Original Investigation

Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes
The SCALE Diabetes Randomized Clinical Trial

Melanie J. Davies, MD; Richard Bergenstal, MD; Bruce Bode, MD; Robert F. Kushner, MD; Andrew Lewin, MD; Trine Vang Skjøth, MD; Arne Haahr Andreasen, MSc; Christine Bjørn Jensen, MD; Ralph A. DeFronzo, MD; for the NN8022-1922 Study Group

IMPORTANCE Weight loss of 5% to 10% can improve type 2 diabetes and related comorbidities. Few safe, effective weight-management drugs are currently available.

OBJECTIVE To investigate efficacy and safety of liraglutide vs placebo for weight management in adults with overweight or obesity and type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS Fifty-six–week randomized (2:1:1), double-blind, placebo-controlled, parallel-group trial with 12-week observational off-drug follow-up period. The study was conducted at 126 sites in 9 countries between June 2011 and January 2013. Of 1361 participants assessed for eligibility, 846 were randomized. Inclusion criteria were body mass index of 27.0 or greater, age 18 years or older, taking 0 to 3 oral hypoglycemic agents (metformin, thiazolidinedione, sulfonylurea) with stable body weight, and glycated hemoglobin level 7.0% to 10.0%.

INTERVENTIONS Once-daily, subcutaneous liraglutide (3.0 mg) (n = 423), liraglutide (1.8 mg) (n = 211), or placebo (n = 212), all as adjunct to 500 kcal/d dietary deficit and increased physical activity (≥150 min/wk).

MAIN OUTCOMES AND MEASURES Three coprimary end points: relative change in weight, proportion of participants losing 5% or more, or more than 10%, of baseline weight at week 56.

RESULTS Baseline weight was 105.7 kg with liraglutide (3.0-mg dose), 105.8 kg with liraglutide (1.8-mg dose), and 106.5 kg with placebo. Weight loss was 6.0% (6.4 kg) with liraglutide (3.0-mg dose), 4.7% (5.0 kg) with liraglutide (1.8-mg dose), and 2.0% (2.2 kg) with placebo (estimated difference for liraglutide [3.0 mg] vs placebo, −4.00% [95% CI, −5.10% to −2.90%]; liraglutide [1.8 mg] vs placebo, −2.71% [95% CI, −4.00% to −1.42%]; $P < .001$ for both). Weight loss of 5% or greater occurred in 54.3% with liraglutide (3.0 mg) and 40.4% with liraglutide (1.8 mg) vs 21.4% with placebo (estimated difference for liraglutide [3.0 mg] vs placebo, 32.9% [95% CI, 24.6% to 41.2%]; for liraglutide [1.8 mg] vs placebo, 19.0% [95% CI, 9.1% to 28.8%]; $P < .001$ for both). Weight loss greater than 10% occurred in 25.2% with liraglutide (3.0 mg) and 15.9% with liraglutide (1.8 mg) vs 6.7% with placebo (estimated difference for liraglutide [3.0 mg] vs placebo, 18.5% [95% CI, 12.7% to 24.4%], $P < .001$; for liraglutide [1.8 mg] vs placebo, 9.3% [95% CI, 2.7% to 15.8%], $P = .006$). More gastrointestinal disorders were reported with liraglutide (3.0 mg) vs liraglutide (1.8 mg) and placebo. No pancreatitis was reported.

CONCLUSIONS AND RELEVANCE Among overweight and obese participants with type 2 diabetes, use of subcutaneous liraglutide (3.0 mg) daily, compared with placebo, resulted in weight loss over 56 weeks. Further studies are needed to evaluate longer-term efficacy and safety.

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Author Affiliations: Diabetes Research Centre, University of Leicester, Leicester, United Kingdom (Davies); International Diabetes Center, Park Nicollet Health Services, Minneapolis, Minnesota (Bergenstal); Atlanta Diabetes Associates, Atlanta, Georgia (Bode); Northwestern University, Chicago, Illinois (Kushner); National Research Institute, Los Angeles, California (Lewin); Novo Nordisk A/S, Søborg, Denmark (Skjøth, Andreasen, Jensen); Texas Diabetes Institute, San Antonio (DeFronzo).

Group Information: The NN8022-1922 Study Group members are listed at the end of this article.

Corresponding Author: Melanie J. Davies, MD, Leicester Diabetes Centre, Leicester General Hospital, Gwendolen Rd, Leicester, LE5 4PW, United Kingdom (melanie.davies@uhl-tr.nhs.uk).

Obesity is a chronic disease[1] and a significant global health challenge.[2] Its associated comorbidities include cardiovascular morbidity and mortality,[3] type 2 diabetes, certain cancers, dyslipidemia, and obstructive sleep apnea.[4] Moreover, obesity reduces health-related quality of life.[5]

Weight loss is recommended for patients with type 2 diabetes.[6] Moderate weight loss (5%-10%) can improve glycemic control[7] and other cardiometabolic risk factors and comorbidities.[8] Achieving and maintaining weight loss through lifestyle interventions alone is often difficult, partly because of the multiple obesity-related hormonal, metabolic, and neuronal adaptations that favor weight regain.[9] Few pharmacological options are currently available for the treatment of obesity.[10] Weight loss is especially challenging for individuals with type 2 diabetes, who often experience a reduced response to weight-management pharmacotherapies compared with individuals without diabetes.[11]

Liraglutide is an analog of the incretin hormone glucagon-like peptide 1 (GLP-1), with 97% homology to human GLP-1 and a unique therapeutic potential for both obesity and type 2 diabetes owing to its dual benefits on body weight and glycemic control.

Liraglutide administered once daily at doses of 1.2 mg and 1.8 mg is approved for treatment of type 2 diabetes and has been shown to be efficacious and generally well tolerated.[12] Weight loss has also been observed with liraglutide at these doses.[12] Liraglutide mediates weight loss in humans mainly by reducing appetite and caloric intake, rather than increasing energy expenditure.[13]

We studied the efficacy and safety of liraglutide (3.0 mg), as an adjunct to diet and exercise, for weight management in participants who were overweight or obese and had type 2 diabetes.

Methods

Study Design and Participants

This 56-week randomized, double-blind, placebo-controlled, parallel-group trial was conducted between June 2011 and January 2013 at 126 sites in 9 countries (France, Germany, Israel, South Africa, Spain, Sweden, Turkey, United Kingdom [England and Scotland only], United States). A 12-week observational off-drug follow-up period was included to assess treatment-cessation effects (total study length, 68 weeks) (eFigure 1 in Supplement 1). Eligible participants were overweight or obese (body mass index [BMI] ≥27.0, calculated as weight in kilograms divided by height in meters squared) adults (age ≥18 years) with a stable body weight (<5-kg change in the last 3 months), diagnosed with type 2 diabetes (hemoglobin A_{1c} [HbA_{1c}] level 7.0%-10.0%)[6] treated with diet and exercise alone or in combination with 1 to 3 oral hypoglycemic agents (metformin, thiazolidinedione, sulfonylurea). Participants taking sulfonylurea were asked to reduce their dose by 50% to mitigate the risk of hypoglycemia (see eMethods in Supplement 1 for more information). Detailed exclusion criteria are available in eTable 1 in Supplement 1. Participant race/ethnicity were self-reported and documented by the clinician as part of the baseline demographics, because the US Food and Drug Administration recommends reporting this information so that potential racial/ethnic differences in treatment responses can be examined in future pooled analyses.[14]

Written informed consent was obtained before trial participation. The local ethics committees and institutional review boards approved the trial protocol (Supplement 2), which adhered to the Declaration of Helsinki.

Randomization and Masking

Participants were randomly assigned (in a blinded fashion; week 0) to 1 of 3 groups: liraglutide (3.0 mg); liraglutide (1.8 mg); or placebo in a 2:1:1 ratio. Treatments were allocated in a centralized manner via an interactive voice/web response system and stratified according to background treatment and baseline HbA_{1c} level (for further details see eMethods in Supplement 1).

Procedures

Trial drug was administered once daily by subcutaneous injection using a modified insulin pen device (FlexPen; Novo Nordisk). The starting dose of the trial drug was 0.6 mg. It was escalated by increments of 0.6 mg weekly to the treatment dose. This occurred over 2 weeks for the 1.8-mg treatment dose and 4 weeks for the 3.0-mg treatment dose. Participants were encouraged to follow a diet containing a maximum of 30% of energy from fat, approximately 20% of energy from protein, and approximately 50% of energy from carbohydrates, with a 500-kcal/d deficit based on estimated total energy expenditure and exercise program (≥150 min/wk of brisk walking; see eMethods in Supplement 1). Participants who discontinued were asked to return at week 56 for follow-up.

Body weight was measured at every visit to week 68. Only weight measurements from fasting visits were used in the primary analysis. Timings of fasting visits and secondary end point measurements are reported in the eMethods in Supplement 1. Blood sample analysis was performed at a central laboratory using standard methods (Quintiles Inc).

Safety and tolerability assessments included adverse events recorded at every visit; standard laboratory tests; calcitonin, amylase, and lipase activity; physical examinations; mental health questionnaires; and electrocardiograms. Regular safety surveillance was performed by a sponsor-organized committee. Specific attention was given to adverse events with increased prevalence in obese individuals or relevant to the drug class (eTable 2 in Supplement 1). Hypoglycemic episodes were recorded using the American Diabetes Association classifications[6] with an additional classification of "minor," defined as a symptomatic, self-treatable episode with confirmed plasma glucose value less than 56 mg/dL (3.1 mmol/L) or as any asymptomatic plasma glucose value less than 56 mg/dL.

End Points

Three coprimary end points were tested in a hierarchical manner at week 56: (1) relative change in body weight; (2) the proportion of participants losing 5% or more of baseline body weight; and (3) proportion losing more than 10% of baseline body weight. Secondary efficacy end points included changes at week 56 in waist circumference, BMI, HbA_{1c} level, prandial plasma glucose increment (difference between premeal and

90-minute postmeal glucose values averaged across 3 meals), fasting plasma glucose level, glucagon level, insulin level, C-peptide level, proinsulin level and proinsulin to insulin ratio, homeostatic model assessment–insulin resistance index (HOMA-IR), blood pressure, levels of fasting lipids (total, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and very-low-density lipoprotein cholesterol [VLDL-C]; free fatty acids; triglycerides), levels of cardiovascular biomarkers (high-sensitivity C-reactive protein, adiponectin, fibrinogen, plasminogen activator inhibitor 1, urinary albumin-to-creatinine ratio), and patient-reported outcome scores (Impact of Weight on Quality of Life-Lite [IWQOL-Lite],[15] and Diabetes Treatment Satisfaction Questionnaire status version[16]).

Statistical Analysis

The sample size was primarily driven by the desire to obtain sufficient power for the 10% responder end point for which it was assumed to be most difficult to achieve statistical significance. The basis for the assumptions of the sample size was the 52-week interim results from the phase 2 dose-finding trial in patients without diabetes (NCT00422058). In that trial, weight loss greater than 10% was achieved by 35.9% of patients taking liraglutide (3.0 mg), 26.7% of those taking liraglutide (1.8 mg), and 9.7% of those taking placebo. Mean weight loss of 9.2% (8.8 kg) was observed for liraglutide (3.0 mg), 6.8% (6.5 kg) for liraglutide (1.8 mg), and 3.1% (3.0 kg) for placebo (data on file).

Because the present study was conducted among patients with diabetes, a more conservative approach was taken in estimating the between-group differences. Assuming 20% responders in the liraglutide (3.0 mg) group and 10% responders in the placebo group, 400 participants taking liraglutide (3.0 mg) and 200 taking placebo would yield an 89% power based on a 2-sided χ^2 with a significance level of 5%. The selected sample size resulted in similar power for all other primary and secondary tests (see eMethods in Supplement 1 for full description).

Equality between liraglutide (3.0 mg) and placebo for the 3 coprimary end points was tested in a hierarchical manner in the order above; if superiority was detected for all coprimary end points, equality between liraglutide (1.8 mg) and placebo was tested in the same manner. No alpha control was applied to the comparison between the 3.0-mg and 1.8-mg doses or for the secondary variables; therefore, these data should be considered exploratory. Results for the coprimary weight end points are estimated means or proportions from multiple imputation models (see Supplement 1 for methodology). Unless otherwise specified, all other changes from baseline data reported are observed raw means. The trial used a modified intent-to-treat analysis. More participants were included in the liraglutide (3.0 mg) group because the safety of the 1.8-mg dose was previously extensively tested in patients with type 2 diabetes.[17]

Efficacy analyses were performed for the full analysis set (participants exposed to ≥1 treatment dose with ≥1 postbaseline efficacy assessment). The 3 coprimary weight end points were analyzed using a multiple imputation approach; all other efficacy variables were analyzed using imputation by last observation carried forward. Multiple sensitivity analyses were performed to assess the robustness of the primary analyses as detailed in eTable 3A in Supplement 1. Safety data were evaluated on the safety analysis set (all exposed participants).

Statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc). All statistical tests were 2-sided at a 5% significance level. We tested the null hypothesis of equality between treatments using an analysis of covariance model for continuous end points, some of which were log-transformed (lipids, glucose metabolism parameters, cardiovascular biomarkers); a linear probability model for categorical weight end points; and a logistic regression analysis model for all other categorical end points (see eMethods in Supplement 1).

Results

Participants

Eight hundred forty-six individuals were enrolled and randomized to receive liraglutide (3.0 mg [n = 423]), liraglutide (1.8 mg [n = 211]), or placebo (n = 212). Participant disposition is shown in **Figure 1**. Eight hundred forty-four participants were exposed to treatment; the proportion of participants who completed the 56-week treatment period was higher with liraglutide (3.0 mg) (76.6% [n = 324]) and liraglutide (1.8 mg) (77.7% [n = 164]) than with placebo (66.0% [n = 140]) (Figure 1). A total of 71 of 218 participants (32.6%) who withdrew during the study attended the final visit at week 56. Baseline demographics were comparable across treatment groups (**Table 1**).

Primary End Points (Body Weight)

From a mean baseline body weight of 105.7 kg for liraglutide (3.0-mg dose), 105.8 kg for liraglutide (1.8-mg dose), and 106.5 kg for placebo, mean weight losses of 6.0% (6.4 kg), 4.7% (5.0 kg) and 2.0% (2.2 kg), respectively, were observed. Weight loss was significantly greater with liraglutide (3.0 mg) and liraglutide (1.8 mg) than placebo for all 3 coprimary end points in the multiple imputation analysis (**Figure 2**, **Table 2**). Estimated treatment differences similar to those reported in the multiple imputation analysis in Figure 2 were observed using multiple sensitivity analyses (eTable 3B in Supplement 1).

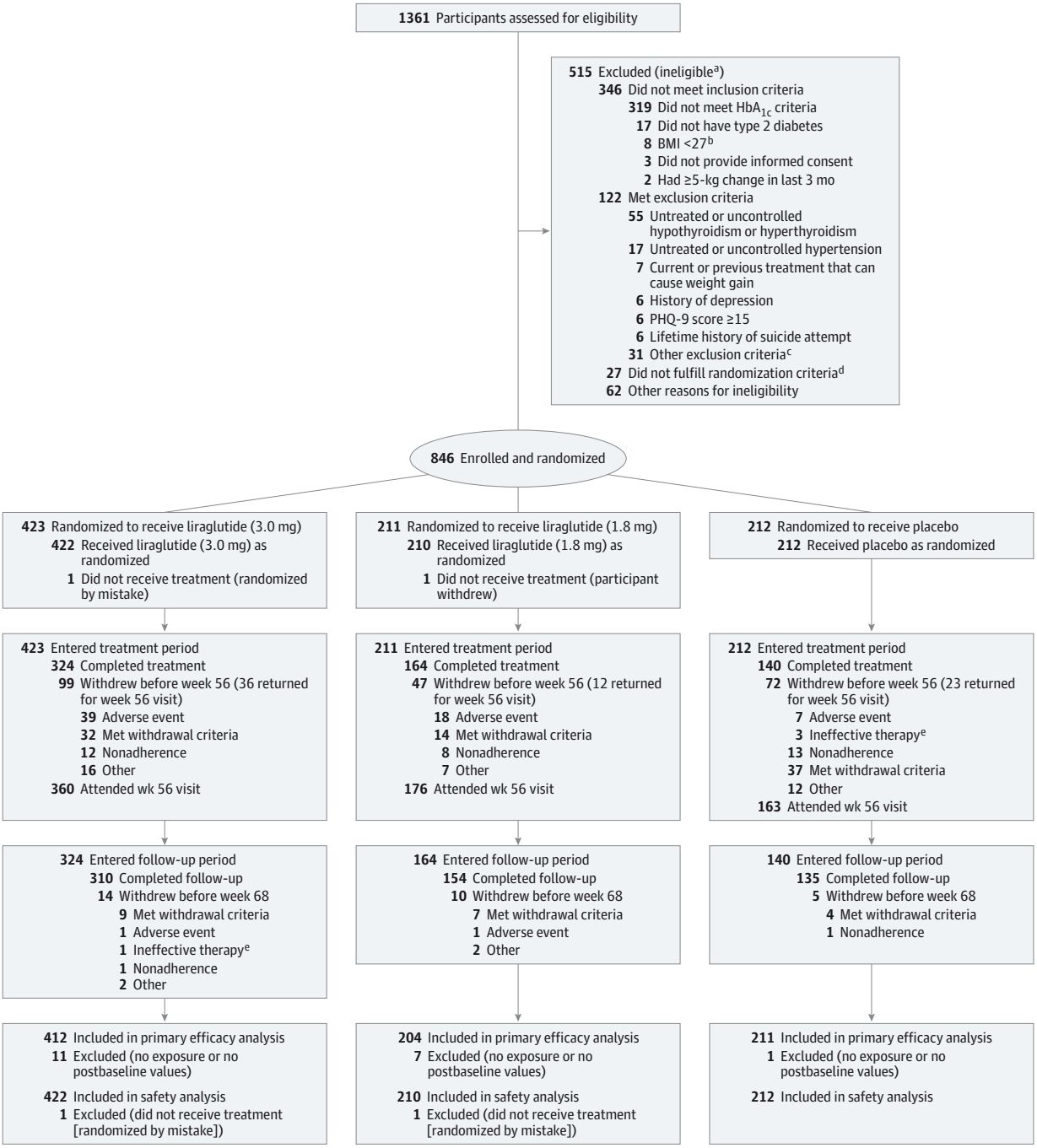
A significantly higher proportion of participants lost 5% or more, or more than 10%, body weight with liraglutide (3.0-mg and 1.8-mg doses) compared with placebo. Sensitivity analyses confirmed the results of the primary analysis for all 3 coprimary end points (eTable 3B in Supplement 1). Effects of treatment cessation on weight are shown in eFigure 3 in Supplement 1.

Secondary Efficacy End Points

Secondary efficacy end point baseline data and end-of-treatment results are reported in Table 1, **Table 3**, and eTable 4 in Supplement 1; data from the off-treatment follow-up period are included in eFigure 3 and eTable 5 in Supplement 1.

Significant reductions in mean waist circumference and BMI were observed with liraglutide (3.0 mg) and liraglutide (1.8 mg) compared with placebo. Liraglutide (3.0 mg) was associated with significantly better glycemic control compared with placebo in terms of change in HbA_{1c} level, proportion of

Figure 1. Participant Disposition



BMI indicates body mass index; HbA_{1c}, hemoglobin A_{1c}; PHQ-9, Patient Health Questionnaire 9.

[a] Participants could check more than 1 exclusion or inclusion criterion.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Previous surgical treatment for obesity (n = 4); treatment with oral antidiabetic drugs (n = 4); history of severe psychiatric disorders (n = 4); treatment with glucagon-like peptide 1 receptor agonists (n = 3); participation in a clinical trial within the last 3 months (n = 3); screening calcitonin value 50 ng/L or higher (n = 3); known or suspected abuse of alcohol or narcotics (n = 2); use of any drug that interferes with glucose level (n = 2); known proliferative retinopathy or maculopathy (n = 2); diet attempts using herbal supplements (n = 1); history of nonfamilial medullary thyroid cancer (n = 1); any suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale (n = 1); recurrent major hypoglycemia or hypoglycemic unawareness (n = 1); history of pancreatitis (n = 1).

[d] To be eligible for randomization, participants had to fulfill the randomization criterion of a mean fasting plasma glucose level less than 220 mg/dL (12.2 mmol/L) at the randomization visit (visit 2). Mean fasting plasma glucose level was based on 2 consecutive glucose measurements by the investigator at the clinic using a glucose meter.

[e] Indicates the primary reason for withdrawal and relates to the primary end point, weight change.

Table 1. Baseline Demographic Characteristics and Secondary Efficacy End Points

	No. (%)		
	Liraglutide		
	3.0 mg	1.8 mg	Placebo
Demographic Characteristics[a]			
Patients, No.	423	211	212
Age, mean (SD), y	55.0 (10.8)	54.9 (10.7)	54.7 (9.8)
Women	203 (48.0)	103 (48.8)	115 (54.2)
Race/ethnicity[b]			
Asian	11 (2.6)	4 (1.9)	4 (1.9)
Black or African American	44 (10.4)	27 (12.8)	27 (12.7)
White	353 (83.5)	177 (83.9)	175 (82.5)
Other	13 (3.1)	3 (1.4)	5 (2.4)
Ethnic origin			
Hispanic or Latino	46 (10.9)	17 (8.1)	24 (11.3)
Non-Hispanic	375 (88.7)	194 (91.9)	187 (88.2)
Body weight, mean (SD), kg	105.7 (21.9)	105.8 (21.0)	106.5 (21.3)
Body mass index, mean (SD)[c]	37.1 (6.5)	37.0 (6.9)	37.4 (7.1)
Body mass index group[c]			
25.0-29.9 (preobese)	52 (12.3)	34 (16.1)	30 (14.2)
30.0-34.9 (obese class I)	139 (32.9)	62 (29.4)	59 (27.8)
35.0-39.9 (obese class II)	108 (25.5)	50 (23.7)	60 (28.3)
>40.0 (obese class III)	124 (29.3)	65 (30.8)	63 (29.7)
Waist circumference, mean (SD), cm	118.0 (14.4)	117.5 (14.7)	117.3 (14.0)
Duration of diabetes, mean (SD), y	7.5 (5.65)	7.4 (5.16)	6.7 (5.07)
Cardiovascular disease[d]			
At screening	69 (16.4)	31 (14.8)	26 (12.3)
At baseline			
Dyslipidemia	295 (69.7)	143 (67.8)	126 (59.4)
Hypertension	293 (69.3)	148 (70.1)	145 (68.4)
Background diabetes treatment[e]			
Diet and exercise only	46 (11.2)	29 (14.2)	20 (9.5)
Metformin only	237 (57.5)	111 (54.4)	126 (59.7)
Metformin + glitazone	22 (5.3)	13 (6.4)	10 (4.7)
Metformin + sulfonylurea	86 (20.9)	44 (21.6)	48 (22.7)
Metformin + sulfonylurea + glitazone	10 (2.4)	4 (2.0)	4 (1.9)
Sulfonylurea	7 (1.7)	2 (1.0)	2 (0.9)
Sulfonylurea + glitazone	4 (1.0)	1 (0.5)	1 (0.5)

(continued)

participants achieving HbA_{1c} targets, prandial plasma glucose increment, fasting plasma glucose level, fasting glucagon level, proinsulin level, proinsulin-to-insulin ratio, and HOMA-IR indices (Table 3). A similar pattern was seen with liraglutide (1.8 mg) except for HOMA-IR, which showed no significant treatment effect. In addition, more participants treated with liraglutide (3.0 mg) and liraglutide (1.8 mg) than placebo reduced their net use of oral hypoglycemic agents after 56 weeks (Table 3; eTable 6 in Supplement 1).

Mean systolic, but not diastolic, blood pressure was reduced significantly more with liraglutide than placebo, without a dose effect. Liraglutide (3.0 mg), but not liraglutide (1.8 mg), significantly improved levels of total cholesterol, VLDL-C, HDL-C, and triglycerides compared with placebo; no effects were observed on LDL-C or free fatty acids. Levels of high-sensitivity C-reactive protein were improved with both liraglutide doses, but only liraglutide (3.0 mg) significantly improved plasminogen activator inhibitor 1 and urinary albumin-to-creatinine ratio (Table 3). Fibrinogen level was slightly, though significantly, increased with liraglutide (3.0 mg) vs placebo, whereas urinary albumin-to-creatinine ratio was 20% lower with liraglutide (3.0 mg) compared with placebo after 56 weeks (Table 3). There was no effect on adiponectin level.

Obesity can adversely affect both physical and mental health as well as overall quality of life.[18,19] Liraglutide (3.0 mg) significantly improved the "total score" of the IWQoL-Lite questionnaire (driven by an improved "physical function" score) and the Diabetes Treatment Satisfaction Questionnaire status version compared with placebo (Table 3). The minimally important difference for the IWQoL-Lite is a 7.7- to

Table 1. Baseline Demographic Characteristics and Secondary Efficacy End Points (continued)

	No. (%)		
	Liraglutide		
	3.0 mg	1.8 mg	Placebo
Secondary Efficacy End Points[f]			
Patients, No.	412	204	211
Glycemic control			
HbA_{1c}, mean (SD), %-point	7.9 (0.8)	8.0 (0.8)	7.9 (0.8)
Fasting plasma glucose, mean (SD), mg/dL	158.4 (32.8)	160.4 (35.1)	155.5 (33.0)
PPG increment, mean (SD), mg/dL	41.4 (34.2)	43.2 (32.4)	43.2 (32.4)
Fasting, geometric mean (CV)			
Glucagon, geometric, pg/mL	89.3 (33.7)	90.8 (36.1)	89.7 (37.0)
Insulin, μIU/mL	17.6 (79.2)	17.3 (77.5)	18.6 (303.0)
C-peptide, ng/mL	2.5 (45.1)	2.6 (44.7)	2.6 (43.0)
Proinsulin, pmol/L	29.1 (85.0)	30.5 (82.3)	31.0 (84.6)
Proinsulin-to-insulin ratio, %	23.8 (73.2)	25.4 (64.7)	24.1 (62.0)
HOMA-B, geometric mean (CV), %	70.4 (83.4)	68.1 (87.7)	77.0 (305.9)
HOMA-IR, geometric mean (CV), %	6.8 (89.3)	6.7 (88.8)	7.0 (286.1)
Blood pressure, mean (SD), mm Hg			
Systolic	128.9 (13.6)	130.5 (14.5)	129.2 (13.6)
Diastolic	79.0 (8.6)	80.1 (9.3)	79.3 (9.5)
Lipid profile			
Cholesterol, geometric mean (CV), mg/dL			
Total	171.0 (21.8)	178.3 (26.4)	169.4 (22.9)
HDL	45.2 (25.0)	44.5 (27.2)	45.4 (24.8)
LDL	86.4 (35.5)	91.5 (38.5)	85.2 (39.3)
VLDL	31.8 (58.5)	33.0 (76.6)	31.1 (54.5)
Triglycerides, geometric mean (CV), mg/dL	162 (73)	170 (98)	158 (66)
Free fatty acids, geometric mean (CV), mg/dL	15.8 (37.7)	15.8 (37.1)	16.1 (38.3)
Cardiovascular biomarkers			
hsCRP, geometric mean (CV), mg/L	3.4 (125.7)	3.9 (127.9)	3.6 (111.5)
Adiponectin, geometric mean (CV), μg/mL	5.6 (64.6)	5.9 (68.0)	5.6 (49.6)
Fibrinogen, geometric mean (CV), g/L	4.1 (23.8)	4.3 (26.7)	4.3 (23.14)
UACR, geometric mean (CV), mg/mmol	1.0 (408.9)	1.1 (300.8)	1.0 (342.2)
Receiving concomitant oral hypoglycemic drugs at baseline, No. (%)	366 (88.8)	175 (85.8)	191 (90.5)
Patient-reported outcomes			
IWQoL-Lite, mean (SD)			
Physical function	64.3 (24.6)	66.2 (23.5)	67.6 (21.8)
Self-esteem	69.7 (27.2)	72.2 (26.2)	72.6 (24.0)
Sexual life	76.3 (28.6)	77.3 (28.0)	80.0 (27.4)
Public distress	83.7 (21.8)	85.7 (20.5)	86.3 (17.8)
Work	83.3 (21.1)	85.4 (18.7)	85.7 (19.3)
Total score	72.6 (20.4)	74.6 (20.0)	75.7 (18.0)
DTSQs, total score, mean (SD)	27.6 (6.7)	28.0 (7.1)	27.9 (6.7)

Abbreviations: CV, coefficient of variation; DTSQs, Diabetes Treatment Satisfaction Questionnaire (status version); HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; HOMA-B, homeostasis model assessment–β; HOMA-IR, homeostasis model assessment–insulin resistance; hsCRP, high-sensitivity C-reactive protein; IWQoL-Lite, Impact of Weight on Quality of Life–Lite; LDL, low-density lipoprotein; PPG, prandial glucose; UACR, urine albumin-to-creatinine ratio; VLDL, very-low-density lipoprotein.

SI conversion factors: To convert glucose values to mmol/L, multiply by 0.0555; insulin values to pmol/L, multiply by 6.945; C-peptide values to nmol/L, multiply by 0.331; total cholesterol, HDL cholesterol, and LDL cholesterol values to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; free fatty acids to mmol/L, multiply by 0.0355.

[a] Baseline characteristics data are for all randomized participants except for background diabetes treatment, which is based on the full analysis set.

[b] Self-reported. Participants from France did not report race or ethnicity; therefore, values do not sum to 100%.

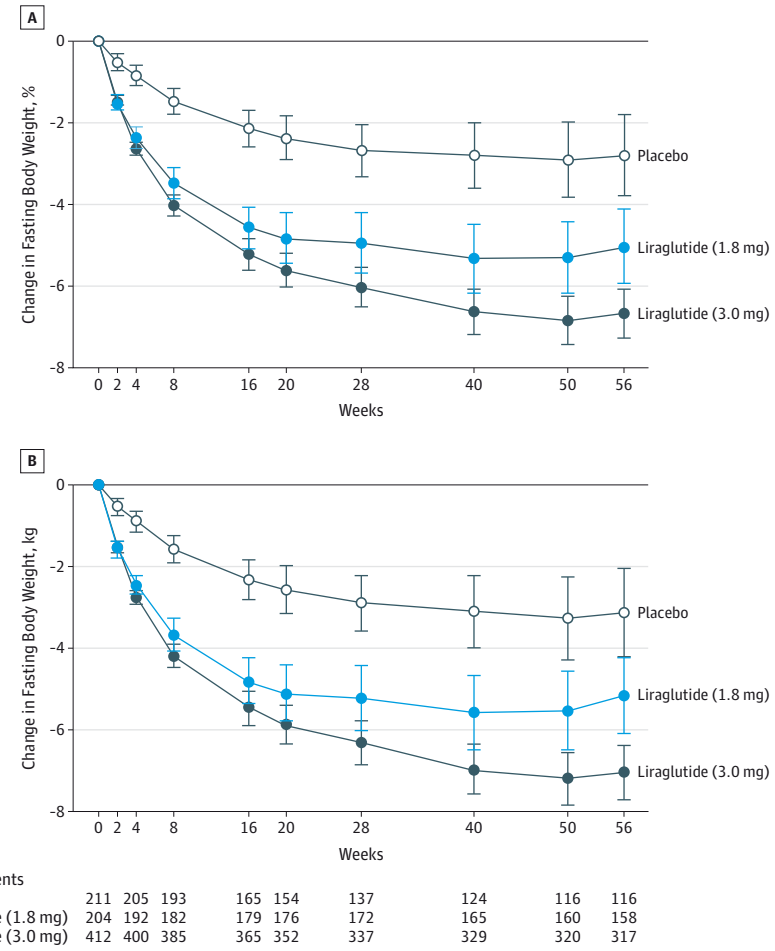
[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Cardiovascular disease defined as ischemic heart disease, cardiac failure and central nervous system hemorrhages, and cerebrovascular conditions and embolic and thrombotic events based on a predefined search on Standard MedDRA Queries (for further information see eTable 2 in Supplement 1). Dyslipidemia and hypertension statuses at baseline were based on reported medical history.

[e] Baseline secondary efficacy end point data are observed mean (SD) or geometric mean (CV) for the full analysis set.

[f] Based on full analysis set.

Figure 2. Time Course of Body Weight Loss From Baseline to Week 56 for Liraglutide (3.0 mg), Liraglutide (1.8 mg), and Placebo



No. of patients

Placebo	211	205	193	165	154	137	124	116	116
Liraglutide (1.8 mg)	204	192	182	179	176	172	165	160	158
Liraglutide (3.0 mg)	412	400	385	365	352	337	329	320	317

Observed mean weight loss at fasting visits. Numbers of patients at 2 weeks were 209 for placebo, 200 for liraglutide (1.8 mg), and 410 for liraglutide (3.0 mg). Mean weight loss was 6.0% (6.4 kg) for liraglutide (3.0-mg dose), 4.7% (5.0 kg) for liraglutide (1.8-mg dose), and 2.0% (2.2 kg) for placebo. Error bars indicate Wald 95% CIs.

Table 2. Summary of Coprimary Efficacy End Points at Week 56[a]

End Point	Baseline Value, Full Analysis Set, Mean (SD), kg	Mean and Categorical Weight Loss at Week 56			Estimated Treatment Difference/Risk Difference (95% CI)			
		Liraglutide			Liraglutide			
		3.0 mg (n = 412)	1.8 mg (n = 204)	Placebo (n = 211)	3.0 mg vs Placebo	*P* Value	1.8 mg vs Placebo	*P* Value
Change from baseline, fasting body weight, %	106.0 (21.5)	-6.0	-4.7	-2.0	−4.00 (-5.10 to -2.90)	<.001	-2.71 (-4.00 to -1.42)	<.001
Observed means, %[b]	106.0 (21.5)	-5.9	-4.6	-2.0	NA	NA	NA	NA
Weight loss ≥5%, %	NA	54.3[c]	40.4[c]	21.4[c]	32.9 (24.6 to 41.2)	<.001	19.0 (9.1 to 28.8)	<.001
Observed proportions, No. (%)[b]	NA	205 (49.9)	72 (35.6)	29 (13.8)	NA	NA	NA	NA
Weight loss, >10%, %	NA	25.2[c]	15.9[c]	6.7[c]	18.5 (12.7 to 24.4)	<.001	9.3 (2.7 to 15.8)	.006
Observed proportions, No. (%)[b]	NA	96 (23.4)	29 (14.4)	9 (4.3)	NA	NA	NA	NA

Abbreviation: NA, not applicable.

[a] Change in body weight values are for the full analysis set and based on fasting values only. Changes in body weight are estimated means, missing observations at week 56 were imputed using a regression method and treatment differences are estimates from an analysis of covariance model. Proportions of participants are estimated proportions, missing observations were imputed using a regression method, and risk differences are estimates from a regression model using an identity link, except where specified otherwise.

[b] Data are for patients in the full analysis set, with last observation carried forward.

[c] Number of participants not estimated.

Table 3. Summary of Secondary Efficacy End Points At Week 56[a]

End Point	Change From Baseline to Week 56 or Percentage At Week 56			Estimate (95% CI)				
	Liraglutide				Liraglutide			
	3.0 mg (n = 411)	1.8 mg (n = 204)	Placebo (n = 211)	Estimate Type	3.0 mg vs Placebo	*P* Value	1.8 mg vs Placebo	*P* Value
Waist circumference, mean (SD), cm[b]	-6.1 (6.5)	-4.8 (5.6)	-2.7 (5.4)	Treatment difference	-3.22 (-4.20 to -2.23)	<.001	-2.06 (-3.20 to -0.92)	<.001
Body mass index, mean (SD)[b,c]	-2.2 (2.1)	-1.7 (2.1)	-0.8 (1.7)	Treatment difference	-1.50 (-1.83 to -1.18)	<.001	-0.95 (-1.33 to -0.57)	<.001
HbA_{1c}, mean (SD), % change[b]	-1.3 (0.9)	-1.1 (1.0)	-0.3 (0.9)	Treatment difference	-0.93 (-1.08 to -0.78)	<.001	-0.74 (-0.91 to -0.57)	<.001
No. of individuals achieving HbA_{1c} target, No. %[d]								
<7.0 %	278 (69.2)	130 (66.7)	56 (27.2)	Odds ratio	8.79 (5.74 to 13.44)	<.001	7.71 (4.76 to 12.51)	<.001
≤6.5 %	227 (56.5)	89 (45.6)	31 (15.0)	Odds ratio	9.61 (6.05 to 15.26)	<.001	5.98 (3.59 to 9.97)	<.001
Fasting plasma glucose, mean (SD), mg/dL[b]	-34.3 (38.5)	-26.8 (50.3)	-0.2 (37.0)	Treatment difference	-31.89 (-38.02 to-25.59)	<.001	-23.06 (-30.27 to -15.86)	<.001
PPG increment, mean (SD), mg/dL[b]	-16.2 (37.8)	-12.6 (37.8)	-5.4 (36.0)	Treatment difference	-9.91 (-15.14 to -4.68)	<.001	-7.93 (-13.87 to -1.98)	.009
Fasting values, geometric mean (CV), %[e]								
Glucagon	-10.4 (34.7)	-7.9 (30.8)	0.6 (33.0)	Ratio	0.87 (0.83 to 0.92)	<.001	0.91 (0.86 to 0.96)	<.001
Insulin	6.87 (67.3)	10.65 (48.7)	1.94 (47.0)	Ratio	1.03 (0.94 to 1.12)	.50	1.07 (0.96 to 1.18)	.21
C-peptide	3.3 (53.4)	2.4 (34.0)	-2.4 (28.5)	Ratio	1.04 (0.98 to 1.10)	.17	1.03 (0.97 to 1.10)	.29
Proinsulin	-34.4 (78.9)	-23.6 (85.2)	-0.5 (61.6)	Ratio	0.65 (0.58 to 0.73)	<.001	0.77 (0.68 to 0.88)	<.001
Proinsulin to insulin ratio	-38.4 (64.4)	-31.6 (87.1)	-2.2 (176.0)	Ratio	0.63 (0.58 to 0.69)	<.001	0.72 (0.64 to 0.79)	<.001
HOMA-B, geometric mean (CV), %[e]	94.3 (419.0)	72.3 (55.1)	9.1 (57.0)	Ratio	1.71 (1.52 to 1.92)	<.001	1.53 (1.34 to 1.74)	<.001
HOMA-IR, geometric mean (CV), %[e]	-20.0 (76.7)	-10.5 (79.4)	-3.3 (79.5)	Ratio	0.84 (0.75 to 0.94)	.003	0.93 (0.82 to 1.07)	.32
Blood pressure, mean (SD), mm Hg[b]								
Systolic	-2.8 (13.5)	-3.5 (12.7)	-0.4 (13.4)	Treatment difference	-2.59 (-4.56 to -0.62)	.01	-2.68 (-4.98 to -0.38)	.02
Diastolic	-0.9 (8.7)	-1.1 (9.4)	-0.5 (9.1)	Treatment difference	-0.36 (-1.69 to 0.96)	.59	-0.19 (-1.74 to 1.36)	.81
Lipid profile[e]								
Cholesterol, geometric mean (CV), %								
Total	-1.46 (16.9)	-2.20 (20.2)	3.80 (16.2)	Ratio	0.96 (0.94to 0.99)	.01	0.97 (0.94 to 1.00)	.06
HDL	4.70 (16.1)	4.45 (14.2)	1.93 (14.3)	Ratio	1.03 (1.00 to 1.05)	.03	1.02 (0.99 to 1.05)	.16
LDL	0.58 (38.8)	-3.07 (30.5)	5.02 (27.3)	Ratio	0.98 (0.93 to 1.03)	.36	0.95 (0.90 to 1.01)	.10
VLDL	-14.10 (43.0)	-8.14 (41.7)	0.53 (35.5)	Ratio	0.87 (0.81 to 0.93)	<.001	0.94 (0.87 to 1.01)	.09
Triglycerides, geometric mean (CV), %	-14.68 (46.9)	-9.45 (47.9)	0.41 (40.5)	Ratio	0.86 (0.80 to 0.92)	<.001	0.93 (0.86 to1.01)	.07
Free fatty acids, geometric mean (CV), %	-13.57 (157.0)	-11.66 (60.6)	-9.02 (42.6)	Ratio	0.94 (0.88 to 1.01)	.10	0.95 (0.88 to1.03)	.22

(continued)

Table 3. Summary of Secondary Efficacy End Points At Week 56[a] (continued)

End Point	Change From Baseline to Week 56 or Percentage At Week 56			Estimate (95% CI)				
	Liraglutide				Liraglutide			
	3.0 mg (n = 411)	1.8 mg (n = 204)	Placebo (n = 211)	Estimate Type	3.0 mg vs Placebo	*P* Value	1.8 mg vs Placebo	*P* Value
Cardiovascular biomarkers[e]								
hsCRP, geometric mean (CV), %	-33.51 (141.0)	-33.34 (119.0)	-10.45 (125.0)	Ratio	0.73 (0.64 to 0.83)	<.001	0.75 (0.65 to 0.88)	<.001
Adiponectin, geometric mean (CV), %	6.6 (1848.0)	3.5 (90.3)	1.3 (35.5)	Ratio	1.06 (0.98 to 1.15)	.17	1.07 (0.97 to 1.18)	.18
Fibrinogen, geometric mean (CV), %	4.54 (32.2)	1.68 (35.8)	-3.11 (33.9)	Ratio	1.05 (1.00 to 1.09)	.046	1.04 (0.98 to 1.09)	.18
PAI-1	NA	NA	NA		0.76 (0.66 to 0.89)	<.001	0.84 (0.71 to 1.00)	.06
UACR, geometric mean (CV), %	-18.36 (165.2)	-10.79 (254.0)	-2.34 (133.1)	Ratio	0.80 (0.68 to 0.94)	.009	0.92 (0.76 to 1.12)	.42
Change in net use of concomitant oral hypoglycemic agents, No. (% patients)[f]								
Decrease	54 (13.1)	17 (8.3)	12 (5.7)					
Increase	21 (5.1)	19 (9.3)	57 (27.0)	Odds ratio	5.63 (3.62 to 8.76)	<.001	3.36 (2.07 to 5.47)	<.001
No change	337 (81.8)	168 (82.4)	142 (67.3)					
Patient-reported outcomes[b]								
IWQoL-Lite score, mean (SD)								
Physical function	15.16 (18.02)	12.50 (17.30)	8.92 (16.13)	Treatment difference	4.92 (2.12 to 7.71)	<.001	2.64 (-0.59 to 5.88)	.11
Self esteem	12.48 (19.31)	9.80 (17.67)	9.61 (18.63)	Treatment difference	1.51 (-1.37 to 4.39)	.30	0.01 (-3.32 to 3.34)	>.99
Sexual life	9.22 (23.72)	6.90 (21.70)	7.78 (21.86)	Treatment difference	-0.70 (-4.27 to 2.88)	.70	-2.03 (-6.16 to 2.11)	.34
Public distress	7.06 (16.94)	4.84 (14.06)	4.11 (12.57)	Treatment difference	1.64 (-0.61 to 3.89)	.15	0.00 (-2.60 to 2.60)	>.99
Work	8.80 (17.23)	5.48 (16.56)	5.45 (15.77)	Treatment difference	1.54 (-0.76 to 3.85)	.19	-1.06 (-3.73 to 1.61)	.44
Total score	11.68 (14.67)	9.07 (14.05)	7.58 (12.57)	Treatment difference	2.75 (0.57 to 4.93)	.01	0.78 (-1.74 to 3.31)	.54
DTSQ, mean (SD)								
Total score	4.15 (7.61)	3.89 (7.62)	2.32 (7.03)	Treatment difference	1.44 (0.40 to 2.48)	.007	1.14 (-0.07 to 2.34)	.06

Abbreviations: CV, coefficient of variation; DTSQ, Diabetes Treatment Satisfaction Questionnaire; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; HOMA-B, homeostasis model assessment-β; HOMA-IR, homeostasis model assessment-insulin resistance; hsCRP, high-sensitivity C-reactive protein; IWQoL-Lite, Impact of Weight on Quality of Life–Lite; LDL, low-density lipoprotein; OHA, oral hypoglycemic agent; PAI-1, plasminogen activator inhibitor 1; PPG, prandial glucose; UACR, urinary albumin-to-creatinine ratio; VLDL, very-low-density lipoprotein.

[a] All data are for patients in the full analysis set, with last observation carried forward.

[b] Data are observed raw mean change (SD) and estimates are treatment differences.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Values are observed proportions, and odds ratios are estimates from a logistic regression model for participants in the full analysis set.

[e] Data have been analyzed on a log scale, and the results are presented as relative change from baseline in observed geometric mean (% and CV).

[f] Change in net use of oral hypoglycemic agents was defined as the composite measure of an increase, no change, or decrease in dose or number of medications.

12-point change depending on baseline severity, which can be used to differentiate between clinically important and statistically significant differences.[20] In this study we observed clinically meaningful mean improvements in IWQoL-Lite scores of 15.2 for liraglutide (3.0 mg), 12.5 for liraglutide (1.8 mg), and 8.9 for placebo.

Exploratory Analyses of Comparisons Between Liraglutide (3.0 mg) and Liraglutide (1.8 mg)

Because comparisons between the 2 liraglutide doses were not controlled for multiplicity, they should be interpreted with caution. Liraglutide (3.0 mg) was statistically significantly better than liraglutide (1.8 mg) on weight-related measures including mean

Table 4. Summary of Safety[a]

	Liraglutide 3.0 mg (n = 422)			Liraglutide 1.8 mg (n = 210)			Placebo (n = 212)		
	No. (%)	Events, No.	Rate[b]	No. (%)	Events, No.	Rate[b]	No. (%)	Events, No.	Rate[b]
Patient-years of exposure	379.9			189.7			179.7		
Treatment-emergent adverse events									
Any	392 (92.9)	3725	981	190 (90.5)	1662	876	182 (85.8)	1039	578
Serious[c]	37 (8.8)	50	13	18 (8.6)	22	12	13 (6.1)	20	11
Severity[d]									
Severe	52 (12.3)	83	22	29 (13.8)	56	30	21 (9.9)	30	17
Moderate	239 (56.6)	742	195	118 (56.2)	381	201	105 (49.5)	289	161
Mild	366 (86.7)	2900	763	176 (83.8)	1224	645	169 (79.7)	720	401
Outcome									
Recovered	382 (90.5)	3392	893	190 (90.5)	1502	792	174 (82.1)	888	494
Adverse event leading to withdrawal	39 (9.2)	51	13	18 (8.6)	25	13	7 (3.3)	7	4
Most common (≥5%) gastrointestinal adverse events									
Gastrointestinal disorders	275 (65.2)	851	224	118 (56.2)	280	148	83 (39.2)	150	83
Gastrointestinal signs and symptoms									
Abdominal distension	26 (6.2)	32	8	10 (4.8)	11	6	3 (1.4)	3	2
Abdominal pain	26 (6.2)	34	9	4 (1.9)	4	2	9 (4.2)	9	5
Abdominal pain, upper	15 (3.6)	21	6	14 (6.7)	17	9	2 (0.9)	2	1
Dyspepsia	47 (11.1)	59	16	14 (6.7)	16	8	5 (2.4)	5	3
Flatulence	22 (5.2)	26	7	8 (3.8)	8	4	4 (1.9)	4	2
Nausea	138 (32.7)	208	55	66 (31.4)	84	44	29 (13.7)	34	19
Vomiting	66 (15.6)	113	30	21 (10.0)	27	14	12 (5.7)	14	8
Gastrointestinal motility and defecation conditions									
Constipation	68 (16.1)	78	21	20 (9.5)	24	13	13 (6.1)	14	8
Diarrhea	108 (25.6)	173	46	37 (17.6)	50	26	27 (12.7)	35	19

[a] Data are from the safety analysis set.

[b] Event rate per 100 patient-years of exposure.

[c] Serious adverse events included death, a life-threatening experience at the time of the event, hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, congenital anomaly or birth defect or important medical events that may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[d] Severity of nonserious adverse events was assessed as mild (no or transient symptoms, no interference with the participant's daily activities), moderate (marked symptoms, moderate interference with the participant's daily activities), severe (considerable interference with the participant's daily activities, unacceptable).

weight loss, 5% or more and more than 10% weight loss responders, as well as waist circumference and BMI (Figure 2; eTable 4 and eTable 7 in Supplement 1). Liraglutide (3.0 mg) was also statistically significantly better than liraglutide (1.8 mg) on glucose-related measures including HbA_{1c} level, HbA_{1c} level 6.5% or lower, fasting plasma glucose level, fasting proinsulin level, proinsulin-to-insulin ratio, HOMA-IR, and net use of oral hypoglycemic agents (eTable 4 in Supplement 1).

Safety

Safety data are summarized in **Table 4** and in eFigure 2, eTable 2, and eTable 8 in Supplement 1. The study was not powered to enable definitive conclusions about safety to be made. The event rates for adverse events and adverse events leading to withdrawal were higher with liraglutide than placebo, mainly driven by a higher rate of gastrointestinal adverse events. Gastrointestinal adverse events, notably nausea, vomiting, diarrhea, and constipation, were the most frequently reported adverse events in all treatment groups, with a greater incidence in the liraglutide (3.0 mg) group compared with the liraglutide (1.8 mg) group; onset of nausea was mainly within the first 4 to 8 weeks of treatment (eFigure 2 in Supplement 1).

Most adverse events were mild in severity (2900/3725 events [78%] with liraglutide [3.0 mg]; 1224/1662 events [74%] with liraglutide [1.8 mg]; 720/1039 events [69%] with placebo). The rate of serious adverse events was 8.8% with liraglutide (3.0 mg), 8.6% with liraglutide (1.8 mg), and 6.1% with placebo, and events generally occurred as single events in single participants with no apparent clustering. One participant in the liraglutide (1.8 mg) group died after 44 days off drug during the follow-up period; death was attributed to pulmonary embolism and thromboembolic stroke (eResults in Supplement 1).

Hypoglycemic episodes were more frequent with liraglutide (3.0 mg) than with placebo (eTable 9 in Supplement 1); rates of documented symptomatic hypoglycemia were 87 events per 100 patient-years of exposure for liraglutide (3.0 mg), 95 events

per 100 patient-years of exposure for liraglutide (1.8 mg), and 31 events per 100 patient-years of exposure with placebo. Across all treatment groups, more episodes occurred in participants with background sulfonylurea use than in those not taking sulfonylurea. Five severe (requiring third-party assistance) episodes occurred among participants receiving liraglutide (3.0 mg) and 3 among those receiving liraglutide (1.8 mg), all in combination with a sulfonylurea.

Mean heart rate increases of 2.0/min and 2.1/min occurred with liraglutide (3.0) mg and liraglutide (1.8 mg) vs −1.4/min for placebo ($P < .001$ vs placebo). The proportion of participants with increases in heart rate of more than 5/min, more than 10/min, and more than 20/min at 2 or more consecutive visits was higher with liraglutide than placebo and appeared comparable between liraglutide (3.0 mg) and liraglutide (1.8 mg) (eTable 10 in Supplement 1). Mean heart rate returned to baseline after treatment cessation (eFigure 3 in Supplement 1). The rate of cardiac arrhythmias was generally low but was higher with liraglutide (3.0 mg) (5 events per 100 patient-years of exposure) and liraglutide (1.8 mg) (5 events per 100 patient-years of exposure) than with placebo (2 events per 100 patient-years of exposure, respectively) (eTable 8 in Supplement 1). Tachycardia and sinus tachycardia were the most frequent cardiac arrhythmias in the liraglutide groups, both reported in 3 to 4 participants. The majority of these events were mild and nonserious, and none led to withdrawal. The remaining events occurred primarily as single events in single participants, including 1 event of atrial fibrillation and 1 event of atrial flutter, both with liraglutide (3.0 mg): both events were considered mild, and the participants recovered while receiving treatment and completed the trial. The number of adjudication-confirmed major adverse cardiovascular events was low: 2 events in 2 participants (0.5%) (1 event per 100 patient-years of exposure) with liraglutide (3.0 mg) and 3 events in 3 participants (1.4%) (2 events per 100 patient-years of exposure) with both liraglutide (1.8 mg) and placebo (eTable 8 in Supplement 1). No changes in either the physical examination or electrocardiogram were observed between liraglutide- and placebo-treated participants.

No cases of acute pancreatitis were reported. Geometric mean serum amylase activity and lipase activity were elevated with liraglutide compared with placebo after 56 weeks of treatment (amylase: 58.5 U/L [from 50.8 U/L] for liraglutide [3.0 mg] and 58.5 U/L [from 52.5 U/L] for liraglutide [1.8 mg] vs 54.7 U/L [from 52.7 U/L] for placebo; lipase: 50.7 U/L [from 37.8 U/L] for liraglutide [3.0 mg] and 50.3 U/L [from 37.6 U/L] for liraglutide [1.8 mg] vs 39.6 U/L [from 38.0 U/L] for placebo). No participants had amylase activity greater than 3 times upper limit of normal range (112 U/L) at any time during treatment, and few participants had lipase activity greater than 3 times upper limit of normal range (60 U/L) (eTable 11 in Supplement 1). Amylase and lipase activity returned to baseline in the off-treatment follow-up period (eFigure 3 in Supplement 1). The incidence of gallbladder-related adverse events was low across groups (1.2% for liraglutide [3.0 mg], 1.9% for liraglutide [1.8 mg], and 0.5% for placebo) (eTable 8 in Supplement 1). Allergic and injection site reactions were infrequent and nonsevere. No adverse events of treatment cessation on binge eating or other safety parameters were observed.

The frequencies and rates of adjudication-confirmed neoplasms were low across treatment groups (eTable 8 in Supplement 1). There were no cases of medullary thyroid carcinoma with liraglutide and 1 case with placebo. No increases in calcitonin concentrations were observed with liraglutide (eTable 12 in Supplement 1).

Discussion

To our knowledge, this is the first study specifically designed to investigate the efficacy of liraglutide for weight management in patients with type 2 diabetes and also the first study to investigate liraglutide at the higher 3.0-mg dose in a population with type 2 diabetes. Data from the SCALE Obesity and Prediabetes trial, in which liraglutide (3.0 mg) was investigated for weight management in patients with or without prediabetes, have recently been published.[21] In the present trial, liraglutide (3.0 mg), as an adjunct to a reduced-calorie diet and increased physical activity, was effective and generally well tolerated and was significantly better than placebo on all 3 coprimary weight-related end points.

The safety profile of liraglutide in this trial was consistent with prior clinical experience in type 2 diabetes[12] and weight management trials.[21-25] No new safety concerns were identified. No cases of pancreatitis were reported. Asymptomatic, dose-independent increases in amylase and lipase activity, which returned to baseline levels on treatment cessation, were observed with liraglutide. Evidence from clinical trials of GLP-1 receptor agonists with systematic monitoring of amylase and lipase activity suggests that elevated levels are not predictive of pancreatitis[26]: ongoing studies should help to establish whether there is any clinical significance. There was no indication of a treatment effect on blood calcitonin levels, and no confirmed events of C-cell hyperplasia or medullary thyroid carcinoma were reported with liraglutide.

As in previous studies,[12,22-25,27] liraglutide increased resting heart rate, but no dose-dependency was observed and the effects were reversible on treatment cessation. The effect on heart rate also has been observed with exenatide (once weekly) and dulaglutide and appears to be a class effect of longer-acting GLP-1 receptor agonists.[27] Given that GLP-1 receptor agonists are also associated with improvements in other cardiovascular risk factors, the long-term clinical relevance of their effect on heart rate remains unknown. In this study, exploratory analyses revealed improvements in several cardiovascular risk factors, including waist circumference, systolic blood pressure, fasting lipid levels, and other cardiovascular biomarkers, although an increase in fibrinogen level with liraglutide (3.0 mg) was observed. The ongoing LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial enrolling more than 9000 participants with type 2 diabetes at high risk of cardiovascular disease will provide comprehensive data regarding the cardiovascular safety and outcomes of liraglutide (1.8 mg) (NCT01179048).

In the present trial, levels of HbA_{1c} and fasting plasma glucose were significantly reduced to similar levels as observed in the type 2 diabetes clinical program with liraglutide administered at doses up to 1.8 mg.[12] Improved glycemic control with liraglutide (3.0 mg) was associated with a significant reduction in participants' use of concomitant oral hypoglycemic agents compared with placebo. Because some oral hypoglycemic agents are known to cause weight gain,[10] a reduction in their use enabled by liraglutide (3.0 mg) may provide additional weight benefits.

Although more hypoglycemic episodes were observed with liraglutide than with placebo, rates appeared similar to those seen previously with a 1.8-mg dose in patients with type 2 diabetes,[12] and no dose-dependency was observed. Few severe hypoglycemic episodes were reported (5 with liraglutide [3.0 mg], 3 with liraglutide [1.8 mg]), all in participants receiving concomitant sulfonylurea therapy.

Measures of weight-related quality of life were significantly improved with liraglutide (3.0 mg) but not liraglutide (1.8 mg), primarily driven by a significant improvement in participants' physical function. It is possible that such improvements in quality of life and treatment satisfaction would lead to better adherence to treatment and lifestyle interventions and reinforce desired behavior, although further studies would be required to confirm this.

Exploratory comparisons between the 2 doses of liraglutide showed that liraglutide (3.0 mg) was statistically significantly better than liraglutide (1.8 mg) on all weight- and glycemic-related end points; the difference between the 3.0-mg dose and the 1.8-mg dose in reduction of HbA_{1c} level, while statistically significant, was small (0.19%), but the 3.0-mg dose did lead to a larger reduction in participants' use of oral hypoglycemic agents compared with liraglutide (1.8 mg). These findings suggest that, in addition to clinically relevant weight loss, liraglutide (3.0 mg) may offer better glycemic control over liraglutide (1.8 mg) while reducing use of oral hypoglycemic agents and maintaining a low risk of hypoglycemia. The safety profile was similar between the doses, with only nausea displaying a clear dose-dependency.

Studies of liraglutide in participants without diabetes have reported modest weight regain on treatment cessation.[23] Such a rebound effect has also been observed with lorcaserin[28] and orlistat.[29] Participants in the present trial regained weight after liraglutide cessation and reductions in systolic blood pressure and levels of fasting plasma glucose were reversed, indicating that continued treatment is necessary to sustain the on-drug benefits. Importantly, no adverse events of treatment cessation on safety or binge eating were noted.

The present study had several limitations. It was not powered to enable conclusions about safety. Moreover, no control for multiplicity or for comparisons between liraglutide (3.0 mg) and liraglutide (1.8 mg) doses or secondary end points was applied; therefore, caution must be exercised when interpreting these results. Although weight loss was maintained until 56 weeks among completers, further studies are required to establish whether these effects are maintained with continuing liraglutide (3.0 mg) treatment in the longer term.

Conclusions

Among overweight and obese participants with type 2 diabetes, use of subcutaneous liraglutide (3.0 mg) daily, compared with placebo, resulted in weight loss over 56 weeks. Further studies are needed to evaluate longer-term efficacy and safety.

ARTICLE INFORMATION

Author Contributions: Dr Davies had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Davies, Bode, Lewin, Skjøth, Jensen.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Davies, Bode, Lewin, Skjøth, Andreasen, Jensen.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Skjøth, Andreasen, Jensen.
Study supervision: Davies, Bergenstal, Lewin, Skjøth, Jensen.

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NN8022-1922 Study Group: *France:* Paul Valensi, Marc Levy, Sonia Benabdallah, Pierre Serusclat, Jean-Pierre Courreges, Didier Gouet, Sylvaine Clavel, Bertrand Cariou; *Germany:* Kerstin Tyler, Markolf Hanefeld, Ralf Jordan, Karsten Milek, Ludger Rose, Joachim Sauter, Joerg Steindorf, Ulrich Wendish, Gottfried Rudofsky, Rudolf Erlinger; *Israel:* Ilana Harman-Boehm, Ofri Mosenzon, Josef Cohen, Avraham Karasik, Oscar Minuchin; *South Africa:* Hans Hendrik Snyman, Stephanus M. Komati, Puvanesveri Naiker, Johannes Jurgens Lombaard, Gracjan Podgorski, Munira Fakir Saleh;

Spain: Manuel Muñoz, Luis De Teresa Parreño, Santiago Durán García, Basilio Moreno Esteban, Margarita Rivas Fernández, Angel Maria Sendón Pérez, Bartolomé Burguera, Clotilde Vázquez; *Sweden:* Joanna Uddén Hemmingsson, Enrique Eizyk, Aslak Rautio, Anders Norrby, Ewa Jasinska; *Turkey:* Abdurrahman Comlekci, Cumali Gokce, Kamile Gul; *United Kingdom:* Peter Mansell, Andrew B. Johnson, Ann Millward, Rudolf Bilous, David Andrew Collier, Graham Hitman, Tom Maxwell, Franklin Joseph, Mark Davis, Patrick Holmes, Sandeep Thekkepay, Adrian Park, Matt Capehorn, Shahad Taheri, Melanie Davies; *United States:* Vanita R. Aroda, Thomas Craig Blevins, Bruce W. Bode, Peter Bressler, Paul Ellis Bristol, Deanna Cheung, Richard M. Bergenstal, David Fitz-Patrick, Kevin Furlong, Darrell Gorman, Priscilla Hollander, David Huffman, Elise Kwon, Andrew Lewin, Robert S. Lipetz, Kathryn Jean Lucas, Jeffrey Pollock, Luis Rivera-Colon, Julio Rosenstock, Herman A. Salazar, Jean Louis Selam, John Shelmet, Henry John Simon, Norman G. Soler, Danny Sugimoto, Scott Touger, Alan Wynne, Steven B. Leichter, Eric J. Klein, Elias M. Kolettis, Lon Lynn, James T. Lane, Harold E. Bays, Ramona Granda-Rodriguez, Robert S. Busch, Kevin Cannon, Anna Chang, Christopher M. Chappel, John Timothy Dow, John Keith Earl, Victor Elinoff, Mildred V. Farmer, Joseph H. Woolley, William Stuart Gonte, Samuel Klein, Robert Kushner, Wendy S. Lane, John Albert Lang, Samuel Lerman, Barry Lubin, Paul A. Martin, Robert E. McNeill, Richard E. Mills, Alexander Vance Murray, Lyle Myers, Shichun Bao, Robert Orr, Stephanie Powell, John Chip Reed, Jackson Rhudy, William Saway, Wilson Sofley, Mark Turner, Michelle Welch, Jonathan Wilson, Tamela Sedacca Zimmerman, Ralph DeFronzo.

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