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ORIGINAL ARTICLE

Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The SCALE Maintenance randomized study

This article has been corrected since online publication and an erratum is also printed in this issue

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OBJECTIVE: Liraglutide, a once-daily human glucagon-like peptide-1 analog, induced clinically meaningful weight loss in a phase 2 study in obese individuals without diabetes. The present randomized phase 3 trial assessed the efficacy of liraglutide in maintaining weight loss achieved with a low-calorie diet (LCD).
METHODS: Obese/overweight participants ($\geqslant$18 years, body mass index $\geqslant 30\,kg\,m^{-2}$ or $\geqslant 27\,kg\,m^{-2}$ with comorbidities) who lost $\geqslant$5% of initial weight during a LCD run-in were randomly assigned to liraglutide 3.0 mg per day or placebo (subcutaneous administration) for 56 weeks. Diet and exercise counseling were provided throughout the trial. Co-primary end points were percentage weight change from randomization, the proportion of participants that maintained the initial $\geqslant$5% weight loss, and the proportion that lost $\geqslant$5% of randomization weight (intention-to-treat analysis). ClinicalTrials.gov identifier: NCT00781937.
RESULTS: Participants ($n=422$) lost a mean 6.0% (s.d. 0.9) of screening weight during run-in. From randomization to week 56, weight decreased an additional mean 6.2% (s.d. 7.3) with liraglutide and 0.2% (s.d. 7.0) with placebo (estimated difference -6.1% (95% class intervals -7.5 to -4.6), $P<0.0001$). More participants receiving liraglutide (81.4%) maintained the $\geqslant$5% run-in weight loss, compared with those receiving placebo (48.9%) (estimated odds ratio 4.8 (3.0; 7.7), $P<0.0001$), and 50.5% versus 21.8% of participants lost $\geqslant$5% of randomization weight (estimated odds ratio 3.9 (2.4; 6.1), $P<0.0001$). Liraglutide produced small but statistically significant improvements in several cardiometabolic risk factors compared with placebo. Gastrointestinal (GI) disorders were reported more frequently with liraglutide than placebo, but most events were transient, and mild or moderate in severity.
CONCLUSION: Liraglutide, with diet and exercise, maintained weight loss achieved by caloric restriction and induced further weight loss over 56 weeks. Improvements in some cardiovascular disease-risk factors were also observed. Liraglutide, prescribed as 3.0 mg per day, holds promise for improving the maintenance of lost weight.

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Keywords: liraglutide; GLP-1 analog; weight loss; weight maintenance

INTRODUCTION

A 5–10% reduction in body weight in overweight and obese individuals improves several risk factors for cardiovascular disease (CVD), including elevated blood glucose, blood pressure and plasma triglyceride concentrations.[1–3] Weight loss of this magnitude can be achieved with a comprehensive lifestyle modification program that combines diet, physical activity and behavior therapy.[4] The health benefits of this approach, however, are attenuated by weight regain.[5] Participants typically regain 35–40% of their lost weight in the year following treatment.[4]

Two approaches facilitate the maintenance of lost weight. Lifestyle counseling, on a twice-monthly or monthly basis, improves weight maintenance for up to 2.5 years compared with no further treatment.[6,7,8] Pharmacological treatment offers another option. Numerous studies have revealed significantly better weight-loss maintenance at 1 or more years in individuals who were randomly assigned, following initial weight loss, to receive weight-loss medication versus placebo.[9–13]

The present 56-week randomized, double-blind, placebo-controlled trial examined the efficacy of liraglutide for maintaining prior weight loss achieved with a low-calorie diet (LCD). Liraglutide, an analog of the incretin hormone glucagon-like peptide-1, is currently approved for the treatment of type 2 diabetes (T2D) at 1.2 or 1.8 mg per day (once-daily subcutaneous injection).[14] Liraglutide at the higher dose of 3.0 mg per day is currently under development for chronic weight management. In patients with T2D, treatment with liraglutide 1.8 mg per day over 26 weeks resulted in weight losses up to 2.6 kg greater than placebo.[15] In obese individuals without T2D, treatment with liraglutide 3.0 mg per day over 20 weeks resulted in a 4.4 kg greater mean weight loss than placebo and a 3.0 kg greater weight loss than orlistat.[16] Weight losses with liraglutide were

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sustained for up to 2 years with continued use of the medication.[17] The present trial provides the first evaluation of liraglutide for maintenance of prior weight loss achieved by treatment with a LCD in obese/overweight individuals without T2D.

PARTICIPANTS AND METHODS

Participants

Participants were recruited between October 2008 and January 2009 at 26 research sites in the United States and 10 research sites in Canada. Eligible participants included men and women aged $\geqslant$18 years, with stable body weight and body mass index (BMI) $\geqslant$30 kg m^{-2} or $\geqslant$27 kg m^{-2} with comorbidities of treated or untreated dyslipidemia and/or treated or untreated hypertension. Main exclusion criteria were as follows: diagnosis of type 1 or T2D mellitus; fasting plasma glucose (FPG) $\geqslant$7 mmol l^{-1} at run-in (week -12); treatment with glucagon-like peptide-1 receptor agonists or medications causing significant weight gain/loss; bariatric surgery; history of idiopathic acute or chronic pancreatitis; history of major depressive disorder or other severe psychiatric disorders; or clinically significant active CVD. (Supplementary Table 1 provides complete inclusion/exclusion criteria.) Participants gave written informed consent. The protocol was approved by local ethics committees, and the trial was performed in accordance with the Declaration of Helsinki[18] and International Conference on Harmonization Good Clinical Practice.[19] The study is registered at ClinicalTrials.gov: NCT00781937.

Trial design and interventions

To qualify for randomization, participants had to lose $\geqslant$5% of initial body weight during a variable-length (4–12 weeks) LCD run-in period (Supplementary Figure 1). During this period, participants were prescribed 1200–1400 kcal per day, which included the daily use of up to three liquid meal replacements (for example, Boost, Ensure and Glucerna). To facilitate dietary adherence, participants met face-to-face, every other week with a nutritionist and had telephone calls on alternate weeks. They were encouraged to exercise regularly (recommended 150 min per week of brisk walking) and were provided with pedometers. As soon as individuals lost $\geqslant$5% of screening body weight, they were randomly assigned 1:1 to receive once-daily liraglutide 3.0 mg ($n=212$) or placebo ($n=210$). Randomization was performed centrally using a telephone- or web-based system. Participants were stratified according to comorbidity status (presence/absence of treated or untreated hypertension or dyslipidemia) and BMI. Treatment allocation was blinded to participants, investigators and sponsors throughout the trial. Liraglutide (6.0 mg per ml) and placebo were provided in modified FlexPen devices (Novo Nordisk A/S, Bagsvaerd, Denmark) and administered by subcutaneous injection in the abdomen, thigh or upper arm. Dosing was initiated at 0.6 mg per day, increasing weekly by 0.6 mg per day throughout a 4-week dose escalation (maximum 5 weeks) to the 3.0 mg dose.

At randomization, participants were prescribed a 500 kcal per day deficit diet, based on estimated 24-h energy expenditure.[16] Recommended macronutrient intake was 30% of energy from fat, 20% from protein and 50% from carbohydrate. Liquid meal replacements were not recommended during this time. Participants were instructed to continue the recommended physical activity. Face-to-face lifestyle counseling visits (15–20 min) were provided at weeks 0, 1, 2, 3 and 4 (during drug escalation) and weeks 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46 and 52, for a total of 17 visits over 56 weeks. (Medical monitoring occurred on the same schedule as lifestyle visits.)

Individuals who withdrew from the trial were asked to return at week 56 (after randomization) for follow-up weight assessment. Following medication discontinuation at week 56, participants completed a 12-week follow-up assessment, which included monthly visits.

Clinical outcomes

Three co-primary end points were tested hierarchically at week 56: (1) mean percentage change in fasting body weight from randomization; (2) the proportion of individuals that maintained the $\geqslant$5% reduction in fasting body weight achieved during LCD run-in; and (3) the proportion that lost $\geqslant$5% of fasting body weight after randomization. Secondary efficacy end points included weight change (kg) from randomization to week 56; the proportion of participants that lost $>$10% of fasting randomization weight; the proportion that maintained $>$50 and $>$75% of fasting weight loss during run-in; and fasting weight change (kg) from randomization to week 68. Additional end points included CVD risk factors and glycemic control parameters. (After the study began, two modifications to the trial's end points were made to comply with requests for changes to the investigational new drug application made by the United States Food and Drug Administration. The end point 'proportion of participants who lost $\geqslant$5% of randomization weight' was added and the treatment phase was increased to 56 weeks. In addition, the secondary end point 'the proportion of participants that lost $>$10% of randomization weight' had originally been 'the proportion that lost $\geqslant$10% of randomization weight' but was changed to comply with the European Medicines Agency guidance.)

Safety end points included physical examination, electrocardiogram, adverse events (AEs), standard laboratory tests and mental health assessed by the Columbia Suicidality Severity Rating Scale (C-SSRS)[20] and the Patient Health Questionnaire (PHQ)-9.[21] Serum calcitonin[16] and the activity of pancreatic enzymes, amylase and lipase (that is, potential markers of acute pancreatitis) were also measured.[22] Clearstone Central Laboratories (North Brunswick, NJ, USA and Ontario, Canada) performed all laboratory analyses according to standard methods, and Celerion (Fehraltorf, Switzerland) measured anti-liraglutide antibodies. A safety committee for data surveillance was established by the sponsor.

Statistical analysis

The planned sample size of 420 participants, with a 1:1 randomization ratio, assumed a 40% drop-out rate and was estimated to be adequate to evaluate the three co-primary end points with a combined power of at least 89% ($P=0.05$, two-sided test).[23]

Prespecified data analysis was performed on the full analysis set, comprising all randomized individuals exposed to trial drug with at least one post-randomization weight assessment.[24] Only fasting observations were included for the co-primary end points. The safety analysis set comprised randomized individuals exposed to trial drug. The three co-primary end points were tested using a closed testing procedure (hierarchical testing procedure) to maintain a significance level of 5% for the three end points. All efficacy analyses tested the hypothesis of no difference between treatment groups against the alternative of difference between groups. Secondary end point evaluations were all based on two-sided testing at a 5% significance level. Continuous efficacy end points were analyzed as change from randomization with an analysis of covariance, and dichotomous end points were analyzed with a logistic regression. Both analysis models included treatment, sex, country and comorbidity stratification as fixed effects, and randomization value as a covariate. Missing values were imputed by carrying forward the last observation (on drug). Sensitivity analyses to evaluate the robustness of the results included a per-protocol completer analysis and a repeated measures analysis (linear mixed-effect model) of the co-primary end points, using all available weight measurements. Both were conducted on the full analysis set of participants. The repeated-measures analysis included the same effects as above, plus treatment-by-visit interaction. SAS version 9.13 for Unix (SAS Institute, Cary, NC, USA) was used for analyses.

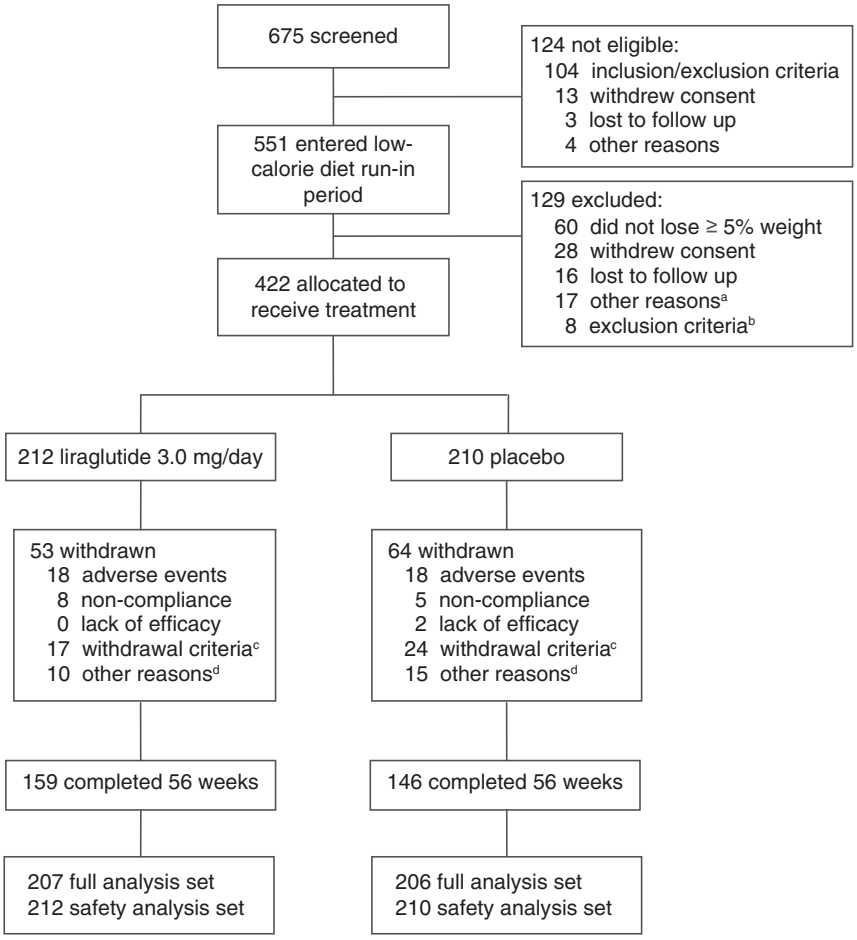

Figure 1. Flow of participants through the trial. [a]Reasons for exclusion of participants during run-in due to 'other reasons' included 'diagnosed with diabetes' and 'attended visit out-of-window'. [b]Reasons for exclusion due to 'exclusion criteria' included 'FPG $\geqslant$126 mg dl^{-1} (7 mmol l^{-1}) at visit 2' and 'positive screening for hepatitis B antigen, hepatitis C antibodies, or positive human immunodeficiency virus antibodies'. [c]Reasons for withdrawal after randomization due to 'withdrawal criteria' included 'diagnosis of type 1 or T2D' and 'withdrew consent'. [d]Reasons for withdrawal after randomization due to 'other reasons' included 'complications due to post surgery pain' and 'subject no longer wished to self-inject'. Important protocol deviations occurred for 11 individuals who violated inclusion/exclusion criteria: two participants were not randomized and nine participants were included in the full analysis set, but they were excluded from the per-protocol analysis. One participant who was incorrectly stratified withdrew. Two of 21 participants with treatment compliance deviations (missed doses or incorrect dosing) were withdrawn; seven participants were excluded from the per-protocol analysis. Out-of-window visits occurred for five participants at week 56 and 10 participant at week 57. These may have had an impact on their final results (week 56) or antibody data (sampled at week 57).

RESULTS

Run-in period

Of 675 applicants screened, 551 entered the LCD run-in and 422 lost $\geqslant$5% of screening body weight and were randomized to treatment (Figure 1). The 422 randomized participants lost a mean 6.0% (s.d. 0.9) of screening weight (6.3 kg (1.6)). Weight loss during the LCD run-in was accompanied by parallel decreases in BMI and waist circumference, the CVD biomarkers high-sensitivity C-reactive protein (hsCRP), adiponectin and fibrinogen, and the glycemic control parameters FPG and fasting plasma insulin (Table 1). There were net mean decreases in all lipids, except for very low-density lipoprotein cholesterol and free fatty acids. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse, which were already within normal range at screening, decreased during the run-in period. (None of these data were analyzed statistically because they were collected before randomization.)

Participants' baseline characteristics and retention

Table 2 shows the demographic and disease-specific characteristics of the 422 participants who were randomly assigned to liraglutide 3.0 mg ($n=212$) or placebo ($n=210$). Demographic characteristics, comorbidities, body weight, BMI and waist circumference were evenly distributed between the treatment groups. Seventy-five percent (159/212) of liraglutide- and 69.5% (146/210) of placebo-treated participants completed the 56-week trial (Figure 1).

Changes in weight post randomization

Figure 2a shows mean percentage change in body weight from screening to week 68 (which includes the 12-week off-drug period). At week 56 (the end of the double-blind period), the liraglutide group lost an additional mean 6.2% (s.d. 7.3) of randomization weight, compared with a mean loss of 0.2% (7.0) for placebo ($P<0.0001$) (Table 3). Significantly, more liraglutide- than placebo-treated participants maintained the $\geqslant$5% weight loss achieved in the LCD run-in (81.4 versus 48.9%; $P<0.0001$). In addition, significantly more patients in the liraglutide group than in the placebo group lost $\geqslant$5% of their randomization weight (50.5 versus 21.8%; $P<0.0001$). Thus, liraglutide was superior to placebo on all three co-primary end points, and was also superior in the percentage of participants who lost $>$10% of their

Table 1. Changes during low-calorie diet run-in

	Liraglutide 3.0 mg (n = *212*)				*Placebo* (n = *210*)			
	Start of run-in	*End of run-in*	*Net change during run-in*	*% change during run-in*	*Start of run-in*	*End of run-in*	*Net change during run-in*	*% change during run-in*
Body weight (kg)	106.7 (22.0)	100.4 (20.8)	− 6.3 (1.5)	− 5.9 (0.9)	105.0 (22.5)	98.7 (21.2)	− 6.3 (1.6)	− 6.0 (0.9)
BMI (kg m^{-2})	38.2 (6.2)	36.0 (5.9)	− 2.3 (0.5)	− 5.9 (0.9)	37.5 (6.2)	35.2 (5.9)	− 2.2 (0.5)	− 6.0 (0.9)
Waist circumference (cm)	114.4 (15.7)	109.4 (15.3)	− 5.0 (5.1)	− 4.3 (4.3)	112.7 (15.2)	107.8 (15.2)	− 4.9 (4.9)	− 4.3 (4.3)
HbA_{1c} (%)	5.6 (0.4)	5.6 (0.4)	0.01 (0.2)	0.2 (4.3)	5.5 (0.4)	5.6 (0.4)	0.0 (0.3)	0.2 (4.7)
FPG (mmol l^{-1})	5.7 (0.5)	5.4 (0.5)	− 0.3 (0.5)	− 4.0 (8.0)	5.7 (0.6)	5.5 (0.6)	− 0.2 (0.5)	− 2.6 (8.8)
Insulin (pmol l^{-1})	115.1 (74.5)	78.1 (49.3)	− 37.4 (58.7)	− 22.1 (46.3)	104.1 (63.4)	78.0 (52.2)	− 26.1 (46.0)	− 16.4 (48.8)
Total cholesterol (mmol l^{-1})	5.0 (0.9)	4.5 (0.9)	− 0.5 (0.6)	− 9.5 (11.0)	5.1(1.0)	4.7 (0.9)	− 0.4 (0.6)	− 8.0 (11.3)
LDL cholesterol (mmol l^{-1})	2.9 (0.7)	2.6 (0.7)	− 0.4 (0.5)	− 11.3 (16.6)	3.0 (0.8)	2.7 (0.8)	− 0.3 (0.5)	− 9.2 (16.8)
HDL cholesterol (mmol l^{-1})	1.3 (0.3)	1.2 (0.3)	− 0.1 (0.2)	− 8.9 (11.3)	1.3 (0.3)	1.2 (0.3)	− 0.1 (0.2)	− 6.6 (12.8)
VLDL cholesterol (mmol l^{-1})	0.7 (0.3)	0.7 (0.3)	− 0.01 (0.2)	5.7 (40.1)	0.8 (0.3)	0.8 (0.3)	− 0.04 (0.3)	6.5 (43.0)
Triglycerides (mmol l^{-1})	1.5 (0.8)	1.2 (0.6)	− 0.2 (0.5)	− 10.6 (28.1)	1.6 (0.9)	1.3 (0.6)	− 0.3 (0.7)	− 7.3 (45.3)
Free fatty acids (mmol l^{-1})	0.47 (0.21)	0.54 (0.22)	0.07 (0.24)	36.2 (90.0)	0.49 (0.22)	0.53 (0.22)	0.04 (0.25)	25.2 (70.6)
hsCRP (nmol l^{-1})	68.4 (79.5)	64.1 (66.7)	− 4.3 (64.2)	15.3 (171.5)	61.4 (82.2)	47.8 (50.4)	− 12.8 (63.1)	− 4.5 (85.5)
Adiponectin (mg l^{-1})	6.0 (3.9)	5.7 (3.5)	− 0.3 (2.0)	1.3 (36.5)	6.7 (4.8)	6.2 (4.4)	− 0.5 (2.2)	− 1.3 (33.5)
Fibrinogen (g l^{-1})	4.1 (1.0)	3.9 (1.0)	− 0.2 (1.0)	− 1.5 (25.4)	3.9(1.0)	3.8 (0.9)	− 0.1 (0.9)	− 0.6 (24.3)
SBP (mm Hg)	122.7 (13.1)	116.6 (12.5)	− 6.1 (11.6)	− 4.5 (8.9)	123.2 (12.3)	117.8 (10.8)	− 5.4 (10.5)	− 3.9 (8.3)
DBP (mm Hg)	78.0 (8.4)	74.2 (9.0)	− 3.8 (8.2)	− 4.5 (10.2)	79.2 (7.5)	75.9 (7.2)	− 3.3 (7.4)	− 3.7 (9.6)
Pulse (b.p.m.)	71.5 (9.7)	68.5 (9.2)	− 3.0 (9.0)	− 3.4 (12.4)	72.9 (9.3)	69.0 (9.1)	− 3.9 (8.6)	− 4.7 (11.8)

Abbreviations: BMI, body mass index; b.p.m., beats per minute; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; SBP, systolic blood pressure. Data shown are mean (s.d.) for all randomized participants.

randomization weight (26.1 versus 6.3%; $P<0.0001$) (Table 3). The liraglutide group compared with placebo also achieved greater mean absolute weight loss (6.0 kg (s.d. 7.3) versus 0.1 kg (s.d. 6.9); $P<0.0001$).

Sensitivity analyses, including a per-protocol completer analysis and repeated measures analysis, confirmed the superiority of liraglutide over placebo for the three co-primary end points (Supplementary Table 2). Results for other secondary weight-maintenance end points are reported in Supplementary Table 3. Participants in both treatment groups regained weight during the 12-week off-drug follow-up. At week 68, those who had received liraglutide maintained a 4.1% (s.d. 8.2) reduction in randomization weight, compared with a gain of 0.3% (s.d. 7.7) above randomization weight for placebo-treated participants (Figure 2a). The 4.2% (95% class intervals − 6.0 to − 2.4) difference between groups was statistically significant ($P<0.0001$; Table 3).

Changes in metabolic and CVD risk factors post-randomization

Liraglutide-treated participants, compared with placebo, achieved significantly greater decreases in BMI and waist circumference at week 56 (Table 3), as well as greater reductions in glycemic parameters and hsCRP (Table 4). Net changes in all lipids from randomization to week 56 were of small magnitude.

Mean SBP, DBP and pulse remained within normal ranges during the randomized treatment period. For all three measures, mean values increased at one or more occasions above randomization values in both treatment groups (Figures 2b–d). At week 56, SBP was significantly lower in the liraglutide versus the placebo group, with no significant differences between groups in DBP or pulse (Figures 2b–d and Table 4). In the liraglutide group, the greatest mean increase in pulse (6.6 beats per min (b.p.m.; s.d. 10.2)) from randomization occurred at week 6 (Figure 2d). Pulse began to return toward the randomization level at week 44. At week 56, pulse was 3.6 b.p.m. (s.d. 9.4) above randomization level with liraglutide compared with + 2.4 b.p.m. (s.d. 8.6) with placebo.

Safety

A similar percentage of participants in the liraglutide- and placebo-treated groups reported experiencing an AE during the study (91.5 and 88.6%, respectively), but more total events occurred with liraglutide (Table 5 and Supplementary Table 4). Of 18 participants in each group who withdrew because of an AE, only six participants did so because of serious events: ischemic colitis, worsening cholelithiasis, ovarian cancer, papillary thyroid carcinoma and bilateral breast cancer in the liraglutide group, and acute appendicitis in the placebo group. In the liraglutide group, most AE withdrawals (11/18) were due to GI disorders—typically nausea, vomiting, constipation and/or diarrhea. Eight of the 11 participants withdrew due to GI events that had onset in the first 4 weeks of the trial during dose escalation. The 11 participants experienced a total of 21 GI events. In the placebo group, no withdrawals were due to GI disorders. Onset of T2D accounted for the largest group of withdrawals (5/18) in the placebo group, whereas T2D did not occur among the participants treated with liraglutide.

GI disorders were the most common side effects in the liraglutide group, occurring at a higher incidence (156/212; 74%) than placebo (95/210; 45%) (Table 5). Most GI disorders (94.8%) with liraglutide were of mild or moderate severity. Nausea was transient, with most incidents occurring during the first 4 weeks of treatment, coinciding with dose escalation (Supplementary Figure 2). About 25% of participants on liraglutide reported nausea in the first 4 weeks, decreasing to < 10% at week 10 and to 3% thereafter. The next most common side effects were of the system organ classes 'infections and infestations', and 'nervous system disorders' (headaches and dizziness), which occurred at similar incidence in both treatment arms.

There were no cases of acute pancreatitis. Median lipase and amylase activity remained in the normal range (13–60 U l^{-1} and 28–100 U l^{-1}, respectively) at week 56 for both treatment groups, and no participants had elevations above three times upper normal range at any time (Supplementary Figures 3a and b). Mean calcitonin levels were below the upper normal range in both groups at week 56, and the geometric mean showed little

Table 2. Demographics and disease-specific characteristics for all randomized individuals

	Liraglutide 3.0 mg (n = 212)	*Placebo (n = 210)*
Age (years) at screening	45.9 (11.9)	46.5 (11)
Men/women (%)	16/84	21/79
Race		
White	170 (80)	185 (88)
Black or African–American	32 (15)	24 (11)
Asian and other	10 (5)	1 (1)
Comorbidities present	94 (44)	96 (46)
Hypertension	71 (33)	61 (29)
Dyslipidemia	59 (28)	65 (31)
Weight (kg)	100.4 (20.8)	98.7 (21.2)
BMI (kg m^{-2})	36.0 (5.9)	35.2 (5.9)
Waist circumference (cm)	109.4 (15.3)	107.8 (15.2)

Abbreviation: BMI, body mass index. Numbers are for individuals in the safety analysis set ($n = 422$) at randomization unless specified. Data are mean (s.d.) or number (%). Dyslipidemia was defined as low-density lipoprotein cholesterol $\geqslant$4.14 mmol l^{-1}, triglycerides $\geqslant$1.7 mmol l^{-1} or high-density lipoprotein cholesterol (HDL cholesterol) $<$1.04 mmol l^{-1} (males) or $<$1.3 mmol l^{-1} (females).[32,33] Hypertension was defined as systolic blood pressure $\geqslant$140 mm Hg and/or diastolic BP $\geqslant$90 mm Hg).[34] Participants receiving anti-hypertensive drugs, or drugs related to HDL cholesterol and triglycerides, were considered to fulfill elevated blood pressure or lipid-related criteria.

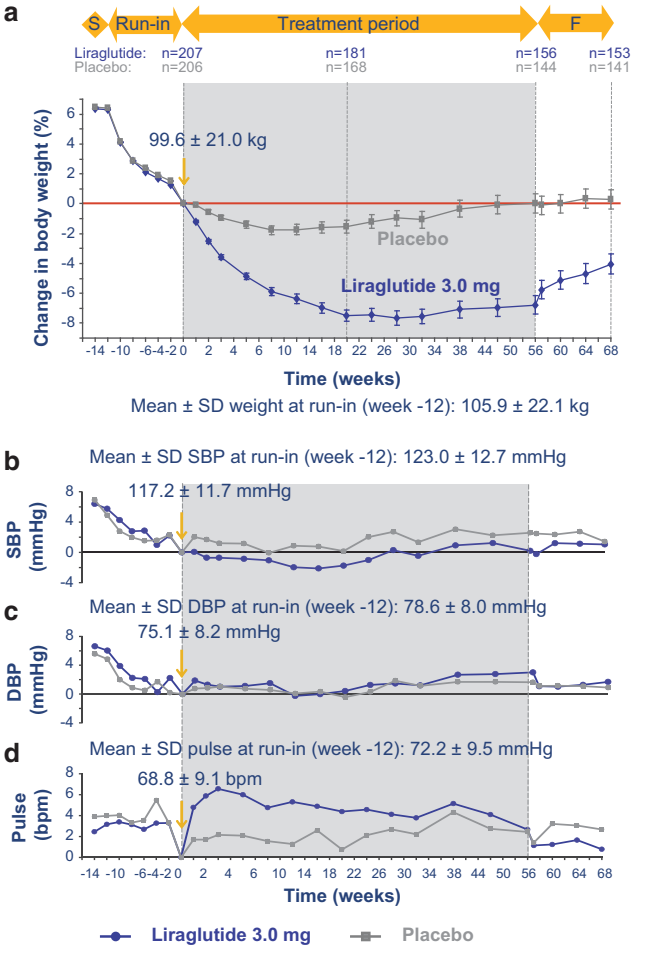

Figure 2. Mean percentage change in body weight and mean changes in vital signs from week −14 (screening) to week 68 (follow-up). Data for body weight (**a**) are observed means ± s.e. for individuals completing each scheduled visit. Data for SBP (**b**) and DBP (**c**) are for the full analysis set ($n = 413$), and for pulse (**d**) are for the safety set ($n = 422$) and are observed means. Values at week 0 (randomization) were arbitrarily set to 0. S, screening period; F, follow-up.

variation during the treatment period (Supplementary Figure 3c). No participants had a shift in calcitonin concentration from $<$ upper normal range to $\geqslant$20 ng ml^{-1}. A total of seven participants (3.3%) tested positive for anti-liraglutide antibodies, five of which had neutralizing activity.

All neoplasms (malignant or benign) were considered unlikely to be related to treatment. There were no reports of medullary (C-cell) thyroid carcinoma in either treatment group. Thyroid neoplasms were reported by three participants in the liraglutide group. All were considered unlikely to be related to treatment based either on proximity of occurrence to first dose or there having been a pre-existing condition. A papillary thyroid carcinoma (serious AE) was discovered 24 days after treatment initiation via biopsy of an enlarged left lobe of the thyroid in a participant who had an enlarged thyroid at screening. Total thyroidectomy was performed, and the participant was withdrawn from the study. In a second participant, ultrasound confirmed the presence of two thyroid nodules, a benign thyroid neoplasm, one of which had first been discovered in 2004. A third participant, 1 day after drug initiation, was found by using ultrasound to have a thyroid neoplasm with bilateral multiple cystic nodules. Its benign/malignant status was not reported. The latter two neoplasms were classified as mild and non-serious, and the participants remained in study. The remaining non-thyroid neoplasms are described in the Supplementary Information.

Sixteen participants exhibited symptomatic hypoglycemia; 11 participants receiving liraglutide reported 18 events, and 5 participants on placebo reported 7 events. No blood glucose measurements were performed, but the events were reported as AEs (Table 5). None of the events was classified as severe, and only two events (11%) in the liraglutide group were reported as moderate. No cardiac disorders in the liraglutide 3.0 mg participants were considered to be serious. Two participants in the liraglutide group exhibited atrial fibrillation or palpitations. Cardiac disorders were more common in the placebo group and included electrocardiogram abnormalities (two participants), atrial fibrillation (two participants), heart murmur (one participant), palpitations (four participants), angina pectoris (one participant) and bradycardia (one participant). There was one fatal episode of cardiac failure in a placebo-treated participant.

Psychiatric disorders occurred in 24 (11.3%) liraglutide-treated and 26 placebo-treated participants (12.4%), classified as anxiety (14 and 11 participants, respectively), depression (8 and 7 participants), sleep disorders (6 and 10 participants) and cognition disorders (1 and 2 participants) (Supplementary Table 5). One case of major depression occurred in the placebo group. There were no severe psychiatric disorders among participants receiving liraglutide, compared with three disorders in three participants taking placebo (depression, major depression and stress). There were no attempted or completed suicides.

PHQ-9 mean scores for depression at screening were similarly low for participants later randomized to liraglutide (2.4 (s.d. 2.7)) and placebo (2.7 (3.3)), and few participants had scores $\geqslant$10 (1.9 and 5.7%, respectively). After participants had lost $\geqslant$5% initial screening weight, mean scores at randomization were 1.2 (2.0) and 1.0 (1.8), respectively), with $\leqslant$1% of participants scoring $\geqslant$10. Most participants treated with liraglutide (76%) and placebo (77%)

Table 3. Changes in body weight measures from randomization

	Change from randomization to week 56		*ETD or OR for liraglutide versus placebo (95% CI),* P-*value*
	Liraglutide 3.0 mg (n = *207*)	*Placebo* (n = *206*)	
Co-primary end points			
Body weight (% change)	− 6.2 (7.3)	− 0.2 (7.0)	ETD = − 6.1 (− 7.5 to − 4.6), *P* < 0.0001
Proportion maintaining > 5% run-in weight loss	81.4%	48.9%	OR = 4.8 (3.0 to 7.7), *P* < 0.0001
Proportion with > 5% weight loss	50.5%	21.8%	OR = 3.9 (2.4 to 6.1), *P* < 0.0001
Secondary end points			
Body weight (kg)	− 6.0 (7.3)	− 0.1 (6.9)	ETD = − 5.9 (− 7.3 to − 4.4), *P* < 0.0001
Proportion with > 10% weight loss	26.1%	6.3%	OR = 5.3 (2.8 to 10.1), *P* < 0.0001
BMI (kg m^{-2})	− 2.1 (2.6)	− 0.0 (2.3)	ETD = − 2.1 (− 2.5 to − 1.6), *P* < 0.0001
Waist circumference (cm)	− 4.7 (7.4)	− 1.2 (6.4)	ETD = − 3.5 (− 4.8 to − 2.2), *P* < 0.0001
	Change from randomization to week 68 (follow-up) for participants entering follow-up		*ETD for liraglutide versus placebo (95% CI),* P-*value*
	(n = *159*)	(n = *144*)	
Body weight (% change)	− 4.1 (8.2)	0.3 (7.7)	− 4.2 (− 6.0 to − 2.4), *P* < 0.0001

Abbreviations: BMI, body mass index; CI, confidence intervals; ETD, estimated treatment difference; OR, odds ratio. Changes from randomization to week 56 or 68 are observed means (s.d.). ETDs are from an analysis of covariance and OR are from a logistic regression analysis, all using the full analysis set and with the last observation carried forward, except for percentage weight-loss data at week 68, which was without last observation carried forward. Body weight was measured in the fasting state.

Table 4. Changes in measures of glycemic control, lipids, cardiovascular biomarkers and vital signs during randomized treatment

	Change from randomization to week 56		*Estimated treatment differences for liraglutide—placebo (95% CI),* P-*value*
	Liraglutide 3.0 mg; n = *207*	*Placebo,* n = *206*	
HbA_{1c} (%)	− 0.1 (0.3)	0.1 (0.3)	− 0.3 (− 0.3 to − 0.2), *P* < 0.0001
FPG (mmol l^{-1})	− 0.5 (0.6)	− 0.2 (0.7)	− 0.4 (− 0.5 to − 0.3), *P* < 0.0001
Fasting insulin (pmol l^{-1})	2.8 (51.2)	16.2 (55.4)	− 13.3 (− 24.0 to − 2.6), *P* = 0.01
Total cholesterol (mmol l^{-1})	0.2 (0.7)	0.3 (0.7)	− 0.1 (− 0.2 to 0.03), *P* = 0.11
LDL cholesterol (mmol l^{-1})	0.2 (0.6)	0.3 (0.6)	− 0.09 (− 0.2 to 0.02), *P* = 0.11
HDL cholesterol (mmol l^{-1})	0.2 (0.2)	0.1 (0.2)	0.0 (− 0.03 to 0.04), *P* = 0.82
VLDL cholesterol (mmol l^{-1})	− 0.2 (0.3)	− 0.1 (0.3)	− 0.03 (− 0.07 to 0.02), *P* = 0.26
Triglycerides (mmol l^{-1})	0.0 (0.5)	0.1 (0.5)	− 0.11 (− 0.20 to − 0.01), *P* = 0.03
Free fatty acids (mmol l^{-1})	− 0.1 (0.3)	− 0.1 (0.3)	− 0.02 (− 0.06 to 0.03), *P* = 0.48
hsCRP (nmol l^{-1})	− 20.1 (60.0)	1.1 (55.0)	− 13.0 (− 23.4 to − 2.6), *P* = 0.01
Adiponectin (mg l^{-1})	2.0 (2.8)	1.7 (4.3)	0.4 (− 0.4 to 1.1), *P* = 0.31
Fibrinogen (g l^{-1})	0.0 (0.8)	− 0.1 (0.8)	0.1 (− 0.1 to 0.2), *P* = 0.20
SBP (mm Hg)	0.2 (12.0)	2.8 (10.4)	− 2.7 (− 4.7 to − 0.8), *P* = 0.007
DBP (mm Hg)	1.4 (8.7)	1.2 (7.7)	− 0.3 (− 1.7 to 1.1), *P* = 0.64
Pulse (b.p.m.)	3.6 (9.4)	2.4 (8.6)	1.0 (− 0.5 to 2.5), *P* = 0.20

Abbreviations: b.p.m, beats per minute; CI, confidence intervals; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SBP, systolic blood pressure; VLDL, very low-density lipoprotein. Changes from randomization to week 56 are means (s.d.) and estimated treatment differences from an analysis of covariance, both using the full analysis set with the last observation carried forward.

had PHQ-9 scores that remained in the same category (none, mild, moderate or severe) throughout the treatment period. Mean scores at week 56 (with the last-observation-carried-forward analysis) were similar to those observed at randomization for both liraglutide- (1.2 (2.2)) and placebo-treated (1.3 (2.3)) participants. A similar proportion of liraglutide-treated (19%) and placebo-treated (18%) participants had PHQ-9 scores that shifted from randomization to a higher category at any assessment visit during the treatment period, mostly from none to mild depression. Fewer participants (3% in both groups) improved from their randomization scores, mostly from mild to no depression.

Two liraglutide-treated participants reported suicidal behavior during the trial (C-SSRS questionnaire). One participant was determined to be referring to incidents that occurred 6 years before the trial. The other answered 'yes' to suicidal behavior at week 14 without defining the behavior, but reported no such behavior at previous or subsequent visits. Five liraglutide- and four placebo-treated participants reported nine and 11 episodes of suicidal ideations (various categories), respectively, during the trial.

DISCUSSION

Maintaining long-term weight loss is the Achilles' heel of obesity therapy. Results of the present trial demonstrated that the combination of liraglutide 3.0 mg per day and lifestyle intervention significantly improved weight maintenance

Table 5. Adverse events with an incidence of 5% or more in any treatment group, by system organ class and preferred term

	Liraglutide 3.0 mg				*Placebo*			
	N	*(%)*	E	R	N	*(%)*	E	R
Safety analysis set	212				210			
Exposure (years)	194.5				184.6			
All adverse events	194	(91.5)	1375	707.1	186	(88.6)	1067	578.0
Adverse events ⩾5%	177	(83.5)	788	405.2	163	(77.6)	512	277.3
Gastrointestinal disorders	156	(73.6)	495	254.5	95	(45.2)	182	98.6
Nausea	101	(47.6)	181	93.1	36	(17.1)	55	29.8
Constipation	57	(26.9)	66	33.9	26	(12.4)	28	15.2
Diarrhea	38	(17.9)	53	27.3	26	(12.4)	34	18.4
Vomiting	35	(16.5)	44	22.6	5	(2.4)	6	3.3
Dyspepsia	20	(9.4)	25	12.9	4	(1.9)	4	2.2
Abdominal pain	14	(6.6)	17	8.7	3	(1.4)	4	2.2
Abdominal distension	13	(6.1)	14	7.2	8	(3.8)	9	4.9
Eructation	11	(5.2)	17	8.7				
Flatulence	11	(5.2)	17	8.7	8	(3.8)	8	4.3
Infections and infestations	123	(58.0)	214	110.0	121	(57.6)	244	132.2
Nasopharyngitis	36	(17.0)	44	22.6	47	(22.4)	63	34.1
Sinusitis	16	(7.5)	17	8.7	27	(12.9)	33	17.9
Upper respiratory tract infection	26	(12.3)	35	18.0	23	(11.0)	33	17.9
Influenza	15	(7.1)	17	8.7	22	(10.5)	25	13.5
Urinary tract infection	15	(7.1)	17	8.7	11	(5.2)	11	6.0
Bronchitis	7	(3.3)	7	3.6	11	(5.2)	15	8.1
Nervous system disorders	57	(26.9)	111	57.1	66	(31.4)	98	53.1
Headache	27	(12.7)	42	21.6	26	(12.4)	37	20.0
Dizziness	22	(10.4)	35	18.0	18	(8.6)	22	11.9
General disorders and administration-site conditions	71	(33.5)	111	57.1	59	(28.1)	93	50.4
Injection-site hematoma	17	(8.0)	18	9.3	24	(11.4)	32	17.3
Fatigue	17	(8.0)	20	10.3	11	(5.2)	12	6.5
Injection-site pain	8	(3.8)	9	4.6	11	(5.2)	11	6.0
Musculoskeletal and connective tissue disorders	53	(25.0)	77	39.6	59	(28.1)	103	55.8
Back pain	11	(5.2)	12	6.2	20	(9.5)	23	12.5
Arthralgia	12	(5.7)	13	6.7	13	(6.2)	13	7.0
Injury, poisoning and procedural complications	49	(23.1)	59	30.3	46	(21.9)	57	30.9
Muscle strain	11	(5.2)	13	6.7	10	(4.8)	11	6.0
Respiratory, thoracic and mediastinal disorders	31	(14.6)	61	31.4	43	(20.5)	63	34.1
Cough	14	(6.6)	15	7.7	11	(5.2)	12	6.5
Metabolism and nutrition disorders	39	(18.4)	50	25.7	28	(13.3)	36	19.5
Decreased appetite	21	(9.9)	22	11.3	3	(1.4)	4	2.2
Hypoglycemia	11	(5.2)	18	9.3	5	(2.4)	7	3.8

Abbreviations: E, number of adverse events; N, number of participants with adverse event; R, event rate per 100 exposure years; %, proportion of participants in analysis set having adverse event.

at 56 weeks, compared with placebo and lifestyle intervention, in overweight and obese individuals who had lost ⩾5% of initial body weight during a LCD run-in. Approximately two-thirds more participants treated with liraglutide than placebo maintained the ⩾5% reduction in initial weight achieved during the LCD run-in. Liraglutide also induced further substantial weight loss during the 56-week trial, with a mean additional reduction of 6.2% of randomization body weight compared with 0.2% for placebo. This trial confirms the efficacy of liraglutide 3.0 mg per day in inducing weight loss[16] and is the first to demonstrate weight-loss maintenance with liraglutide.

The placebo-subtracted weight-loss difference of 5.9 kg at week 56 observed in the present study is consistent with the 5.8 kg difference reported at 1 year by Astrup *et al.*[17] (with the same dose). Liraglutide-treated participants in the present study achieved a cumulative weight loss of ~12 kg, calculated from the start of the LCD. This compares favorably to the cumulative 7.2 kg weight loss achieved with orlistat at 1 year in a study that used a diet run-in period similar to that employed in the present study.[25] The approximately monthly lifestyle counseling provided in the present study was effective in preventing weight regain, as indicated by the weight stability of the placebo group over the 56 weeks. The addition of liraglutide enhanced the benefit of the lifestyle intervention, consistent with the previously observed additive effects of pharmacotherapy and behavior therapy.[26]

Both lorcaserin[13] and the combination of phentermine and topiramate[9] were recently approved in the United States for

chronic weight management. Neither medication has been assessed as a means of facilitating the maintenance of lost weight achieved with an initial LCD, as used in the present study. However, lorcaserin was found to improve long-term weight loss that was initially induced with the medication. Participants who lost a mean 5.8 kg weight after 1 year of treatment with lorcaserin were randomly assigned to remain on medication or to receive placebo. At year 2, those who had been switched to placebo had regained most of their lost weight, whereas those who remained on medication sustained a significantly greater weight loss.[13] Similar findings were observed in two 2-year trials of orlistat that used the same experimental design.[10,11] The weight regain observed in the present study, during the 12-week off-drug follow-up, is consistent with these prior findings.

The aforementioned trials of lorcaserin and orlistat underscore that weight loss medications must likely be taken long-term in order to maintain the initial weight losses achieved. Further study is needed of the frequency of medication usage required to facilitate weight loss maintenance. Trials of both phentermine[27] and sibutramine[28] found equivalent induction of weight loss (over 36 and 44 weeks) in persons who took medication intermittently (for example, every other month) as compared with daily. Studies of newly approved medications are needed to determine the frequency of use required to facilitate the maintenance of weight loss.

As anticipated, several cardiometabolic risk factors improved during the LCD run-in period, in which participants lost a mean 6.0% of screening weight, and were further improved (HbA_{1c}, FPG, hsCRP and SBP) or maintained (fasting insulin) with liraglutide but not placebo during the randomized period. Improvements in HbA_{1c} and FPG are consistent with the effects of liraglutide on glycemic control in T2D patients.[14] The improvements in CRP and SBP are consistent with the effects of additional weight loss; it is not clear whether liraglutide directly affected either outcome, beyond weight loss.

Liraglutide was not associated with additional clinically meaningful reductions in lipids following initial decreases observed during the LCD. Concentrations of many lipids, notably total- and low-density lipoprotein cholesterol, typically reach their nadir during the early weeks of dieting, reflecting the effects of caloric restriction, as well as weight loss.[29,30] At the end of treatment, mean SBP and DBP in both groups remained below screening values and within normal limits, as did other CVD risk factors (that is, lipids and pulse). The reduction in SBP achieved during run-in was maintained to a greater extent with liraglutide than placebo, but the mechanism responsible for the reduction remains unknown. Pulse fell during the LCD run-in period and then rose above randomization values in liraglutide-treated participants. Values approached near-randomization levels after longer treatment duration (after week 44). The clinical implications of the increase in pulse, which has been observed in previous trials of liraglutide and other glucagon-like peptide-1 receptor agonists, are not yet clear. However, in a *post-hoc* evaluation of the cardiovascular safety of liraglutide in phase 2–3 clinical development trials, liraglutide was associated with low rates ($<1\%$) of major adverse cardiovascular events that were similar to or lower than those estimated for the comparator arms.[31]

Liraglutide was generally well tolerated. Principal complaints associated with the medication were transient nausea, constipation, diarrhea and vomiting, as previously observed.[14,16,17] Maximum weight loss did not coincide with maximum rates of nausea, however. GI events, including nausea, accounted for the greatest number of study withdrawals from liraglutide, whereas the onset of T2D accounted for most withdrawals from placebo.

Strengths of the present study include the high retention rates in both liraglutide (75.0%) and placebo (69.5%) groups, the lifestyle intervention program and the high percentage of liraglutide-treated participants who maintained a loss of $\geqslant 5\%$ of screening weight at week 56. Limitations include the inability to determine the precise effects of liraglutide on metabolic and CVD risk factors because of changes in these variables during the LCD run-in. There were more neoplasms among the liraglutide-treated than the placebo-treated participants (12 versus 4). However, the 56-week length of the trial and the limited number of participants were insufficient to allow extrapolation of an overall cancer risk. Finally, the favorable long-term weight losses in the present trial, for both placebo- and liraglutide-treated participants, may have been attributable, in part, to the prior identification of successful short-term weight losers ($\geqslant 5\%$) using the LCD run-in. Participants not pre-selected in this manner may have achieved smaller long-term weight losses. (We also note that a larger percentage of individuals who enrolled in the run-in period may have lost $\geqslant 5\%$ of initial weight if weekly, rather than every-other-week, face-to-face lifestyle counseling had been provided.)

In summary, the current phase 3 randomized, controlled trial demonstrates the efficacy of liraglutide 3.0 mg per day, combined with lifestyle modification, in facilitating the maintenance of clinically meaningful weight loss. Liraglutide, compared with placebo, improved weight maintenance and induced additional reductions in CVD risk factors, including waist circumference, FPG, SBP and hsCRP.

CONFLICT OF INTEREST

PMH is an employee of Novo Nordisk, and also owns stock in the company. TAW serves on advisory boards for Novo Nordisk and Orexigen Pharmaceuticals. PH serves on an advisory board and is a consultant for Novo Nordisk. SK is a consultant for Takeda Pharmaceuticals and Vivus. KN is a consultant for Novo Nordisk and has done commercially sponsored research for Novo Nordisk. VW serves on advisory boards, has held paid lectures or has done commercially sponsored research for Novo Nordisk, Eli Lilly, Sanofi, Bristol-Myers Squibb, AstraZeneca and Boehringer Ingelheim. LA is a consultant or receives research support from Amylin Pharmaceuticals, F Hoffman-La Roche, Abbott Laboratories, Ethicon Endo-Surgery, Orexigen Therapeutics, Vivus, GlaxoSmithKline Consumer Healthcare, LP, Takeda Pharmaceuticals and Zafgen. He has ownership interest in Cardiometabolic Support Network, LLC and Atlas Therapeutics.

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APPENDIX

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