1 day AE of suicidal ideation on day 327 of the trial. The AE was reported as mild and ‘unlikely’ to be related to study drug. On the C-SSRS the patient reported ‘wish to be dead’ at screening and at week 50. She recovered 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.
- The fourth patient was a 42-year-old female with a medical history of depression who reported a suicide attempt on day 113 of treatment. She was hospitalized after taking an overdose of an unknown medication with suicidal ideation following an argument with her mother. The patient

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 counseling for her suicidal ideations. Eight months later, the patient 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 patient 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 patient 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.

Antibodies

With regard to anti-liraglutide antibodies, 24 of 875 (2.7%) exposed patients who had a post-baseline antibody measurement and who did not continue in the 2-year trial extension developed anti-liraglutide antibodies; two had antibodies that cross-reacted with native GLP-1 and 11 had antibodies with *in vitro* neutralizing capability (none had both neutralizing and cross-reacting antibodies). Antibody data for patients with prediabetes will be reported after completion of the 2-year extension.

Vital Signs

Changes in vital signs during the trial are shown in Supplemental Fig. S9. For pulse, a persistent increase of more than 20 beats per min at 2 or more consecutive visits occurred in 127/2481 (5.1%) of patients with liraglutide vs. 17/1242 (1.4%) with placebo (Supplemental Table S12).

Hypoglycemic Events

Hypoglycemia adverse events were recorded for 11.9% of patients in the liraglutide group and 3.3% of those in the placebo group; most of these events resulted from biochemical measurements taken during the oral glucose tolerance test and/or visits where fasting plasma glucose was measured, irrespective of symptoms. The majority (91.4%) of the events for patients in the liraglutide group were registered at visits when fasting plasma glucose was measured (26.0%) or when an oral glucose tolerance test was performed (65.4%). A similar pattern was seen in the placebo group, where most (67.4%) of the events were registered at fasting glucose (21.7%) or oral glucose tolerance test visits (45.7%). Of events recorded during fasting visits or OGTT, most were associated with blood glucose measurements above 56 mg/dl (3.1 mmol/liter) and at least 30% were asymptomatic (Supplemental Table S18). For a full breakdown of hypoglycemia events see Supplemental Tables S17 and S18.

Pregnancies

In total, 39 women became pregnant (1.4% vs. 1.2% for liraglutide and placebo, respectively); 10 of the pregnancies resulted in spontaneous abortion (8 with liraglutide [30%] and 2 with placebo [17%]). A similar proportion of pregnant women gave birth to healthy children (52% and 33% of pregnancies for liraglutide and placebo, respectively).

Re-randomized follow-up period

After treatment cessation, a mean weight regain of 2.9% occurred in the group that switched from liraglutide 3.0 mg to placebo (Supplemental Table S19) but mean weight loss remained greater than that achieved with placebo (6.8% vs. 3.1%) at week 68. Fasting plasma glucose reverted to placebo levels within 2 weeks of treatment cessation. Mean pulse rapidly decreased to baseline levels in the group that switched from liraglutide to placebo (Supplemental Fig. S9). Systolic blood pressure increased in the group that switched from liraglutide to placebo but it did not return to baseline levels during the 12-week follow up period, diastolic blood pressure remained at approximately the same level during

follow-up. Lipase and amylase levels also returned to baseline levels during the 12-week follow-up period in the group that switched from liraglutide to placebo.

Supplemental Figures

Figure S1. Trial Design

The main double-blinded trial was of 56 weeks duration plus a 12-week re-randomized treatment period. Patients were stratified according to whether or not they had prediabetes (according to ADA 2010 criteria)[2] at screening. After 56 weeks, patients in the liraglutide group without prediabetes at screening were re-randomized to continue on liraglutide or switch to placebo. Those on placebo remained on placebo. The trial has an ongoing 2-year extension period for patients with prediabetes at screening (not shown).

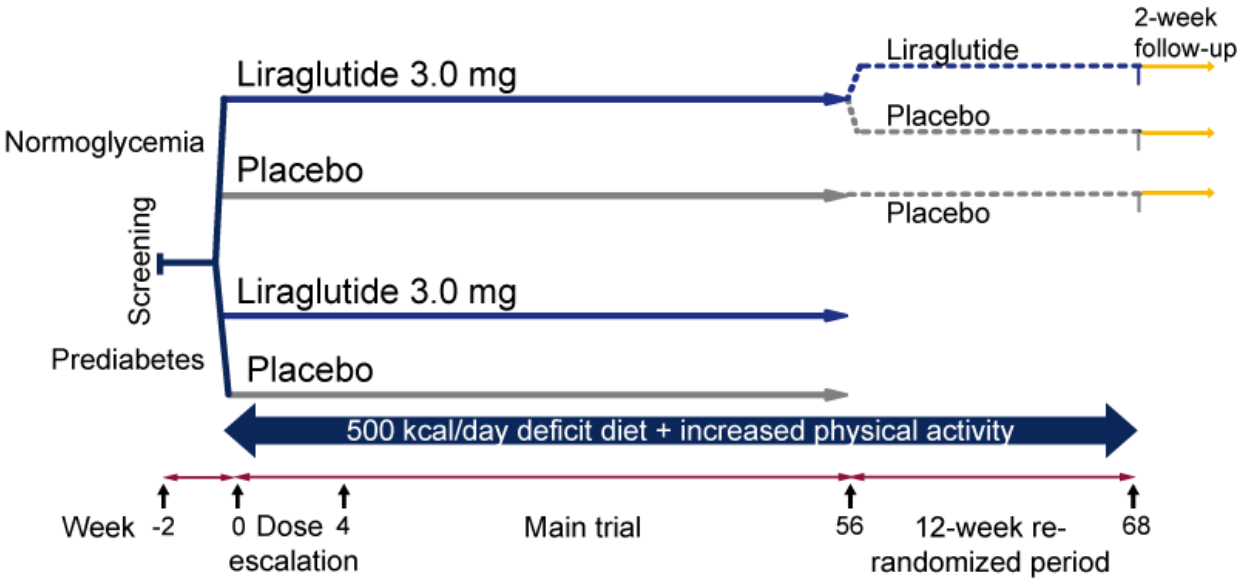
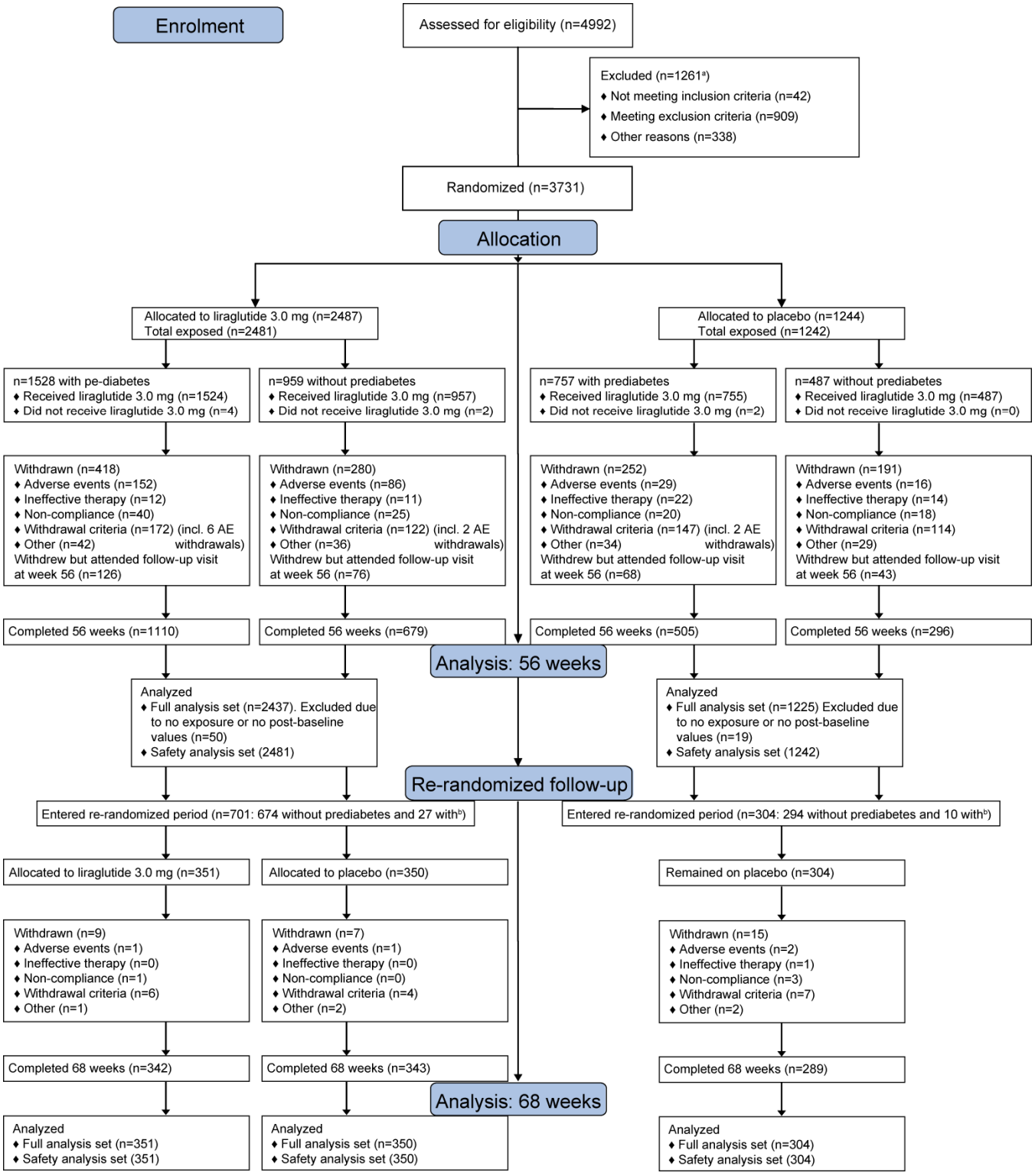


Figure S2. Trial Flow Diagram

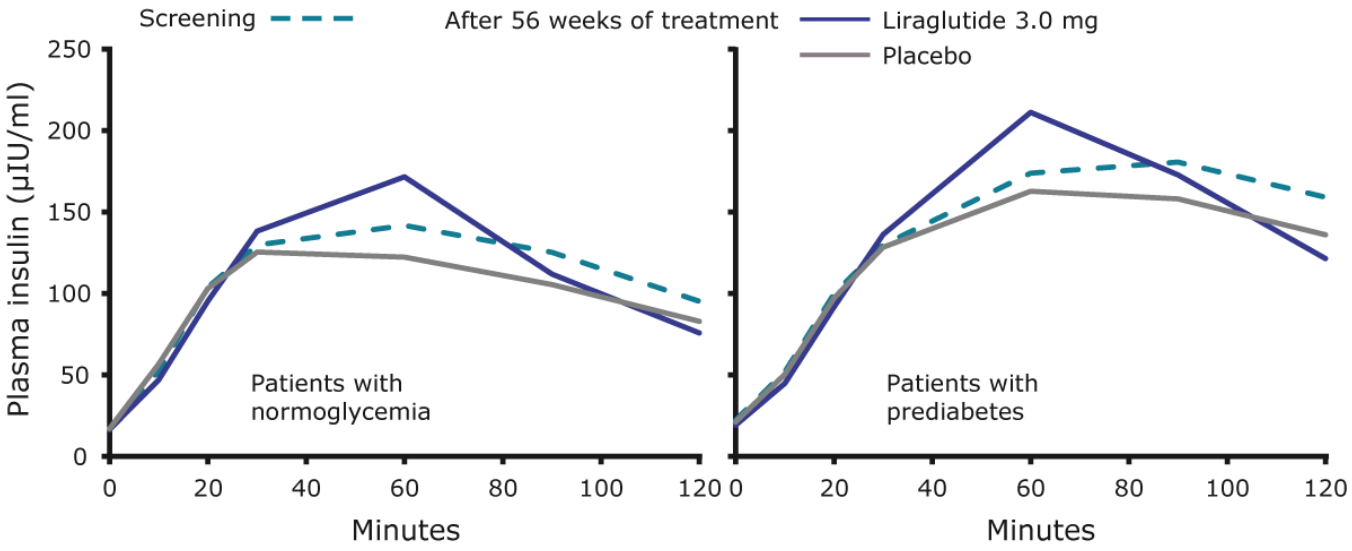


[a]Patients could be excluded for more than 1 criterion
[b]37 patients with prediabetes who entered the re-randomized period were incorrectly stratified
AE: adverse event

Figure S3. Effects of Liraglutide 3.0 mg s.c. on Insulin and C-peptide during Oral Glucose Tolerance Test

Mean plots of plasma insulin and C-peptide during a 75 g oral glucose tolerance test (OGTT) are shown according to prediabetes status for the full analysis set (Panels A and B). The OGTT was done at screening for the diagnosis of prediabetes (see the Supplemental Methods).

A Insulin during Oral Glucose Tolerance Test, Screening vs. Week 56



B C-peptide during Oral Glucose Tolerance Test, Screening vs. Week 56

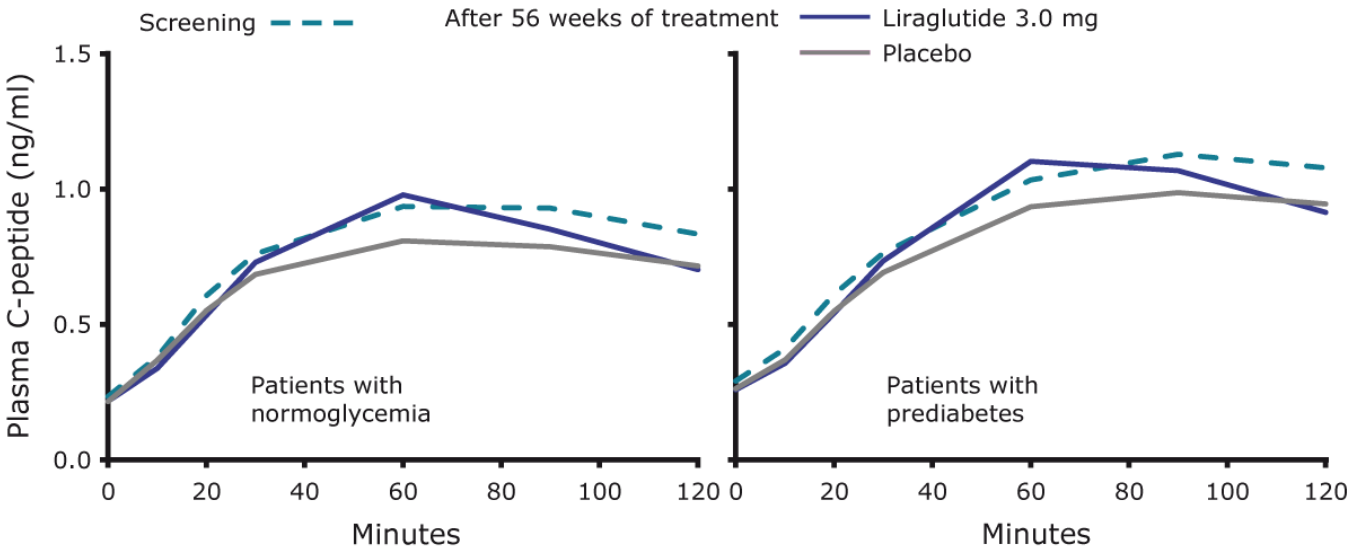
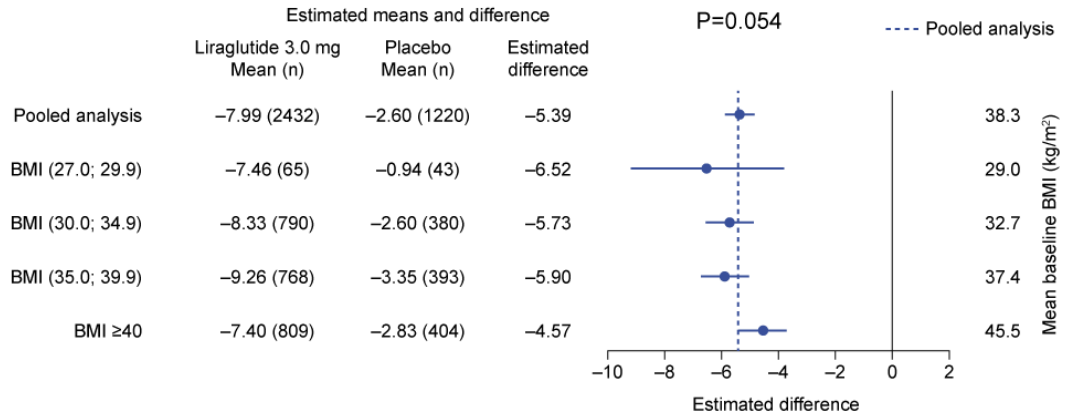


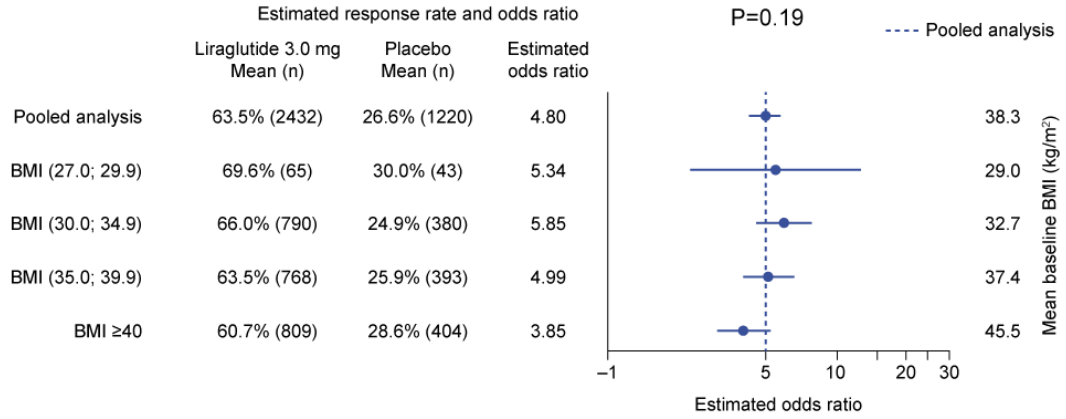
Figure S4. Changes in Body Weight after 56 Weeks by Baseline BMI Categories

For mean weight loss (%) in panel A, 5% weight loss in panel B and 10% weight loss in panel C, the right-hand panel illustrates the estimated treatment effect together with 95% confidence interval for the full analysis set with last-observation-carried forward imputation. P values for tests of no interaction between treatment and baseline BMI category are shown.
BMI denotes the body-mass index and n the number of patients contributing to the analysis.

A



B



C

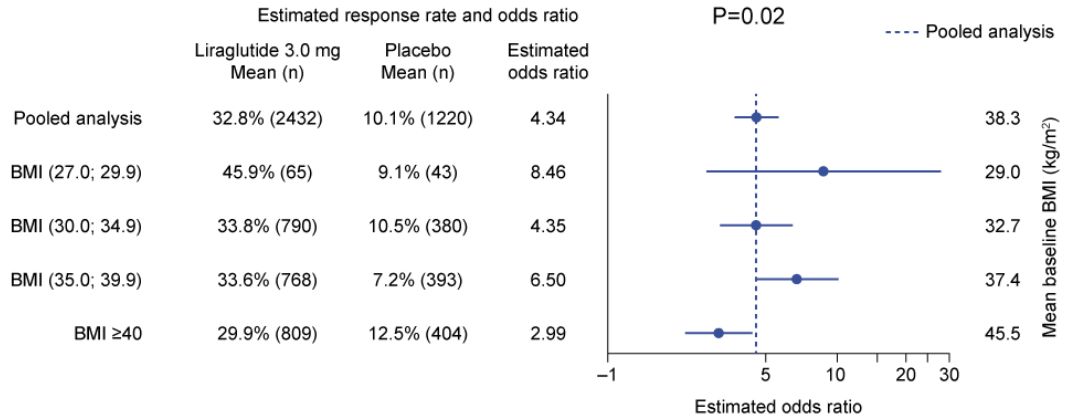


Figure S5. Effects of Liraglutide 3.0 mg s.c. on Quality of Life

Mean changes in the score for A (IWQoL-Lite) and B (SF-36) are shown; both questionnaires have a 100-point scale with an increase indicating improvement. For the SF-36, overall physical and mental health scores are shown at the right. For C, TRIM–Weight (also on a 100-point scale), mean scores at week 56 are shown and are not changes from baseline values as the questionnaire was not completed at baseline. Data are observed means with standard error bars for the full analysis set with last-observation-carried forward imputation.

IWQoL-Lite denotes the Impact of Weight on Quality of Life-Lite version questionnaire, SF-36 the 36-item Short-Form health status survey, and TRIM-Weight the Treatment Related Impact Measure-Weight. *P<0.05.

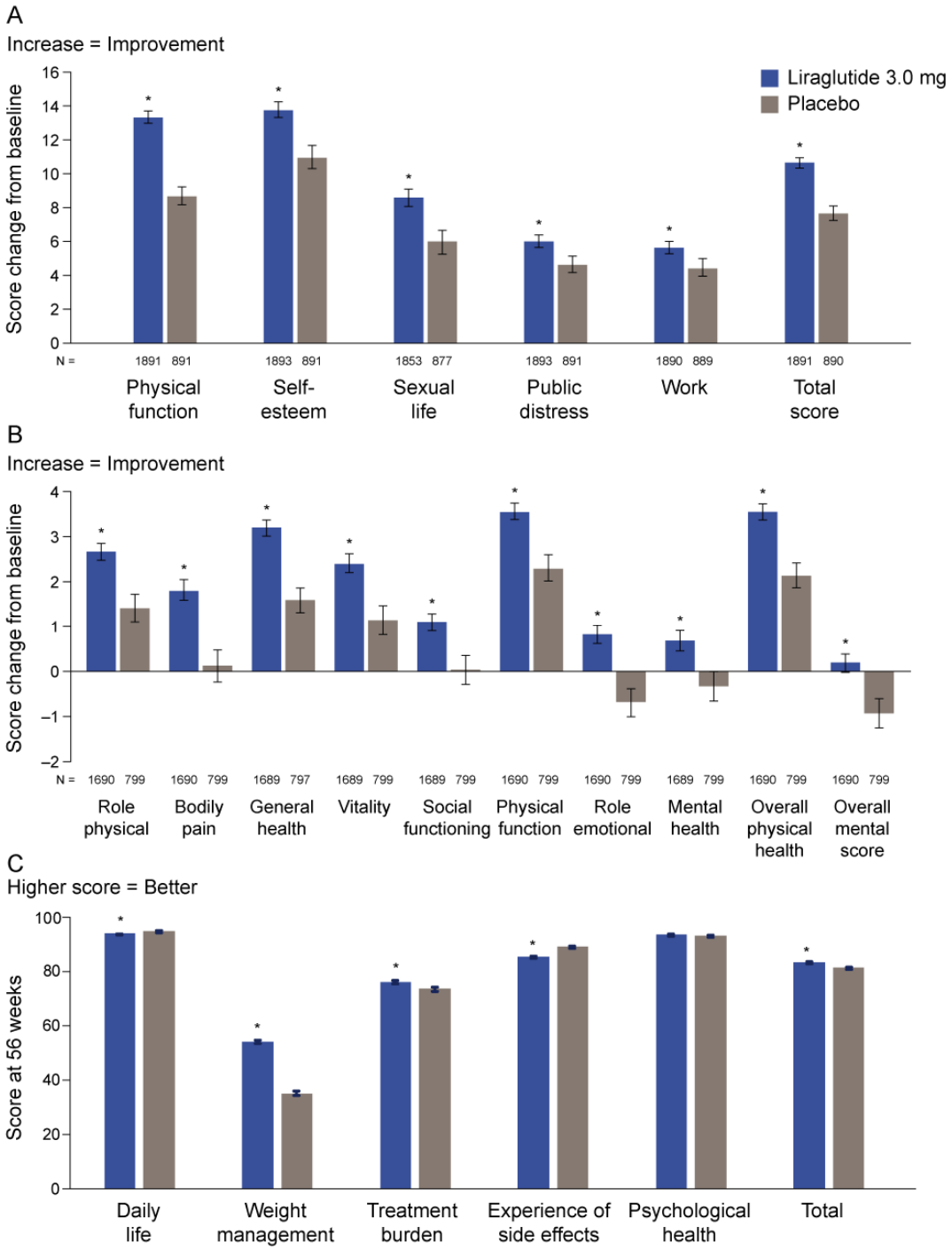


Figure S6. Adverse Events Leading to Discontinuation of 0.2% or More Patients in Either Group, by Treatment Group and up to Week 56*

*Adverse events are presented by preferred term and are observed mean data for the safety analysis set (liraglutide N=2481; placebo N=1242). Adverse events are treatment-emergent, defined as an event that has onset date on or after the first day of randomized treatment and no later than 14 days after the last day of randomized treatment.

E denotes the number of adverse events, R the event rate per 100 exposure years, and % the proportion of patients reporting the adverse event.

	Liraglutide 3.0 mg			Placebo		
	%	R	E	%	R	E
Nausea	3.0	3.4	75	0.3	0.4	4
Vomiting	1.9	2.1	47	0.1	0.1	1
Diarrhea	1.3	1.5	33	0.0	0.0	0
Abdominal pain	0.7	0.8	18	0.0	0.0	0
Constipation	0.6	0.6	14	0.0	0.0	0
Fatigue	0.5	0.6	13	0.0	0.0	0
Dizziness	0.5	0.5	12	0.1	0.1	1
Abdominal pain upper	0.3	0.4	8	0.1	0.1	1
Gastroesophageal reflux disease	0.3	0.3	7	0.0	0.0	0
Lipase increased	0.3	0.3	7	0.1	0.1	1
Dyspepsia	0.2	0.3	6	0.1	0.1	1
Headache	0.2	0.2	5	0.1	0.1	1
Pancreatitis acute	0.2	0.2	5	0.0	0.0	0
Depression	0.1	0.1	4	0.3	0.4	4
Abdominal distension	0.2	0.2	4	0.1	0.1	1
Injection site reaction	0.2	0.2	4	0.0	0.0	0
Injection site rash	0.1	<0.1	2	0.2	0.2	2
Injection site hematoma	0.0	0.0	5	0.2	0.2	2
Injection site hemorrhage	0.0	0.0	5	0.2	0.2	2
Injection site pain	0.0	0.0	4	0.2	0.2	2

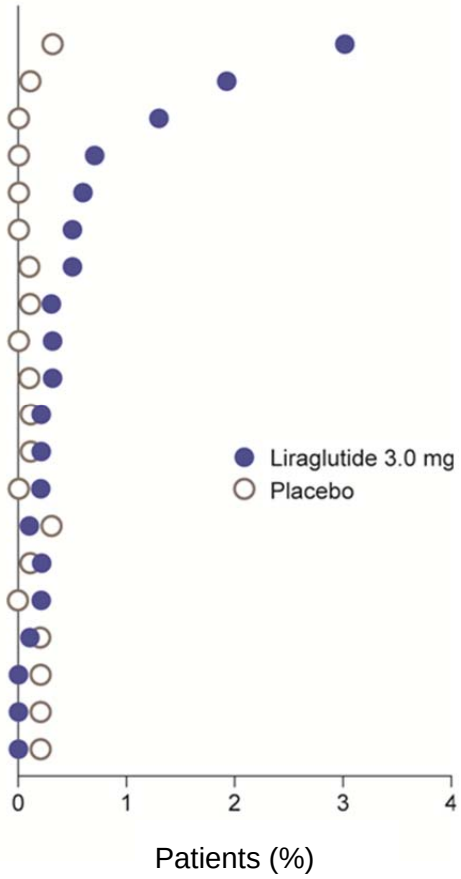


Figure S7. Percentage of Patients with Ongoing Nausea by Week and Treatment

Observed mean data for the safety analysis set (liraglutide N=2481; placebo N=1242). 75 patients in the liraglutide group withdrew owing to nausea compared with 4 in the placebo group.

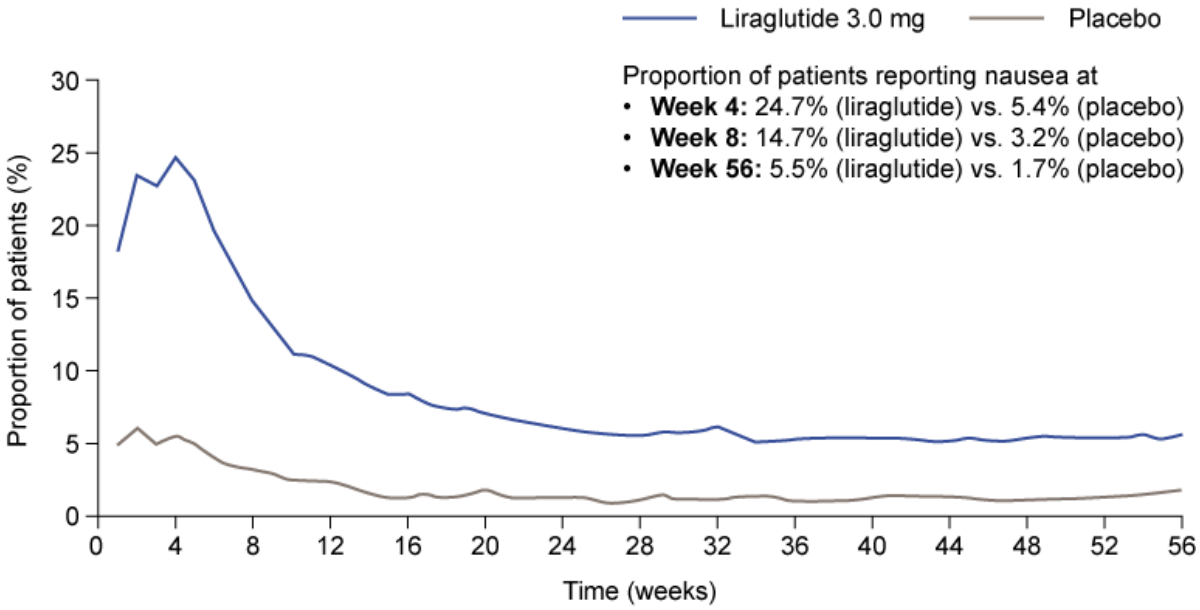


Figure S8. Gallbladder-related Events by Weight Loss

Onset of gallbladder-related events (based on the system organ class hepatobiliary disorders) by weight loss at time of onset. Data are from the full analysis set (% weight loss) and safety analysis set. The lines represent the mean weight loss by liraglutide- and placebo-treated patients in the analysis; each event is plotted by time of event and the weight loss experienced by the patient at the time of the event. Patients were randomized 2:1 to liraglutide 3.0 mg and placebo.

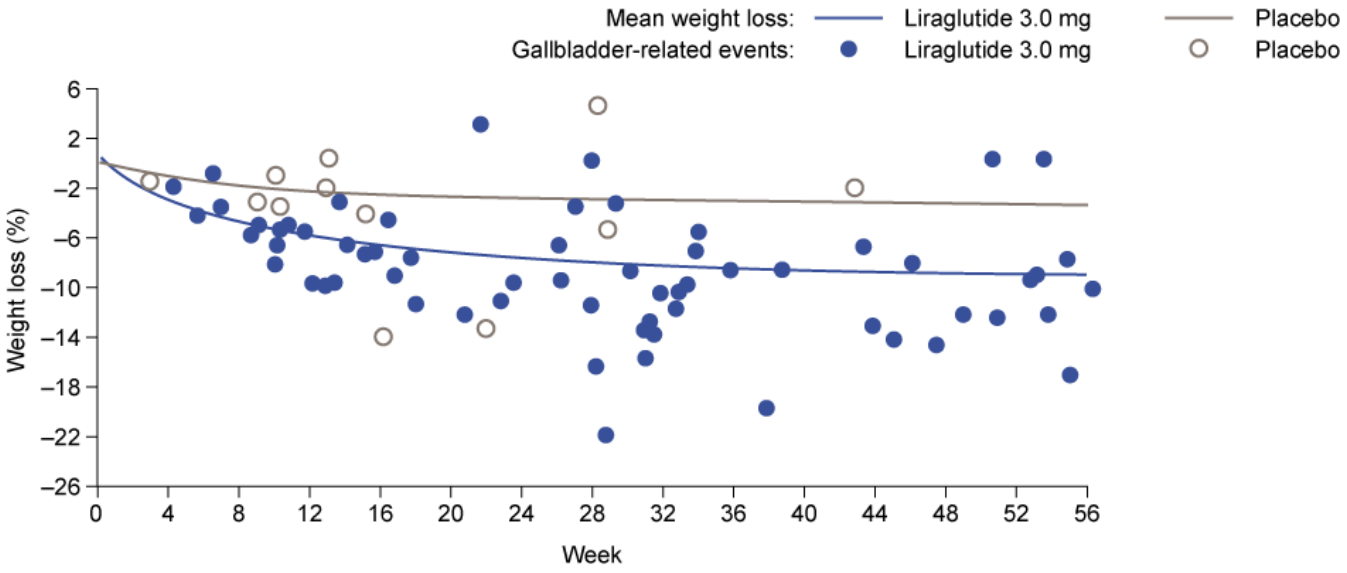
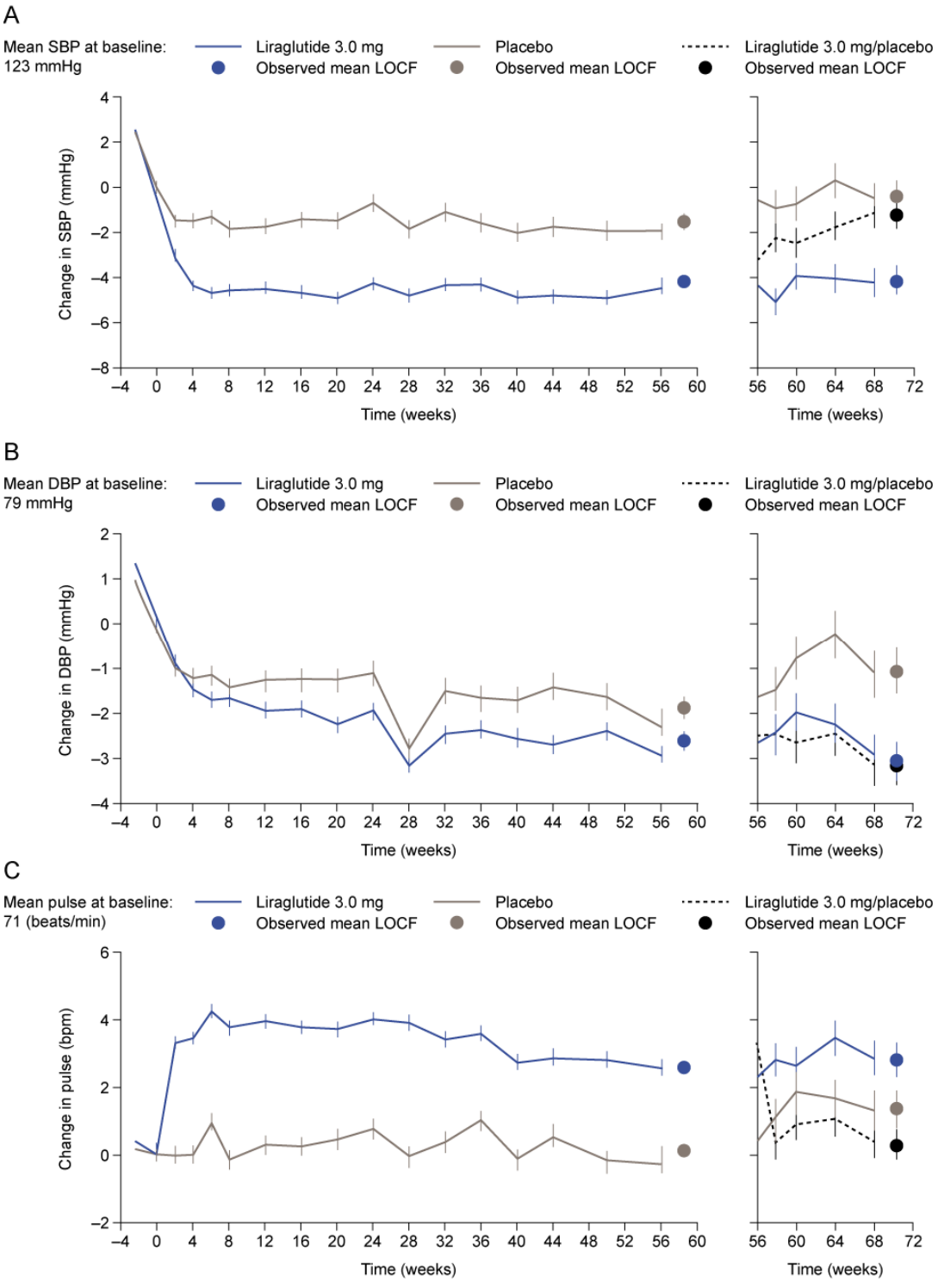


Figure S9. Blood Pressure and Pulse Changes over the Course of the Trial (From Baseline to Week 56, and Week 56 to 68)

Data are observed means with standard error bars for the full analysis set (blood pressure) or safety analysis set (pulse), with last-observation-carried-forward (LOCF) imputation at week 56.
BPM denotes beats per minute, DBP diastolic blood pressure, and SBP systolic blood pressure.



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 dyslipidemia[†] 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 ≥126 mg/dl (7.0 mmol/liter) or 2-hour post-challenge plasma glucose ≥200 mg/dl (11.1 mmol/liter) (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/liter or <0.4 mIU/liter
Screening calcitonin ≥50 ng/liter
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 organized weight reduction program 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 (PHQ-9) score of ≥15
Any lifetime history of a suicidal attempt
A history of any suicidal behavior in the last month prior to randomization.
Any suicidal ideation of type 4 or 5 on the Columbian Suicidality Severity Rating Scale (C-SSRS) in the last month prior to randomization

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 randomized 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
Subjects from the same house hold 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 vasectomized partner. UK: adequate contraceptive measures are defined as sterilization, intra-uterine device, oral contraceptives, consistent use of barrier methods, male sterilization 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 patient 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.[10,11]

[‡]Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.[12]

BMI denotes body-mass index, GLP-1 glucagon-like peptide-1.

Table S2. Adverse Events of Special Focus

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
Revascularization procedure	Yes	Yes
Hospitalization 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 hypoglycemic 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 denotes 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 tumors (SMQ), Biliary tumors of unspecified malignancy (SMQ), Breast neoplasms - malignant and unspecified (SMQ), Breast malignant tumors (SMQ), Breast tumors of unspecified malignancy (SMQ), Liver neoplasms - malignant and unspecified (SMQ), Liver malignant tumors (SMQ), Liver tumors of unspecified malignancy (SMQ), Malignant or unspecified tumors (SMQ), Malignant tumors (SMQ), Tumors of unspecified malignancy (SMQ), Ovarian neoplasms - malignant and unspecified (SMQ), Ovarian malignant tumors (SMQ), Ovarian tumors 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 tumors (SMQ), Prostate tumors of unspecified malignancy (SMQ), Skin neoplasms - malignant and unspecified (SMQ), Skin malignant tumors (SMQ), Skin tumors of unspecified malignancy (SMQ), Uterine and fallopian tube neoplasms - malignant and unspecified (SMQ), Uterine and fallopian tube malignant tumors (SMQ), Uterine and fallopian tube tumors of unspecified malignancy (SMQ), Tumor markers (SMQ)

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

[f]Acute renal failure (SMQ)

[g]ADA Workgroup on Hypoglycemia.[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 Randomized Trial Patients by Treatment Group.*

Characteristic	Liraglutide 3.0 mg s.c. (N=2487)	Placebo (N=1244)
Dyslipidemia and hypertension – no. (%)†	417 (16.8)	213 (17.1)
Cardiovascular disease – no. (%)‡	216 (8.7)	105 (8.5)
Gallbladder disease – no. (%)§	349 (14.0)	163 (13.1)
Treated with anti-hypertensive drugs – no. (%)	754 (30.9)	404 (33.0)
Treated with lipid-lowering drugs – no. (%)	386 (15.8)	183 (14.9)
hsCRP – mg/liter	3.9±146.6	3.8±109.3
PAI-1 – ng/ml	14.7±103.8	14.7±97.4
Adiponectin – µg/ml	7.4±48.1	7.4±59.1
Fibrinogen – g/liter	4.3±23.4	4.3±22.7
Urinary albumin:creatinine ratio (mg/g)	3.6±315.4	3.6±627.2
IWQoL-Lite total score	73.0±18.2	72.6±17.9
SF-36 overall physical health score	48.2±8.4	47.7±8.7
SF-36 overall mental health score	53.8±8.1	54.0±7.9

*Plus–minus values are observed means ± SD, except for cardiovascular biomarkers, where plus–minus values are geometric means and CV%. Scores on the Impact of Weight on Quality of Life-Lite (IWQoL-Lite) questionnaire and the 36-item Short-Form health status survey (SF-36) can range from 0 to 100, with higher scores indicating a better quality of life. To convert values for high-sensitivity C-reactive protein (hsCRP) to nanomoles per liter, multiply by 9.524. To convert values for plasminogen activator inhibitor-1 (PAI-1) to picomoles per liter, multiply by 19.231. CV denotes coefficient of variation.

†Dyslipidemia and hypertension were based on reported medical history.

‡Based on standardized MedDRA queries ischemic heart disease, cardiac failure, central nervous system hemorrhages, cerebrovascular conditions, embolic and thrombotic events.

§Includes patients previously diagnosed with gallbladder disease, gallstones or cholecystitis.

There were no statistically significant differences between the two groups for any characteristic.

Table S4. Baseline Characteristics of All Randomized Trial Patients by Treatment Group and Prediabetes Status*

Characteristics were comparable between the two groups, except that mean age was lower in patients with normoglycemia than in those with prediabetes, and mean body weight, glycated hemoglobin (HbA_{1c}), fasting glucose and the proportions of patients with dyslipidemia, hypertension and cardiovascular disease were higher in patients with prediabetes.

Characteristic	Patients with normoglycemia		Patients with prediabetes§	
	Liraglutide 3.0 mg s.c. (N=959)	Placebo (N=487)	Liraglutide 3.0 mg s.c. (N=1528)	Placebo (N=757)
Sex – no. (%)				
Female	801 (83.5)	390 (80.1)	1156 (75.7)	581 (76.8)
Male	158 (16.5)	97 (19.9)	372 (24.3)	176 (23.2)
Age – years	41.6±11.7	41.5±11.5	47.4±11.8	47.2±11.8
Race – no. (%)†				
White	831 (86.7)	426 (87.5)	1276 (83.5)	635 (83.9)
Black or African-American	94 (9.8)	42 (8.6)	148 (9.7)	72 (9.5)
Asian	14 (1.5)	7 (1.4)	76 (5.0)	39 (5.2)
American Indian or Alaska Native	0 (0)	2 (0.4)	5 (0.3)	2 (0.3)
Native Hawaiian or other Pacific Islander	1 (0.1)	1 (0.2)	1 (<0.1)	1 (0.1)
Other	19 (2.0)	9 (1.8)	22 (1.4)	8 (1.1)
Ethnic group – no. (%)†				
Hispanic or Latino	114 (11.9)	63 (12.9)	145 (9.5)	71 (9.4)
Weight – kg	104.0±20.1	103.6±21.2	107.6±21.8	107.9±21.8
Body-mass index‡	37.5±6.2	37.4 ±6.2	38.8±6.4	39.0±6.3
27–29.9 – overweight	27 (2.8)	21 (4.3)	39 (2.6)	23 (3.0)
30–34.9 – obese class I	372 (38.8)	190 (39.0)	434 (28.4)	198 (26.2)
35–39.9 – obese class II	288 (30.0)	147 (30.2)	499 (32.7)	251 (33.2)
≥40 – obese class III	272 (28.4)	129 (26.5)	556 (36.4)	285 (37.6)
Waist circumference (cm)	112.2±14.0	111.0±14.1	116.7±14.4	116.7±14.0
Glycated hemoglobin – %	5.3±0.3	5.3±0.3	5.8±0.3	5.7±0.3
Fasting glucose – mg/dl	90.8±7.4	91.0±8.1	99.0±11.1	98.3±9.8
Fasting insulin – µIU/ml	14.2±85.1	14.4±107.1	17.9±76.4	17.4±79.3
Blood pressure – mm Hg				
Systolic	120.3±12.6	120.5±12.4	124.8±12.9	125.0±12.8
Diastolic	77.5±8.8	77.3±8.6	79.4±8.4	79.9±8.3
Cholesterol – mg/dl				
Total	195.6±19.2	191.3±18.4	192.7±19.0	196.4±19.0
LDL	113.1±27.9	109.7±26.7	110.9±27.9	114.0±28.1
HDL	53.6±25.9	52.3±26.4	50.0±26.1	50.1±26.6
VLDL	23.4±54.0	24.2±45.2	26.4±46.7	26.8±51.2
Free fatty acids – mmol/liter	0.42±40.7	0.43±41.1	0.47±39.8	0.48±38.3
Triglycerides – mg/dl	117.2±61.7	121.2±48.0	132.5±54.0	134.8±66.4
Dyslipidemia – no. (%)§	233 (24.3)	113 (23.2)	504 (33.0)	246 (32.5)
Hypertension – no. (%)§	211 (22.0)	130 (26.7)	639 (41.8)	316 (41.7)
Dyslipidemia and hypertension – no. (%)§	99 (10.3)	58 (11.9)	318 (20.8)	155 (20.5)

Cardiovascular disease – no. (%)[#]	66 (6.9)	29 (6.0)	150 (9.8)	76 (10.1)
Gallbladder disease – no. (%)[&]	137 (14.3)	50 (10.3)	212 (13.9)	113 (14.9)
Treated with anti-hypertensive drugs – no. (%)	173 (18.4)	111 (23.2)	581 (38.9)	293 (39.3)
Treated with lipid-lowering drugs – no. (%)	94 (10.0)	50 (10.4)	292 (19.5)	133 (17.8)
HsCRP – mg/liter	3.5±182.0	3.3±119.5	4.2±125.5	4.2±102.3
PAI-1 – ng/ml	10.8±108.4	11.1±104.7	17.7±99.0	17.6±91.3
Adiponectin – µg/ml	8.1±49.0	8.0±70.6	7.0±46.2	7.1±45.4
Fibrinogen – g/liter	4.2±24.4	4.2±24.1	4.4±22.7	4.4±21.8
Urinary albumin:creatinine ratio – mg/g	0.37±280.7	0.37±428.8	0.43±320.7	0.43±624.4
IWQoL-Lite total score	74.8±17.0	74.9±16.1	72.0±18.6	70.7±18.8
SF-36 overall physical health	49.7±7.6	49.2±8.0	47.3±8.7	46.6±9.0
SF-36 overall mental health	53.8±8.1	53.8±7.8	53.9±8.0	54.0±8.0

*Plus–minus values are observed means±SD. For fasting insulin, fasting C-peptide, HOMA-B, HOMA-IR, lipids and cardiovascular biomarkers, plus–minus values are geometric means and CV%. Data for fasting insulin, fasting C-peptide, HOMA-B, HOMA-IR, blood pressure, lipids, cardiovascular biomarkers and patient-reported outcomes are reported for the full analysis set (the 3662 randomized patients who were exposed to at least one dose of liraglutide or placebo and had at least one post-baseline assessment): 2437 patients in the liraglutide group and 1225 in the placebo group. Scores on the Impact of Weight on Quality of Life-Lite (IWQoL-Lite) questionnaire and the 36-item Short-Form health status survey (SF-36) can range from 0 to 100, with higher scores indicating a better quality of life. To convert values for glucose to millimoles per liter, multiply by 0.0555. To convert values for cholesterol to millimoles per liter, multiply by 0.0259. To convert values for high-sensitivity C-reactive protein (hsCRP) to nanomoles per liter, multiply by 9.524. To convert values for plasminogen activator inhibitor-1 (PAI-1) to picomoles per liter, multiply by 19.231. CV denotes coefficient of variation, HDL high-density lipoprotein, HOMA-B homeostasis model assessment of beta-cell function, HOMA-IR homeostasis model assessment of insulin resistance, LDL low-density lipoprotein, and VLDL very low density lipoprotein.

[†]Race and ethnic group were self-reported. Patients from France did not report race or ethnicity.

[‡]The body-mass index is the weight in kilograms divided by the square of the height in meters.

[§]Prediabetes was defined according to ADA 2010 criteria.[2] Dyslipidemia and hypertension were based on reported medical history.

[#]Based on standardized MedDRA queries ischemic heart disease, cardiac failure, central nervous system hemorrhages, cerebrovascular conditions, embolic and thrombotic events.

[&]Includes patients previously diagnosed with gallbladder disease, gallstones or cholecystitis.

Table S5. Sensitivity Analyses for Primary End Points

End point	Type of analysis	Description
1, 2 and 3	Completer population	Same analysis as the primary applied to completers (week 56) in FAS with a valid non-imputed measurement at week 56
	Baseline weight carried forward for patients without a valid post-baseline measurement	Same analysis as the primary applied to all randomized patients allowing for baseline carried forward for patients without a post-baseline measurements
	Only excluding values after rescue medication	Same analysis as the primary applied to the FAS including the fasting and non-fasting weight measurements, off-drug weight measurements and the follow-up weight measurements 56 weeks after randomization for patients with early withdrawals
	All available measurements	Same analysis as the primary applied to the FAS, including the fasting and non-fasting weight measurements, off drug weight measurements, and the follow-up weight measurements 56 weeks after randomization and weight measurements following rescue medication
	Multiple imputation	Same analysis as the primary but imputing missing observations with a regression method
1 only	Repeated measures analysis	Linear mixed-effect model
2 and 3 only	All withdrawals counted as non-responders	Same analysis as the primary applied in the FAS, but regarding patients without a valid assessment of fasting body weight at 56 weeks of treatment as non-responders, i.e. not having lost 5% or 10% of their fasting body weight, respectively (For patients that withdrew prematurely from the trial, their follow-up weights at 56 weeks after randomization, if available, were used).

1: Change in body weight. 2: Proportion of patients achieving ≥5% reduction of baseline body weight (5% responders). 3: Proportion of patients achieving >10% reduction of baseline body weight (10% responders).

FAS denotes the full analysis set, defined as all randomized patients that were exposed to at least one treatment dose and had at least one post-baseline efficacy assessment.

Table S6. Results of Prespecified Sensitivity Analyses for Primary End Points

End point	Type of analysis	Liraglutide 3.0 mg s.c.	Placebo	Estimated treatment difference/odds ratio for liraglutide vs. placebo (95% CI)*	P value
1: Change in body weight (%)				**Treatment difference**	
	Primary analysis	N=2432	N=1220		
		-8.0	-2.6	-5.4 (-5.8 to -5.0)	<0.001
	Completer population	N=1781	N=798		
		-9.2	-3.5	-5.7 (-6.3 to -5.1)	<0.001
	Repeated measures	N=2432	N=1220		
		-8.5	-2.7	-5.8 (-6.3 to -5.3)	<0.001
	Baseline weight carried forward for patients without a valid post-baseline measurement	N=2481	N=1239		
		-7.8	-2.6	-5.3 (-5.7 to -4.8)	<0.001
	All available measurements	N=2437	N=1225		
		-7.8	-2.6	-5.2 (-5.6 to -4.7)	<0.001
	Multiple imputation	N=2437	N=1225		
		-8.3	-2.7	-5.5 (-6.0 to -5.0)	<0.001
2: Proportion of patients achieving ≥5% weight loss (%)				**Odds ratio**	
	Primary analysis	N=2432	N=1220		
		63.5	26.6	4.8 (4.1 to 5.6)	<0.001
	Completer population	N=1781	N=798		
		73.3	35.7	5.0 (4.1 to 6.0)	<0.001
	Baseline weight carried forward for patients without a valid post-baseline measurement	N=2481	N=1239		
		62.3	26.2	4.6 (4.0 to 5.4)	<0.001
	All available measurements	N=2437	N=1225		
		63.2	27.7	4.5 (3.8 to 5.2)	<0.001
	Multiple imputation	N=2437	N=1225		
		67.8	32.5	4.4 (3.7 to 5.2)	<0.001

End point	Type of analysis	Liraglutide 3.0 mg s.c.	Placebo	Estimated treatment difference/odds ratio for liraglutide vs. placebo (95% CI)*	P value
	All withdrawals counted as non-responders	N=2432	N=1220		
		54.3	23.4	3.9 (3.3 to 4.6)	<0.001
3: Proportion of patients achieving >10% weight loss (%)				**Odds ratio**	
	Primary analysis	N=2432	N=1220		
		32.8	10.1	4.3 (3.5 to 5.3)	<0.001
	Completer population	N=1781	N=798		
		40.7	14.5	4.1 (3.3 to 5.1)	<0.001
	Baseline weight carried forward for patients without a valid post-baseline measurement	N=2481	N=1239		
		32.1	10.0	4.3 (3.5 to 5.2)	<0.001
	All available measurements	N=2437	N=1225		
		32.9	10.8	4.1 (3.3 to 5.0)	<0.001
	Multiple imputation	N=2437	N=1225		
		36.5	12.5	4.0 (3.3 to 4.9)	<0.001
	All withdrawals counted as non-responders	N=2432	N=1220		
		30.0	9.6	4.1 (3.3 to 5.0)	<0.001

*Data for liraglutide and placebo are estimated means. Estimated treatment differences (mean weight loss, ANCOVA) and odds ratios (categorical weight loss, logistic regression) are shown together with 95% CIs.
CI denotes confidence interval, N the number of patients contributing to the analysis.

Table S7. Observed Mean Changes in Cardiovascular Biomarkers and Quality of Life between Baseline and Week 56.*

End point	Liraglutide 3.0 mg s.c. (N=2437)	Placebo (N=1225)	Estimated treatment difference for liraglutide vs. placebo (95% CI)†	P value
Cardiovascular biomarkers				
hsCRP (%)	-37.8	-10.1	-30.5 (-34.3 to -26.5)	<0.001
PAI-1 (%)‡	–	–	-21.3 (-25.7 to -16.7)	<0.001
Adiponectin (%)	11.5	3.0	8.5 (5.5 to 11.6)	<0.001
Fibrinogen (%)	1.0	0.6	0.5 (-1.2 to 2.1)	0.59
Urinary albumin:creatinine ratio (%)	12.6	14.9	-3.6 (-10.1 to 3.4)	0.31
Quality of life				
IWQoL-Lite total score	10.6±13.3	7.7±12.8	3.1 (2.2 to 4.0)	<0.001
SF-36 overall physical health score	3.6±6.8	2.1±7.7	1.7 (1.2 to 2.2)	<0.001
SF-36 overall mental health score	0.2±8.1	-0.9±9.1	0.9 (0.3 to 1.5)	0.003
TRIM-Weight total score#	–	–	2.1 (1.3 to 3.0)	<0.001

*Plus–minus values for quality of life are observed means ± SD. For cardiovascular biomarkers, the relative change from baseline is presented.

†Estimated treatment differences are from an analysis of covariance using the full analysis set (FAS) with last-observation-carried-forward (LOCF) imputation. The FAS was defined as randomized patients who were exposed to at least one dose of liraglutide or placebo and had at least one post-baseline assessment (69 randomized patients were excluded from the FAS; 61 due to lack of valid post-baseline efficacy assessments and 8 due to no exposure to trial drug). Data for cardiovascular biomarkers are log-transformed for analysis and presented as relative treatment differences. To convert values for high-sensitivity C-reactive protein (hsCRP) to nanomoles per liter, multiply by 9.524. To convert values for plasminogen activator inhibitor-1 (PAI-1) to picomoles per liter, multiply by 19.231. IWQoL-Lite denotes Impact of Weight on Quality of Life–Lite version, SF-36 Short-Form (36-item) health status survey, and TRIM-Weight Treatment Related Impact Measure-Weight.

‡PAI-1 was analyzed using different methods at baseline and week 56, therefore changes between baseline and week 56 cannot be calculated. The analysis adjusted for patient baseline values.

#Changes from baseline are not available as the TRIM-Weight questionnaire was not completed at baseline.

Table S8. Estimated Mean Changes in Cardiometabolic Risk Factors and Quality of Life between Baseline and Week 56*

End point	Liraglutide 3.0 mg s.c. (N=2437)	Placebo (N=1225)	Estimated treatment difference for liraglutide vs. placebo (95% CI)	P value
Body weight-related end points				
BMI (kg/m^2)†	–3.0	–1.0	-2.0 (-2.2 to -1.9)	<0.001
Waist circumference (cm)	–8.2	–4.0	-4.2 (-4.7 to -3.7)	<0.001
Glycemic control parameters				
Glycated hemoglobin (%)	-0.29	-0.07	-0.23 (-0.25 to -0.21)	<0.001
Fasting glucose (mg/dl)	-7.0	-0.10	-6.9 (-7.5 to -6.3)	<0.001
Blood pressure				
Systolic (mm Hg)	-4.3	-1.5	-2.8 (-3.6 to -2.1)	<0.001
Diastolic (mm Hg)	-2.7	-1.8	-0.9 (-1.4 to -0.4)	<0.001
Quality of life				
IWQoL-Lite total score	10.7	7.5	3.1 (2.2 to 4.0)	<0.001
SF-36 overall physical health score	3.7	1.9	1.7 (1.2 to 2.2)	<0.001
Use of concomitant medications				
Anti-hypertensive drugs – net use	-	-	1.7 (1.3 to 2.10)	<0.001
Increased use (%)	3.7	5.7		
Decreased use (%)	6.0	3.8		
Lipid-lowering drugs – net use	-	-	1.5 (1.1 to 2.2)	0.02
Increased use (%)	2.1	3.7		
Decreased use (%)	1.5	1.3		

*Values are estimated means. Estimated treatment differences are from an analysis of covariance using the full analysis set (FAS) with last-observation-carried-forward (LOCF) imputation.

Changes in the use of concomitant medications are analyzed by logistic regression using the FAS with LOCF, and are presented as the proportions of patients (%) and odds ratios. Change was defined as an increase or decrease in dose or number of medications (defined as net use).

To convert values for glucose to millimoles per liter, multiply by 0.0555.

BMI denotes body-mass index, IWQoL-Lite the Impact of Weight on Quality of Life–Lite version questionnaire and SF-36 the Short-Form (36-item) health status survey.

†BMI is the weight in kilograms divided by the square of the height in meters.

Table S9. Mean Changes in Glycemic Control Parameters between Baseline and Week 56, by Prediabetes Status*

	Patients with normoglycemia				Patients with prediabetes				
End point	**Liraglutide 3.0 mg s.c. (N=942)**	**Placebo (N=479)**	**Estimated treatment difference for liraglutide vs. placebo (95% CI)**	**P value**	**Liraglutide 3.0 mg s.c. (N=1495)**	**Placebo (N=746)**	**Estimated treatment difference for liraglutide vs. placebo (95% CI)**	**P value**	**P value for inter-action**
Glycated hemoglobin (%)	-0.22	-0.03	-0.19 (-0.22 to -0.16)	<0.001	-0.32	-0.07	-0.25 (-0.28 to -0.23)	<0.001	<0.001
Fasting glucose (mg/dl)	-5.12	-0.06	-5.07 (-6.03 to -4.10)	<0.001	-8.20	-0.11	-8.09 (-8.86 to -7.33)	<0.001	<0.001
Fasting insulin (%)	-12.9	-4.3	-10 (-15 to -4)	0.001	-12.4	-4.6	-8 (-12 to -3)	<0.001	0.68
Fasting C-peptide (%)	-9.6	-8.4	-1 (-4 to 3)	0.75	-8.4	-7.5	-1 (-4 to 2)	0.51	0.87
Glucose AUC (hr*mg/dl)	-31.6	-4.2	-27.4 (-32.6 to -22.1)	<0.001	-55.8	-13.9	-41.9 (-46.0 to -37.8)	<0.001	<0.001
Insulin AUC (%)	0.36	-7.9	9 (2 to 16)	0.007	-0.23	-9.7	10 (5 to 16)	<0.001	0.73
C-peptide AUC (%)	-6.0	-11.6	6 (2 to 10)	0.001	-4.7	-11.5	8 (5 to 11)	<0.001	0.58

*Values are estimated means and treatment differences from an analysis of covariance using the full analysis set (FAS) with last-observation-carried-forward (LOCF) imputation. For insulin and C-peptide, relative changes from baseline are shown and the data are log-transformed for analysis and presented as relative treatment differences. The P value at the far right is for the test for interaction and a statistically significant value shows that prediabetes status had an effect on treatment.

To convert values for glucose to millimoles per liter, multiply by 0.0555.

AUC denotes area under the concentration-time curve, CI confidence interval, N the number of patients.

Table S10. Measures of Insulin Resistance and Beta-cell Function

End point	Liraglutide 3.0 mg s.c. (N=2437)	Placebo (N=1225)	Relative difference for liraglutide vs. placebo (95% CI)*	P value
HOMA-IR (%)	-19.1	-4.5	-15 (-18; -11)	<0.001
Matsuda index (insulin sensitivity) (%)†	21	10	10 (5.5; 15)	<0.001
HOMA-B (%)	13.7	-3.9	18 (13; 22)	<0.001
Disposition index (%)‡	35	11	20 (13; 27)	<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.[14]

†Completer exploratory analysis, based on estimation of the Matsuda index during an 75 g OGTT.[4]

‡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.[7] 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.

OGTT denotes oral glucose tolerance test.

Table S11. Pancreatitis Events Confirmed by External Adjudication Committee of Medical Experts

Over the full period of the trial, including the re-randomized treatment period, nine cases of treatment-emergent pancreatitis were confirmed by independent adjudication: seven events with liraglutide, one with placebo and one event in a patient initially treated with liraglutide and subsequently re-randomized to placebo at week 56, 12 days after the last dose of liraglutide. Most incidences were mild according to the Atlanta classification[15] and were of short duration (2–15 days). All patients recovered following treatment discontinuation. An additional two cases of pancreatitis were judged to be non-treatment emergent, occurring 74 and 125 days after liraglutide treatment was discontinued. Gallstone-related pancreatitis was defined as indicated by gallstones on imaging and/or alanine aminotransferase levels 3 or more times the upper limit of the normal range (ULN).[16]

Treatment	Preferred term	Exposure at onset (days)*	Diagnostic criteria fulfilled	Severity (Revised Atlanta criteria**)	Gallstone (Y/N)	Elevated ALT (Y/N)
Treatment emergent events						
Liraglutide 3.0 mg	Pancreatitis acute	24	Abdominal pain, enzymes	Mild	N	N
	Pancreatitis acute	29	Abdominal pain, enzymes (imaging not done)	Mild	N	N
	Pancreatitis acute	31	Abdominal pain, enzymes	Mild	N	Y ALT 4×ULN
	Pancreatitis acute	43	Abdominal pain, imaging	Mild	N	N
	Lipase increased	277	Abdominal pain, enzymes	Mild	N	N
	Pancreatitis	283	Abdominal pain, enzymes, imaging	Mild	Y	Y ALT 8×ULN
	Pancreatitis acute	330	Abdominal pain, imaging	Mild	N	Y ALT <1.5×ULN
Liraglutide 3.0 mg/ Placebo[†]	Pancreatitis acute	392	Abdominal pain, enzymes	Mild	N	Y ALT 5×ULN
Placebo	Pancreatic disorder	287	Abdominal pain, imaging	Mild	Y	Y ALT 2.5×ULN
Non-treatment emergent events reported by withdrawn patients						
Liraglutide 3.0 mg	Pancreatitis	35[‡]	Abdominal pain, enzymes, imaging	Mild	N	Y ALT 3×ULN
	Pancreatic pseudocyst	170[§]	Abdominal pain, enzymes, imaging	Moderately severe	Y	Unknown; AST 24×ULN

Data are from the safety analysis set. ALT denotes alanine aminotransferase, AST aspartate aminotransferase and ULN the upper limit of the normal range.

*Exposure during trial for events after trial drug stop. **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.[15]

[†]Re-randomized period; event onset 12 days after last dose of liraglutide.

[‡]Event onset 74 days after last dose of liraglutide.

[§]Event onset 124 days after last dose of liraglutide.

Table S12. Mean Changes in Resting Pulse, by Treatment

Pulse category	Liraglutide 3.0 mg s.c. (N=2481) N (%)	Placebo (N=1242) N (%)
Change in pulse >5 bpm at ≥2 consecutive visits	1497 (60.3)	552 (44.4)
Change in pulse >10 bpm at ≥2 consecutive visits	870 (35.1)	249 (20.0)
Change in pulse >20 bpm at ≥2 consecutive visits	127 (5.1)	17 (1.4)

Bpm denotes beats per minute, N the number of patients, and % the percentage of patients.

Table S13. Malignant and Pre-malignant Breast Neoplasms in Women Confirmed by Independent Medical Experts

Treatment	Diagnosis trial day	Age/BMI	Screen detected	Grade	Stage				E/P/HER 2 status	Weight loss, %
					T	N	M	AJCC[1]/EAC		
Malignant neoplasms										
Liraglutide 3.0 mg s.c.	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: localized	+/+/-	-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
	342	55/32.9	Y	3	T1c	N0	M0	I/Stage 1: localized	-/-/-	-12.2
	413	57/36.3	Y	2	pT1c	pN1a		IIA/Stage 3: advanced	+/+/-	-30.0
Placebo	282	40/34.3	Y	2	T2	pN1	M0	IIB/Stage 3: advanced node positive	+/+/-	+0.5
	477	62/39.6	U	2	pT2	pN0	pMX	IIA/Stage 1:localized	+/+/-	-4.8
Pre-malignant neoplasms										
Liraglutide 3.0 mg s.c.	31	54/44.2	Y	3	pTis	Nx	Mx	0/Stage 0: *in situ*	+/+/U	-2.6
	152	47/31.6	Y	3	Tis	Nx	Mx	0/Stage 0: *in situ*	+/+/U	-7.6
	302	59/44.5	Y	2	pTis	Nx	Mx	0/Stage 0: *in situ*	+/-/U	-9.4
Placebo	169	49/41.2	Y	2	pTis	Nx	Mx	0/Stage 0: *in situ*	+/+/U	+1.4

*Patient had 2 events; E/P/HER 2: estrogen/progesteron/human epidermal growth factor receptor 2.

AJCC denotes American Joint Committee on Cancer, BMI body-mass index, EAC Event adjudication Committee and U unknown. The AJCC has designated staging by tumor, node, and metastasis (TNM) classification to define breast cancer.[17]

Table S14. Overview of PHQ-9 Scores at Baseline, End of Trial and Categorical Increases by Treatment

PHQ-9	Liraglutide 3.0 mg s.c.	Placebo
Mean Scores		
Mean PHQ-9 total score at baseline	2.88	3.00
Mean PHQ-9 total score at end-of-treatment	1.61	1.76
Percentage of patients with total score above cut-off		
≥10 at end-of-treatment (week 56 LOCF)	1.1	0.6
≥10 at any time during trial	1.8	1.8
≥15 at end-of-treatment (week 56 LOCF)	0.1	0.2
≥15 at any time during trial	0.5	0.4
≥20 at end-of-treatment (week 56 LOCF)	0.1	0.2
≥20 at any time during trial	0.1	0.2

LOCF denotes last observation carried forward and PHQ-9 the patient health questionnaire 9.

Table S15. PHQ-9 Total Scores - Shift to Maximum from Baseline to End of Trial

	Liraglutide 3.0 mg s.c.		Placebo	
	N	(%)	N	(%)
Number of patients	2481		1242	
Total number of patients improving from baseline to highest score	236	(9.5)	116	(9.3)
Mild to none	170	(6.9)	81	(6.5)
Moderate to none	24	(1.0)	10	(0.8)
Moderate to mild	42	(1.7)	23	(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 patients worsening from baseline to highest score	483	(19.5)	246	(19.8)
None to mild	359	(14.5)	180	(14.5)
None to moderate	44	(1.8)	26	(2.1)
None to moderately severe	9	(0.4)	7	(0.6)
None to severe	0	(0.0)	4	(0.3)
Mild to moderate	51	(2.1)	19	(1.5)
Mild to moderately severe	10	(0.4)	5	(0.4)
Mild to severe	2	(0.1)	2	(0.2)
Moderate to moderately severe	6	(0.2)	2	(0.2)
Moderate to severe	2	(0.1)	1	(0.1)
Moderately severe to severe	0	(0.0)	0	(0.0)
No change	1741	(70.2)	866	(69.7)
Missing	21	(0.8)	14	(1.1)

N denotes the number of patients, % the percentage of patients and PHQ-9 the patient health questionnaire 9.

No depression: PHQ-9 total score of 0-4; Mild depression: PHQ-9 total score of 5-9; Moderate depression: PHQ-9 total score of 10-14; Moderate severe depression: PHQ-9 total score of 15-19; Severe depression: PHQ-9 total score of ≥20.

Table S16. Post-baseline C-SSRS (Any Time during the Treatment Period) - Suicidal Behavior and Suicidal Ideation

	Liraglutide 3.0 mg s.c.			Placebo		
	N	n	(%)	N	n	(%)
Number of patients	2481			1242		
Number of patients answering the C-SSRS	2464			1234		
Years of exposure	2235			1067		
Patients with suicidal behavior and/or ideation		11	(0.45)		11	(0.89)
Patients with suicidal ideation on the C-SSRS		11	(0.45)		11	(0.89)
1. Wish to be dead		8	(0.32)		10	(0.81)
2. Active suicidal ideation, non-specific thoughts		4	(0.16)		2	(0.24)
3. Active suicidal ideation with any methods (no plan) without intent		2	(0.08)		1	(0.08)
4. Active suicidal ideation with some intent to act, without specific plan		0	(0.00)		0	(0.00)
5. Active suicidal ideation with specific plan and intent		0	(0.00)		0	(0.00)
Patients with suicidal behavior on the C-SSRS		0	(0.00)		0	(0.00)
1. Completed Suicide		0	(0.00)		0	(0.00)
2. Actual suicide attempt		0	(0.00)		0	(0.00)
3. Interrupted attempt		0	(0.00)		0	(0.00)
4. Aborted suicide attempt		0	(0.00)		0	(0.00)
5. Preparatory acts towards imminent suicidal behaviors		0	(0.00)		0	(0.00)
Suicidal behavior (item)		0	(0.00)		0	(0.00)
Non-suicidal self-injurious behavior		0	(0.00)		0	(0.00)

C-SSRS denotes the Columbia-suicide severity rating scale, N the number of patients, n the number of patients answering yes, and % the percentage based on the total N.

Table S17. Overview of Hypoglycemic Events from Baseline to Week 56

Visit type	Liraglutide 3.0 mg s.c. (N=2481)			Placebo (N=1242)		
	N	%	E	N	%	E
All Events	**296**	**11.9**	**431**	**41**	**3.3**	**46**
Spontaneously reported	32	1.3	37	13	1.0	15
Reported at FPG visit	90	3.6	112	10	0.8	10
Reported at OGTT visit	205	8.3	282	18	1.4	21

E denotes the number of adverse events, FPG fasting plasma glucose, N the number of patients, OGTT oral glucose tolerance test, and % the proportion of patients reporting the adverse event.

Table S18. Hypoglycemic Events and Laboratory Measurements in Patients Reporting Hypoglycemic Events in Relation to FPG and OGTT Visits from Baseline to Week 56

Visit type	Nominal time	Criteria	Liraglutide 3.0 mg s.c. (N=2481)			Placebo (N=1242)		
			N	%	E	N	%	E
Laboratory measurements of FPG/PG								
Reported at FPG visit		FPG ≤70 mg/dl	88	3.5	110	10	0.8	10
		FPG <56 mg/dl	2	0.1	2	0	0.0	0
		All events	90	3.6	112	10	0.8	10
		Asymptomatic events*	35 / 112 = 31.3%			3 / 10 = 30.0%		
Reported at OGTT visits								
Before glucose intake	0 min	FPG ≤70 mg/dl	45	1.8	61	2	0.2	2
		FPG <56 mg/dl	1	0.0	1	0	0.0	0
After glucose intake	>0 min	PG ≤70 mg/dl	187	7.5	263	15	1.2	18
		PG <56 mg/dl	57	2.3	75	2	0.2	2
	10 min	PG ≤70 mg/dl	10	0.4	11	0	0.0	0
		PG <56 mg/dl	1	0.0	1	0	0.0	0
	20 min	PG ≤70 mg/dl	3	0.1	6	0	0.0	0
		PG <56 mg/dl	0	0.0	0	0	0.0	0
	30 min	PG ≤70 mg/dl	4	0.2	7	1	0.1	1

Visit type	Nominal time	Criteria	Liraglutide 3.0 mg s.c. (N=2481)			Placebo (N=1242)		
			N	%	E	N	%	E
		PG <56 mg/dl	0	0.0	0	0	0.0	0
	60 min	PG ≤70 mg/dl	34	1.4	52	1	0.1	2
		PG <56 mg/dl	7	0.3	11	0	0.0	0
	90 min	PG ≤70 mg/dl	96	3.9	141	5	0.4	6
		PG <56 mg/dl	18	0.7	23	1	0.1	1
	120 min	PG ≤70 mg/dl	148	6.0	207	14	1.1	16
		PG <56 mg/dl	43	1.7	56	1	0.1	1
		All events	205	8.3	282	18	1.4	21
		Asymptomatic events*	117 / 282 = 41.5%			7 / 21 = 33.0%		

E denotes the number of adverse events, FPG fasting plasma glucose, N the number of patients, OGTT oral glucose tolerance test, PG plasma glucose, and % the proportion of patients reporting the adverse event.

*Based on investigator reported term on the adverse event forms.

To convert values for glucose to millimoles per liter, multiply by 0.0555.

Table S19. Mean Changes in Efficacy End Points between Baseline and Week 68 during a 12-week Re-randomized Treatment Period for Patients without Prediabetes at Screening

End point	Liraglutide / liraglutide (N=351)	Liraglutide / placebo (N=350)	Placebo (N=304)
Body weight (% and kg)			
Week 56 (%)	-9.09±6.91	-9.33±7.58	-3.47±7.18
Change at week 68 (%)	0.69±2.58	2.91±3.01	0.28±2.39
Week 56 (kg)	-9.33±7.43	-9.34±8.00	-3.71±8.22
Change at week 68 (kg)	0.61±2.42	2.63±2.71	0.30±2.43
Waist circumference (cm)			
Week 56	-9.44±7.62	-9.40±7.34	-4.85±7.48
Change at week 68	0.31 ± 3.58	1.73±3.51	0.08±3.90
Fasting plasma glucose (mg/dl)			
Week 56	-6.39±7.96	-5.55±9.04	-0.29±8.54
Change at week 68	0.74±7.86	4.21±8.85	0.41±7.66
Systolic blood pressure (mm Hg)			
Week 56	-4.35±13.06	-3.25±11.24	-0.60±11.41
Change at week 68	0.21±10.98	2.13±10.41	0.06±10.52
Diastolic blood pressure (mm Hg)			
Week 56	-2.64±8.79	-2.51±8.77	-1.65±8.52
Change at week 68	-0.44±7.84	-0.63±8.17	0.60±7.98

Plus–minus values are observed means±SD for the full analysis set with last-observation-carried-forward imputation.
To convert values for glucose to millimoles per liter, multiply by 0.0555.

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