Efficacy and Safety of Liraglutide 3.0 mg in Individuals With Overweight or Obesity and Type 2 Diabetes Treated With Basal Insulin: The SCALE Insulin Randomized Controlled Trial

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OBJECTIVE

Most individuals with type 2 diabetes also have obesity, and treatment with some diabetes medications, including insulin, can cause further weight gain. No approved chronic weight-management medications have been prospectively investigated in individuals with overweight or obesity and insulin-treated type 2 diabetes. The primary objective of this study was to assess the effect of liraglutide 3.0 mg versus placebo on weight loss in this population.

RESEARCH DESIGN AND METHODS

Satiety and Clinical Adiposity—Liraglutide Evidence (SCALE) Insulin was a 56-week, randomized, double-blind, placebo-controlled, multinational, multicenter trial in individuals with overweight or obesity and type 2 diabetes treated with basal insulin and less than or equal to two oral antidiabetic drugs.

RESULTS

Individuals were randomized to liraglutide 3.0 mg ($n = 198$) or placebo ($n = 198$), combined with intensive behavioral therapy (IBT). At 56 weeks, mean weight change was −5.8% for liraglutide 3.0 mg versus −1.5% with placebo (estimated treatment difference −4.3% [95% CI −5.5; −3.2]; $P < 0.0001$). With liraglutide 3.0 mg, 51.8% of individuals achieved ≥5% weight loss versus 24.0% with placebo (odds ratio 3.41 [95% CI 2.19; 5.31]; $P < 0.0001$). Liraglutide 3.0 mg was associated with significantly greater reductions in mean HbA_{1c}, mean daytime glucose values, and less need for insulin versus placebo, despite a treat-to–glycemic target protocol. More hypoglycemic events were observed with placebo than liraglutide 3.0 mg. No new safety or tolerability issues were observed.

CONCLUSIONS

In individuals with overweight or obesity and insulin-treated type 2 diabetes, liraglutide 3.0 mg as an adjunct to IBT was superior to placebo regarding weight loss and improved glycemic control despite lower doses of basal insulin and without increases in hypoglycemic events.

Obesity is a chronic, progressive disease (1) associated with multiple complications that, individually and in combination, confer morbidity and mortality risk (2). The risk of developing type 2 diabetes increases with adiposity and increasing BMI (3,4), and the global rise in the prevalence of this disease closely follows that of obesity (5,6). In turn, obesity in individuals with type 2 diabetes can exacerbate deterioration of glycemic control (7).

There is substantial evidence that weight-loss interventions can lower blood glucose (BG) levels, and, although weight loss remains a key recommendation in diabetes guidelines (8–10), it is frequently poorly implemented (11). Type 2 diabetes is a progressive disease, and despite improved oral and injectable glucose-lowering agents available today, many individuals with long-standing type 2 diabetes eventually require insulin (12).

Weight gain following initiation of insulin or sulfonylureas (SUs) is common, with increases of ~4 kg often observed with insulin and ~2 kg with SUs (13). Given that insulin use is associated with weight gain (14), weight management in individuals with coexistent obesity and type 2 diabetes requiring insulin is particularly challenging. This population would benefit from greater availability of pharmacotherapeutic agents that address obesity. Accordingly, the American Association of Clinical Endocrinologists diabetes guidelines, Endocrine Society obesity guidelines, and the latest European Association for the Study of Diabetes/American Diabetes Association (ADA) consensus advise that the effect on weight should be considered when choosing diabetes treatment (8–10,15), and given their glucose- and weight-lowering effects, glucagon-like peptide 1 (GLP-1) receptor agonists have an advantage over many glucose-lowering agents in this regard.

Liraglutide is an analog of GLP-1 and in doses up to 1.8 mg is approved for use in combination with insulin (16). It is also approved as a fixed-ratio combination with insulin degludec (17), as an adjunct to diet and exercise for type 2 diabetes treatment. Liraglutide 3.0 mg (18) is approved for chronic weight management in individuals with overweight or obesity and has been investigated in individuals with type 2 diabetes as part of the Satiety and Clinical Adiposity—Liraglutide Evidence (SCALE) phase 3a program. SCALE Diabetes was a 56-week trial of liraglutide 1.8 mg and 3.0 mg in individuals with overweight or obesity and diabetes treated with less than or equal to two oral antidiabetic drugs (OADs) but excluded insulin-treated individuals. In this previous study, weight loss of 4.7% and 6.0% was observed with liraglutide 1.8 mg and 3.0 mg, respectively, versus 2.0% with placebo (19). While liraglutide 1.8 mg is indicated in combination with insulin for diabetes treatment, liraglutide 3.0 mg combined with insulin for weight management has not previously been studied. Furthermore, to our knowledge, no medications approved for chronic weight management have been prospectively investigated in individuals with overweight or obesity and insulin-treated type 2 diabetes.

The current study aimed to evaluate the efficacy and safety of liraglutide 3.0 mg for weight management in individuals with overweight (BMI $\geq$27 kg/m^2) or obesity (BMI $\geq$30 kg/m^2) and type 2 diabetes treated with basal insulin and up to two OADs.

RESEARCH DESIGN AND METHODS

Study Overview

SCALE Insulin (NCT02963922) was conducted from February 2017 to September 2018 at 53 sites globally. The trial protocol was approved by local ethics committees or institutional review boards, and the trial was conducted in accordance with the principles of the Declaration of Helsinki and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines (20). The sponsor, Novo Nordisk A/S, developed the study protocol, planned and performed the statistical analyses, provided editorial and writing assistance, and provided the trial medications.

Study Objective

The primary objective was to confirm superiority of liraglutide 3.0 mg versus placebo, as an adjunct to intensive behavioral therapy (IBT), on weight-loss efficacy in individuals with overweight or obesity and type 2 diabetes treated with basal insulin and less than or equal to two OADs. Secondary objectives aimed to investigate the liraglutide 3.0 mg effects on other relevant efficacy end points and to establish the safety and tolerability of liraglutide 3.0 mg versus placebo, as an adjunct to IBT.

Participants

Eligible individuals were aged $\geq$18 years with a BMI of $\geq$27 kg/m^2, stable body weight (maximum 5 kg self-reported weight change within 90 days before screening), diagnosed with type 2 diabetes with an HbA_{1c} $\geq$6.0 to $\leq$10% (42–86 mmol/mol) at screening and receiving stable treatment with any basal insulin ($\geq$90 days; no requirement for minimum or maximum dose), and less than or equal to two OADs. Individuals were excluded if they had type 1 diabetes, recurrent severe hypoglycemic episodes within the last year, or use of dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists, bolus insulin, or medications known to induce significant weight change in the previous 90 days. Other exclusion criteria included a recent history of cardiovascular event, history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, pregnancy, breast-feeding, or intention to become pregnant, or a history of pancreatitis.

Study Design

SCALE Insulin was a 56-week, randomized, double-blind, placebo-controlled, multinational, multicenter trial (Supplementary Fig. 1). A total of 396 individuals were randomized centrally using an interactive voice/web response system, to receive either liraglutide 3.0 mg or placebo (1:1) as adjunct to IBT. Individuals treated with SUs were stratified between the two arms. Liraglutide 3.0 mg or placebo was administered once daily by subcutaneous injection. During the first 4 weeks postrandomization, the dose was escalated by 0.6 mg weekly to reach the maintenance dose of 3.0 mg. A 4-week follow-up period was included after the 56-week treatment period. To promote individual retention and improve data quality, individuals were permitted to stop and restart the study drug, without re-escalating the dose, or with re-escalation if three consecutive doses had been missed.

IBT

IBT consisted of a hypocaloric diet, increased physical activity, and behavioral therapy delivered in frequent counseling sessions and is described in detail elsewhere (21) and the Supplementary Data. Individuals attended a total of 23 individual or group counseling sessions during the 56-week period, delivered by a registered dietitian or similarly qualified health care professional.

Concomitant Diabetes Medication

It was recommended that, after randomization and at the investigator's discretion, individuals should reduce their dose of SUs by 50% to lower the likelihood of SU-induced hypoglycemia. In individuals with HbA_{1c} ≤8% (64 mmol/mol) at randomization, it was recommended to reduce the dose of basal insulin by 15–20% owing to anticipated glycemic improvements. Insulin doses were adjusted based on self-measured BG (SMBG) values to ensure that similar levels of fasting glucose were maintained between the two arms, regardless of background medication (Supplementary Table 1). In individuals using once-daily basal insulins, weekly adjustments were based on the mean of three prebreakfast SMBG values with a target range of 4 to 5 mmol/L (71–90 mg/dL). In individuals using twice-daily basal insulins, adjustment was based on the mean of three prebreakfast and predinner SMBG measurements. Basal insulin dose was not to exceed the entry dose within the first 5 weeks. Furthermore, the initiation of bolus insulin was permitted after the 5-week period and only after optimization of basal insulin dose. The type and dose of other OADs were kept constant throughout the trial, unless unacceptable hypoglycemia occurred that could not be managed by a reduction of basal insulin.

Hypoglycemia Classification

Hypoglycemia was defined using the ADA classification (22). Severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate or glucagon or take other corrective actions. Documented symptomatic and asymptomatic hypoglycemia were defined as a plasma glucose concentration ≤70 mg/dL (3.9 mmol/L) with and without typical symptoms of hypoglycemia, respectively. Hypoglycemia was also assessed using Novo Nordisk's classification, which, together with ADA criteria, is included in the Supplementary Data.

Study End Points

Coprimary end points were change in body weight (percentage) from baseline to week 56 and proportion of individuals losing ≥5% of baseline body weight at week 56. Confirmatory secondary end points included the proportion of individuals losing >10% of baseline body weight at week 56 and the change from baseline to week 56 in waist circumference, HbA_{1c}, fasting plasma glucose (FPG), SF-36 version 2.0 acute, physical functioning score, and Impact of Weight on Quality of Life-Lite for Clinical Trial Version (IWQOL-Lite for CT), physical function domain (five-items) score.

Key supportive end points were change from baseline to week 56 in total daily insulin dose (units), mean daytime glucose value (based on seven-point SMBG values), systolic and diastolic blood pressure, lipids, the SF-36 physical component summary, mental component summary and subdomains, the IWQOL-Lite for CT subdomains, and the weight-related sign and symptom measure total score. Additionally, two composite end points of HbA_{1c} <7% (53 mmol/mol) plus weight loss ≥5% and HbA_{1c} <7% (53 mmol/mol) plus weight loss ≥5% plus no documented symptomatic hypoglycemia were prespecified. A post hoc analysis of the change in the seven-point SMBG profile was also carried out.

Safety was assessed by adverse events (AEs) and hypoglycemic episodes, physical examination, resting pulse, electrocardiogram, and laboratory measurements. Two different observation periods were used: the on-drug period, used for all safety end points, with the exception of neoplasms, for which the in-trial period was used. The in-trial period included time from randomization to the final follow-up visit (or date of last contact) regardless of trial product discontinuation. On-drug safety was assessed from the first treatment day to 14 days after the last treatment day, excluding potential off-drug time intervals triggered by at least 2 weeks of consecutive missed doses.

Statistical Considerations

The planned sample size for this trial of 400 participants, along with a 1:1 randomization and assuming a 30% discontinuation rate, resulted in a combined power of 95.2%, which was estimated to be adequate to evaluate the two coprimary end points. Power for the continuous end point, percentage weight change, was calculated with a two-group Satterthwaite test; the power for the categorical end point, ≥5% responders, was calculated using a Pearson χ^2 test, both at a 5% significance level. The two coprimary end points were tested in hierarchal order with change in body weight at week 56 as a percentage of baseline body weight first, followed by proportion of individuals losing ≥5% of baseline body weight at week 56.

To estimate the intervention effect, the treatment policy estimand (primary estimand) was defined for each efficacy end point. The treatment policy estimand evaluated the effect of liraglutide 3.0 mg versus placebo at week 56 for all randomized individuals, regardless of premature discontinuation of trial product. This estimand reflects the intention-to-treat principle as defined in the ICH E9. Missing values at week 56 were imputed from the placebo arm using a jump-to-reference multiple-imputation approach based on 100 iterations of the data set (23).

For the coprimary end points and confirmatory secondary end points, the trial product estimand (secondary estimand), based on a mixed model for repeated measurements, evaluated the treatment effect of liraglutide 3.0 mg versus placebo at week 56 for all randomized individuals with the assumption that all individuals had remained on trial product for the entire planned trial duration, using assessments only from individuals who were taking the randomized treatment until end of trial or at first discontinuation (see Supplementary Data for detailed description). The treatment policy and trial product estimands correspond to the updated ICH Good Clinical Practice regulatory guidelines on quantifying treatment effects of medications (24).

Continuous primary and secondary end points were analyzed using ANCOVA with randomized treatment, BMI and sex as factors, and baseline end point as a covariate. The estimates and SDs were pooled using Rubin's formula. All categorical end points were assessed at week 56 and analyzed using logistic regression with the same factors and covariate as the continuous end point analysis.

For analyses of end points, the estimated treatment difference (ETD) for continuous and the estimated odds ratio (OR) for the categorical end points are reported with the associated two-sided 95% CI and corresponding *P* value. All analyses were undertaken using UNIX SAS (version 9.4) on the Statistical Computing Environment.

RESULTS

Trial Population

A total of 551 individuals were screened, and 396 were randomized: 198 to liraglutide 3.0 mg combined with IBT and 198 to placebo combined with IBT. Baseline demographics were similar between treatment arms (Table 1).

A high proportion of individuals returned for the final evaluation at week 56 (96.5% in the liraglutide 3.0 mg arm and 97.5% in the placebo arm) and remained on study drug up to week 56 (83.8% and 84.8%, respectively). Two individuals on liraglutide 3.0 mg and four on placebo were lost to follow-up (Supplementary Fig. 2 and Supplementary Table 2).

Primary, confirmatory, and supportive secondary end points relating to the treatment policy estimand are presented in Table 2. Corresponding trial product estimand end points are presented in Supplementary Table 3 where applicable.

Body Weight and Waist Circumference

Figure 1*A* shows observed mean weight loss over time in the two groups. For the treatment policy estimand (intention-to-treat principle), mean weight loss at 56 weeks was −5.8% with liraglutide 3.0 mg and −1.5% with placebo (ETD −4.3% [95% CI −5.5; −3.2]; $P < 0.0001$) (Table 2 and Supplementary Fig. 3*A*). For the trial product estimand (if-all-adhered principle), estimated mean weight change at 56 weeks was −6.4% for liraglutide 3.0 mg and −1.3% for placebo (ETD −5.1% [95% CI −6.3; −3.9]; $P < 0.0001$) (Supplementary Table 3 and Supplementary Fig. 3*B*). For individuals on trial product at 56 weeks, mean observed change in weight was −6.5% ($n = 163$) with liraglutide 3.0 mg and −1.7% ($n = 168$) with placebo (Fig. 1*A*).

The proportion of individuals who achieved ≥5% weight loss was 51.8% with liraglutide 3.0 mg and 24.0% with placebo (OR 3.41 [95% CI 2.19; 5.31]; $P < 0.0001$). The proportion who lost >10% was 22.8% and 6.6%, respectively (OR 4.21 [95% CI 2.2; 8.2]; $P < 0.0001$) (Supplementary Fig. 4). A significant decrease was observed in waist circumference at 56 weeks in the liraglutide 3.0-mg group versus placebo (−5.28 cm vs. −2.56 cm [ETD −2.71 (95% CI −3.90; −1.53); $P < 0.0001$]) (Table 2).

Glycemic Parameters

Figure 1*B* shows observed changes in HbA_{1c} over time in the two groups. For the treatment policy estimand at 56 weeks, a significantly greater reduction in mean HbA_{1c} was observed with liraglutide 3.0 mg (−1.1% [−11.9 mmol/mol]) versus placebo (−0.6% [−6.0 mmol/mol]; ETD −0.5% [95% CI −0.8; −0.3]; $P < 0.0001$). There was no significant difference in the reduction of mean FPG (mmol/L) between the liraglutide 3.0 mg (−1.0 mmol/L) and the placebo group (−0.6 mmol/L; ETD −0.4 [95% CI −0.9; 0.1]; $P = 0.1502$) (Table 2), in keeping with the trial design to target the same FPG in both groups. Change in FPG over time is shown in Supplementary Fig. 5. Liraglutide 3.0 mg was associated with lower pre- and postprandial glucose values over the course of the day, as evident in the mean daytime glucose value (Supplementary Fig. 6*A*) and the seven-point SMBG profile at week 16 and week 56 (Supplementary Fig. 6*B–D*). Relative to placebo, there was a significantly smaller increase in insulin dose required to achieve target fasting BG (+3 units with liraglutide 3.0 mg vs. +18 units with placebo; ETD −15.0 [95% CI −22.0; −8.0]; $P < 0.0001$) (Fig. 1*C*). A total of 24 individuals who had completed the trial (21 with liraglutide and 3 with placebo) were no longer using insulin at the study end.

Cardiometabolic Parameters and Quality of Life

Mean systolic blood pressure decreased significantly with liraglutide 3.0 mg (−5.6 mmHg) versus placebo (−1.6 mmHg; ETD −4.0 [95% CI −6.4; −1.5], $P = 0.0014$), and changes in diastolic blood pressure were not significant (Table 2). There was a trend for improved lipids with liraglutide 3.0 mg versus placebo, although with the exception of total cholesterol, no significant differences between treatment arms were observed at 56 weeks. Individuals on liraglutide 3.0 mg and placebo both reported increased physical functioning at week 56 as determined by the SF-36 physical functioning domain score (Supplementary Fig. 7*A*) and the IWQOL-Lite for CT Physical Function domain score (Supplementary Fig. 7*B*), but there were no significant differences between treatment groups.

Composite End Points

The proportion of individuals achieving ≥5% weight loss plus ADA HbA_{1c} target of <7% (53 mmol/mol) was 39.0% with liraglutide 3.0 mg and 13.9% with placebo (OR 3.94 [95% CI 2.38; 6.53]; $P < 0.0001$). The proportion of individuals achieving ≥5% weight loss plus ADA HbA_{1c} target of <7% (53 mmol/mol) plus who did not report any documented symptomatic hypoglycemia was 17.8% with liraglutide 3.0 mg and 6.2% with placebo (OR 3.28 [95% CI 1.66; 6.48]; $P = 0.0006$).

Safety

Liraglutide 3.0 mg in combination with IBT was generally well tolerated, with no new safety signals identified. Safety data are summarized in Table 3. AE incidence was similar for liraglutide 3.0 mg and placebo, except for gastrointestinal AEs, which had a greater incidence with liraglutide 3.0 mg (62.1% vs. 46.7%). AEs reported by ≥5% of participants and more frequently by participants in the liraglutide arm than the placebo arm included nausea, nasopharyngitis, diarrhea, headache, and upper respiratory tract infection (Supplementary Table 4). The incidence of nausea was greater with liraglutide 3.0 mg (29.7%) than with placebo (11.7%), and most events were mild or moderate in severity. There was no significant difference in change in heart rate for liraglutide versus placebo. The proportion of individuals reporting a serious AE was 8.2% (23 events in 16 individuals) with liraglutide 3.0 mg and 9.6% (25 events in 19 individuals) with placebo. There were no AEs with fatal outcomes in the trial.

Using ADA criteria, greater than or equal to one episode of hypoglycemia occurred in 71.8% (742.3 events per 100 patient-years) of the liraglutide 3.0-mg group, compared with 71.1% (937.9 events per 100 patient-years) of the placebo group (Table 3). Documented symptomatic hypoglycemia occurred at rates of 336.1 and 441.7 events per 100 patient-years of exposure with liraglutide 3.0 mg and placebo, respectively. There were three severe hypoglycemic episodes (requiring assistance of another person) with liraglutide 3.0 mg versus two episodes with placebo. Rates of hypoglycemia determined by Novo-Nordisk criteria are shown in Supplementary Table 5. A greater number of hypoglycemic episodes occurred in individuals treated with SUs in both arms (Supplementary Table 6).

Three acute gallstone disease events occurred in the trial, two with liraglutide 3.0 mg (both cholelithiasis) and one with placebo (gallbladder disorder); none of these were serious AEs. Two cases of pancreatitis in one individual (acute pancreatitis and pancreatitis, both serious) were reported with placebo. A similar number of neoplasm events were reported

Table 1—Baseline demographics and medications

	Liraglutide 3.0 mg (n = 198)	Placebo (n = 198)
Male sex, *n* (%)	90 (45.5)	99 (50.0)
Mean age, years (SD)	55.9 (11.3)	57.6 (10.4)
Race, *n* (%)		
White	174 (87.9)	180 (90.9)
Black	17 (8.6)	11 (5.6)
Asian	3 (1.5)	5 (2.5)
Ethnicity: not Hispanic or Latino, *n* (%)	155 (78.3)	169 (85.4)
Mean body weight, kg (SD)*	100.6 (20.8)	98.9 (19.9)
Mean BMI, kg/m^2 (SD)	35.9 (6.5)	35.3 (5.8)
Mean waist circumference, cm (SD)	114.8 (13.7)	114.2 (13.2)
Mean HbA_{1c}, % (SD)	7.9 (1.1)	8 (1.0)
Mean HbA_{1c}, mmol/mol (SD)	63.0 (11.5)	63.6 (11.3)
Mean FPG, mmol/L (SD)	7.8 (2.2)	8.1 (2.5)
Mean FPG, mg/dL (SD)	141 (40)	146 (46)
Mean diabetes duration, years (SD)	11.4 (6.8)	12.8 (6.9)
Mean heart rate, bpm (SD)†	74.0 (10.0)	75.0 (11.0)
Mean SBP, mmHg (SD)	129.0 (14.0)	132.0 (16.0)
Mean DBP, mmHg (SD)	78.0 (9.0)	78.0 (9.0)
Mean total cholesterol, mmol/L (SD)	4.5 (1.0)	4.4 (0.9)
Mean total cholesterol, mg/dL (SD)	172 (39)	171 (36)
Mean LDL cholesterol, mmol/L (SD)	2.4 (0.9)	2.4 (0.8)
Mean LDL cholesterol, mg/dL (SD)	94 (33)	94 (29)
Mean HDL cholesterol, mmol/L (SD)	1.2 (0.3)	1.2 (0.3)
Mean HDL cholesterol, mg/dL (SD)	45 (12)	45 (11)
Mean VLDL cholesterol, mmol/L (SD)	0.9 (0.4)	0.8 (0.4)
Mean VLDL cholesterol, mg/dL (SD)	33 (16)	32 (15)
Mean triglycerides, mmol/L (SD)	2.0 (1.2)	1.9 (1.0)
Mean triglycerides, mg/dL (SD)	174 (105)	168 (89)
Mean free fatty acids, mmol/L (SD)	0.6 (0.2)	0.6 (0.3)
Mean free fatty acids, mg/dL (SD)	15.9 (6.9)	15.5 (7.3)
Antidiabetic medications at screening, *n* (%)		
Biguanides	175 (88.4)	176 (88.9)
SUs	68 (34.3)	71 (35.9)
SGLT-2i	44 (22.2)	44 (22.2)
Thiazolidinediones	4 (2.0)	6 (3.0)
Combination BG-lowering drugs (oral)	4 (2.0)	3 (1.5)
α-Glucosidase inhibitors	2 (1.0)	0 (0.0)
Other BG-lowering drugs, excluding insulins	1 (0.5)	5 (2.5)
Insulins/analogs (injection), *n* (%)		
Long-acting	180 (90.9)	184 (92.9)
Intermediate-acting	18 (9.1)	14 (7.1)

DBP, diastolic blood pressure; SBP, systolic blood pressure; SGLT2-i, sodium–glucose cotransporter 2 inhibitor. *Body weight measurements include both fasting and nonfasting measures. †Safety analysis set; liraglutide, n = 195; placebo, n = 197.

with liraglutide 3.0 mg (23 events in 19 individuals) and placebo (21 events in 17 individuals) during the in-trial period. Six neoplasm events with liraglutide 3.0 mg and two with placebo were serious (Supplementary Table 7). With the exception of one case of thyroid adenoma, all serious neoplasm events were assessed as malignant; all remaining neoplasm events were benign. There were no reports of breast cancer or medullary thyroid carcinoma with liraglutide 3.0 mg. There were a similar number of cases of depression and suicidal ideation/behavior AEs with liraglutide 3.0 mg and placebo (eight events in seven individuals vs. eight events in eight individuals with placebo).

CONCLUSIONS

Weight-loss therapy as a primary treatment approach in individuals with overweight or obesity and type 2 diabetes goes beyond glucose control in favor of a more holistic approach addressing the full range of complications and underlying pathophysiological mechanisms driving weight gain. Recently published European Association for the Study of Diabetes/ADA guidelines recommend considering the effect on weight when choosing diabetes treatment (8,9), and the American Association of Clinical Endocrinologists obesity guidelines regard the objective of weight-loss therapy to be prevention and treatment of weight-related complications, including type 2 diabetes (10). Weight-loss medications have been shown to have a highly favorable therapeutic profile in individuals with obesity/overweight and type 2 diabetes; however, efficacy has not been examined in all subgroups of individuals with diabetes as a function of specific concomitant diabetes medication.

To our knowledge, SCALE Insulin is the first randomized clinical trial to specifically investigate the efficacy and safety of an approved antiobesity medication in individuals with overweight or obesity and type 2 diabetes treated with basal insulin. Our findings demonstrate superiority of liraglutide 3.0 mg versus placebo regarding both percentage of weight loss (ETD −4.3% [95% CI −5.5; −3.2]; $P < 0.0001$) and proportion of individuals reaching a clinically relevant ≥5% weight loss at week 56 (liraglutide 3.0 mg: 51.8%; placebo: 24.0%; $P < 0.0001$). Thus, the two primary objectives of the trial were met.

The weight-loss findings in the SCALE Insulin trial are in line with those observed in the previously described SCALE Diabetes trial, in which insulin-treated individuals were excluded (19). In SCALE Diabetes, placebo-adjusted weight loss in individuals with overweight or obesity and type 2 diabetes was 2.7% and 4.0% with liraglutide 1.8 mg and 3.0 mg, respectively. Similarly, the proportion of individuals reaching ≥5% weight loss with liraglutide 3.0 mg and placebo in SCALE Insulin was also comparable to SCALE Diabetes (liraglutide 3.0 mg, 54.3%; placebo, 21.4%, respectively) (19). Notably, the placebo arm in SCALE Insulin demonstrated greater weight loss than in the SCALE Diabetes trial, despite the fact that the trial population was older, had a greater number of complications, and was on weight-promoting insulin.

Table 2—Change in primary and secondary end points from baseline to week 56: treatment policy estimand

	Liraglutide 3.0 mg (n = 198)	Placebo (n = 198)	ETD/OR* (95% CI)	P value
Primary end points				
Change in body weight from baseline, %	−5.8	−1.5	−4.3 (−5.5; −3.2)	<0.0001
Proportion of individuals achieving ≥5% weight loss,* %	51.8	24.0	3.4 (2.2; 5.3)	<0.0001
Secondary confirmatory end points				
Proportion of individuals achieving >10% weight loss,* %	22.8	6.6	4.2 (2.2; 8.2)	<0.0001
Change in waist circumference from baseline, cm	−5.3	−2.6	−2.7 (−3.9; −1.5)	<0.0001
Change in HbA_{1c} from baseline, %	−1.1	−0.6	−0.5 (−0.8; −0.3)	<0.0001
Change in HbA_{1c} from baseline, mmol/mol	−11.9	−6.0	−5.8 (−8.3; −3.4)	<0.0001
Change in FPG from baseline, mmol/L	−1.0	−0.6	−0.4 (−0.9; 0.1)	0.1502
Change in FPG from baseline, mg/dL	−18.4	−11.5	−6.9 (−16.4; 2.5)	0.1502
Change in SF-36 Physical Functioning score from baseline	2.7	2.3	0.4 (−1.0; 1.8)	0.5716
Change in IWQOL-Lite for CT Physical Function domain score from baseline	8.2	5.7	2.5 (−1.5; 6.4)	0.2218
Secondary supportive end points				
Change in total daily insulin dose from baseline, units	2.8	17.8	−15.0 (−22.0; −8.0)	<0.0001
Change in mean daytime glucose value from baseline, mmol/L	−2.2	−1.5	−0.7 (−1.1; −0.2)	0.0032
Change in mean daytime glucose value from baseline, mg/dL	−39.6	−27.3	−12.4 (−20.6; −4.1)	0.0032
Individuals achieving ≥5% weight loss and HbA_{1c} <7% at week 56*	39.0	13.9	3.9 (2.4; 6.5)	<0.0001
Individuals achieving ≥5% weight loss, HbA_{1c} <7%, and no documented symptomatic hypoglycemia at week 56*	17.8	6.2	3.3 (1.66; 6.48)	0.0006
Change in systolic blood pressure from baseline, mmHg	−5.6	−1.6	−4.0 (−6.4; −1.5)	0.0014
Change in diastolic blood pressure from baseline, mmHg	−2.3	−0.9	−1.4 (−3.0; 0.2)	0.0905
Total cholesterol†	0.97	1.01	0.97 (0.94; 1.00)	0.0463
LDL cholesterol†	0.97	1.01	0.96 (0.91; 1.01)	0.1027
HDL cholesterol†	1.04	1.02	1.02 (0.99; 1.04)	0.2778
VLDL cholesterol†	0.89	0.94	0.94 (0.88; 1.01)	0.0830
Triglycerides†	0.88	0.94	0.94 (0.87; 1.01)	0.0715
Free fatty acids†	0.79	0.84	0.95 (0.85; 1.07)	0.3936

Baseline to week 56 vs. placebo. Full analysis set. Statistical analysis is ANCOVA with jump-to-reference multiple imputation. *The end point is analyzed in a logistic regression model. †Data are treatment ratios (liraglutide 3.0 mg/placebo).

This is most likely attributable to a more intensive lifestyle intervention. Improvements in several cardiovascular risk factors such as waist circumference, systolic blood pressure, and total cholesterol were also in line with findings of the SCALE Diabetes trial. Direct comparisons between these two trials should take into account differences in trial designs and statistical analyses, including the more intensive lifestyle intervention in the current trial (IBT).

In the Dual Action of Liraglutide and Insulin Degludec (DUAL) II trial, the contribution of liraglutide in a fixed-ratio combination with insulin degludec was investigated regarding efficacy and safety (25). The trial demonstrated that insulin degludec alone had a minimal effect on weight; however, when combined with liraglutide, it resulted in an ETD of −2.5 kg (95% CI −3.2; −1.8; $P < 0.0001$). While comparisons of these findings to SCALE Insulin should be cautious given the differences in liraglutide doses and study designs, the studies demonstrate that basal insulin combined with liraglutide can result in clinically significant weight loss relative to treatment with insulin alone.

Regarding the parameters of glycemic control in SCALE Insulin, individuals in the liraglutide 3.0-mg group achieved statistically significant and clinically meaningful improvements from baseline to week 56 in HbA_{1c} and mean daytime glucose values. At 56 weeks, there was no significant difference between treatment groups concerning improvements in FPG. Given that all individuals were actively treated with basal insulin to achieve the same glycemic targets in both treatment arms (Supplementary Table 1), this was expected. Importantly, however, similar fasting glucose levels were achieved with an average of 15 units/day lower insulin requirement in the liraglutide group compared with placebo. Superiority with liraglutide 3.0 mg versus placebo was confirmed for reductions in mean HbA_{1c} and mean daytime glucose values despite lower basal insulin requirements. Given the broad range of baseline HbA_{1c} (6–10% [42–86 mmol/mol]), these glycemic improvements are likely the result of the preferential effects of liraglutide on postprandial, rather than preprandial, glucose (as indicated by daily seven-point SMBG profiles) (Supplementary Fig. 6) combined with the significantly greater weight loss versus placebo.

Although treatment with insulin often results in weight gain, the extent to which the weight loss observed with liraglutide 3.0 mg in the present trial was the result of the direct action of liraglutide on feelings of hunger and satiety and possible delay in gastric emptying (26,27), or the result of indirectly reducing insulin requirements and use of SUs, requires further investigation. Furthermore, while individuals on SUs were stratified between the two treatment arms and insulin doses were titrated to achieve similar levels of glycemic control, we are unable

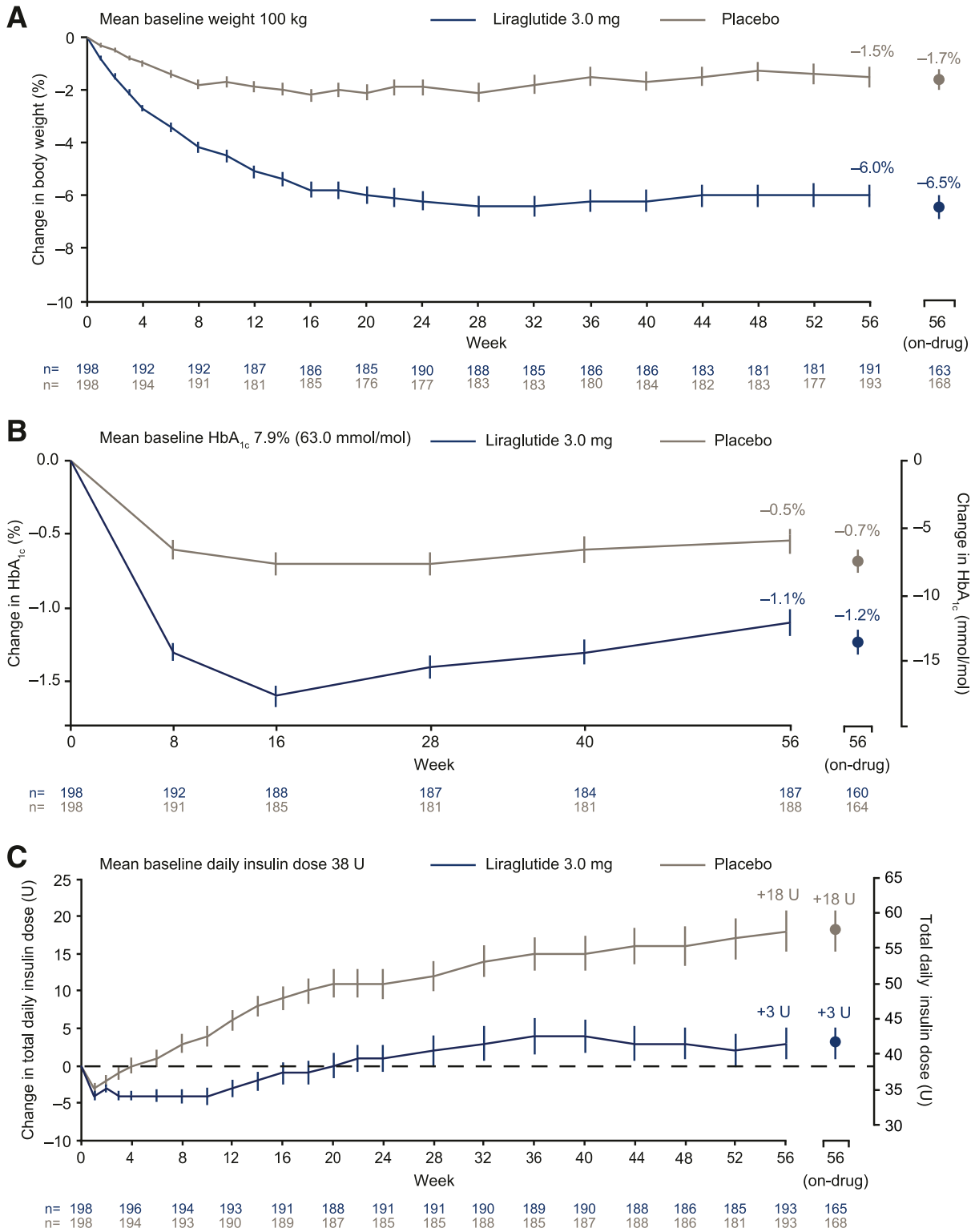

Figure 1—Change in body weight and glycemic control over time. *A*: Change in body weight (percentage); observed mean data ± SEM. *n* values refer to all individuals who attended visit regardless of treatment status; on-drug *n* values refer to individuals who are still on active treatment at time of visit. *B*: Change in HbA_{1c}; observed mean data ± SEM. *n* values refer to all individuals who attended visit regardless of treatment status; on-drug *n* values refer to individuals who are still on active treatment at time of visit. *C*: Change in total daily insulin dose; graph shows observed mean data ± SEM. *n* values refer to all individuals who attended visit regardless of treatment status; on-drug *n* values refer to individuals who are still on active treatment at time of visit. U, units.

to quantify the effect of other OADs on weight. Despite the marked reduction in insulin dose needed to meet glycemic targets with liraglutide 3.0 mg versus placebo, both groups required an increase in total daily insulin dose, as evident at week 56. This was expected in these actively treated individuals with long-standing type 2 diabetes, given the trial duration and the purposeful titration of basal insulin to achieve the same glycemic targets in all individuals. Given the

Table 3—Safety data (on-drug)

	Liraglutide 3.0 mg			Placebo		
	n (%)	E	R	*n* (%)	E	R
Number of individuals	195	—	—	197	—	—
Total AEs	180 (92.3)	1,139	578.3	175 (88.8)	1,053	531.2
Serious AEs	16 (8.2)	23	11.7	19 (9.6)	25	12.6
Fatal AEs	0 (0.0)	0	0.0	0 (0.0)	0	0.0
Events leading to treatment discontinuation	15 (7.7)	17	8.6	6 (3.0)	6	3.0
GI AEs	121 (62.1)	408	207.1	92 (46.7)	202	101.9
Nausea	58 (29.7)	105	53.3	23 (11.7)	27	13.6
Constipation	28 (14.4)	36	18.3	17 (8.6)	21	10.6
Diarrhea	45 (23.1)	77	39.1	30 (15.2)	54	27.2
Vomiting	32 (16.4)	53	26.9	12 (6.1)	13	6.6
Abdominal discomfort	11 (5.6)	17	8.6	8 (4.1)	11	5.5
Hypoglycemic episodes	140 (71.8)	1,462	742.3	140 (71.1)	1,859	937.9
ADA classified						
Severe	3 (1.5)	3	1.5	2 (1.0)	2	1.0
Asymptomatic	116 (59.5)	742	376.7	116 (58.9)	988	498.4
Documented symptomatic	92 (47.2)	662	336.1	102 (51.8)	816	411.7
Pseudohypoglycemia	17 (8.7)	42	21.3	14 (7.1)	31	15.6
Probable symptomatic	8 (4.1)	10	5.1	18 (9.1)	22	11.1
Unclassifiable	2 (1.0)	3	1.5	0 (0.0)	0	0

Safety analysis set. Hypoglycemic episodes were classified using ADA criteria and recorded in individual diaries. Data are from individuals on-drug. E, number of events; GI, gastrointestinal; *n*, number of individuals experiencing at least one event; %, percentage of individuals experiencing at least one event; R, event rate per 100 patient-years of exposure.

superior weight loss and beneficial glycemic effects of liraglutide 3.0 mg, this treatment group experienced a substantially reduced need for exogenous insulin compared with placebo-treated individuals. It is of interest to consider that being accustomed to treatment with injectable insulins may have had a positive influence on treatment adherence in this trial (84.3% of individuals were on drug at week 56).

In SCALE Insulin, no new safety signals were observed, and the safety profile observed with liraglutide 3.0 mg was in line with that reported in previous trials, with the most common AEs being gastrointestinal in nature. As trial participants were informed about possible gastrointestinal side effects related to treatment prior to the start of the trial, we cannot exclude the possibility of a "precebo effect" having been observed. Gastrointestinal AE findings are also subject to limitations of self-reporting used in current and other SCALE trials. Fewer serious AEs occurred in the liraglutide 3.0-mg group compared with placebo. Improvements in glycemic outcomes in the present trial were achieved with fewer hypoglycemic events per 100 patient-years of exposure compared with the placebo group. This may be related to the higher insulin dose required to achieve glycemic targets in the placebo group when compared with those randomized to liraglutide 3.0 mg and/or the ability of liraglutide to reduce glycemic variability (28). Taken together, liraglutide 3.0 mg had a favorable therapeutic profile; namely, greater weight loss with better glycemic control, with less need for basal insulin, and without any increase in hypoglycemia.

Conclusion

In individuals with overweight or obesity and basal insulin-treated type 2 diabetes, liraglutide 3.0 mg was superior to placebo with respect to mean and categorical weight loss at 56 weeks, as well as improvements in glycemic control despite a lower need for basal insulin. No new safety or tolerability issues were observed during the trial, and fewer hypoglycemic events were observed with liraglutide 3.0 mg versus placebo.

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