Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study

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Summary

Background The frequency of obesity has risen dramatically in recent years but only few safe and effective drugs are currently available. We assessed the effect of liraglutide on bodyweight and tolerability in obese individuals without type 2 diabetes.

Methods We did a double-blind, placebo-controlled 20-week trial, with open-label orlistat comparator in 19 sites in Europe. 564 individuals (18–65 years of age, body-mass index 30–40 kg/m²) were randomly assigned, with a telephone or web-based system, to one of four liraglutide doses (1·2 mg, 1·8 mg, 2·4 mg, or 3·0 mg, n=90–95) or to placebo (n=98) administered once a day subcutaneously, or orlistat (120 mg, n=95) three times a day orally. All individuals had a 500 kcal per day energy-deficit diet and increased their physical activity throughout the trial, including the 2-week run-in. Weight change analysed by intention to treat was the primary endpoint. An 84-week open-label extension followed. This study is registered with ClinicalTrials.gov, number NCT00422058.

Findings Participants on liraglutide lost significantly more weight than did those on placebo (p=0·003 for liraglutide 1·2 mg and p<0·0001 for liraglutide 1·8–3·0 mg) and orlistat (p=0·003 for liraglutide 2·4 mg and p<0·0001 for liraglutide 3·0 mg). Mean weight loss with liraglutide 1·2–3·0 mg was 4·8 kg, 5·5 kg, 6·3 kg, and 7·2 kg compared with 2·8 kg with placebo and 4·1 kg with orlistat, and was 2·1 kg (95% CI 0·6–3·6) to 4·4 kg (2·9–6·0) greater than that with placebo. More individuals (76%, n=70) lost more than 5% weight with liraglutide 3·0 mg that with placebo (30%, n=29) or orlistat (44%, n=42). Liraglutide reduced blood pressure at all doses, and reduced the prevalence of prediabetes (84–96% reduction) with 1·8–3·0 mg per day. Nausea and vomiting occurred more often in individuals on liraglutide than in those on placebo, but adverse events were mainly transient and rarely led to discontinuation of treatment.

Interpretation Liraglutide treatment over 20 weeks is well tolerated, induces weight loss, improves certain obesity-related risk factors, and reduces prediabetes.

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Introduction

Over the past 20 years, the rate of obesity has risen three-fold and is more than 30% in some European countries.[1] Around 50% of all adults in Europe are classified as overweight.[2,3] Obesity increases the risk of hypertension, diabetes, and atherosclerosis, all risk factors for the leading cause of death worldwide—cardiovascular disease.[4,5] Moreover, obesity is associated with a reduced quality of life.[6,7] Few safe and effective drugs are currently available for the treatment of obesity. Therefore, alternative approaches to weight loss that are safe and well tolerated and that can lower the risks associated with obesity are needed.

Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue with a 97% structural homology to human GLP-1, a gut-derived incretin hormone. Native GLP-1 has a short elimination half-life of 1–2 min, whereas liraglutide has a long half-life of about 13 h and can be administered once a day by subcutaneous injection.[8,9] Liraglutide was initially developed for the treatment of type 2 diabetes mellitus and has shown benefits for glycaemic control at doses up to 1·8 mg a day.[10–14] Because liraglutide causes a dose-dependent weight loss, decreasing the concentration of glycosylated haemoglobin (HbA_{1c}),[13,15,16] as well as improving β-cell function[11,17,18] and systolic blood pressure,[13] it could be an attractive treatment option for both type 2 diabetes and obesity.

The underlying mechanisms that mediate the effects of weight reduction of liraglutide are most probably a combination of effects on the gastrointestinal tract and the brain. Native GLP-1 suppresses appetite and energy intake in both normal-weight and obese individuals,[19–21] as well as in people with type 2 diabetes,[22–24] and delays gastric emptying.[25,26] Weight loss and decreased food intake have also been shown in studies with liraglutide in minipigs and rats.[27–29] Feeding frequency and meal size were reduced in the minipig obesity model during liraglutide treatment.[27] GLP-1 receptors are expressed in several brainstem nuclei involved in appetite regulation,[29] and subcutaneously administered liraglutide might also reach these sites.

Our aim was to assess the effect on bodyweight of liraglutide (at doses up to 3·0 mg per day), in combination with an energy-deficit low-fat diet and physical activity

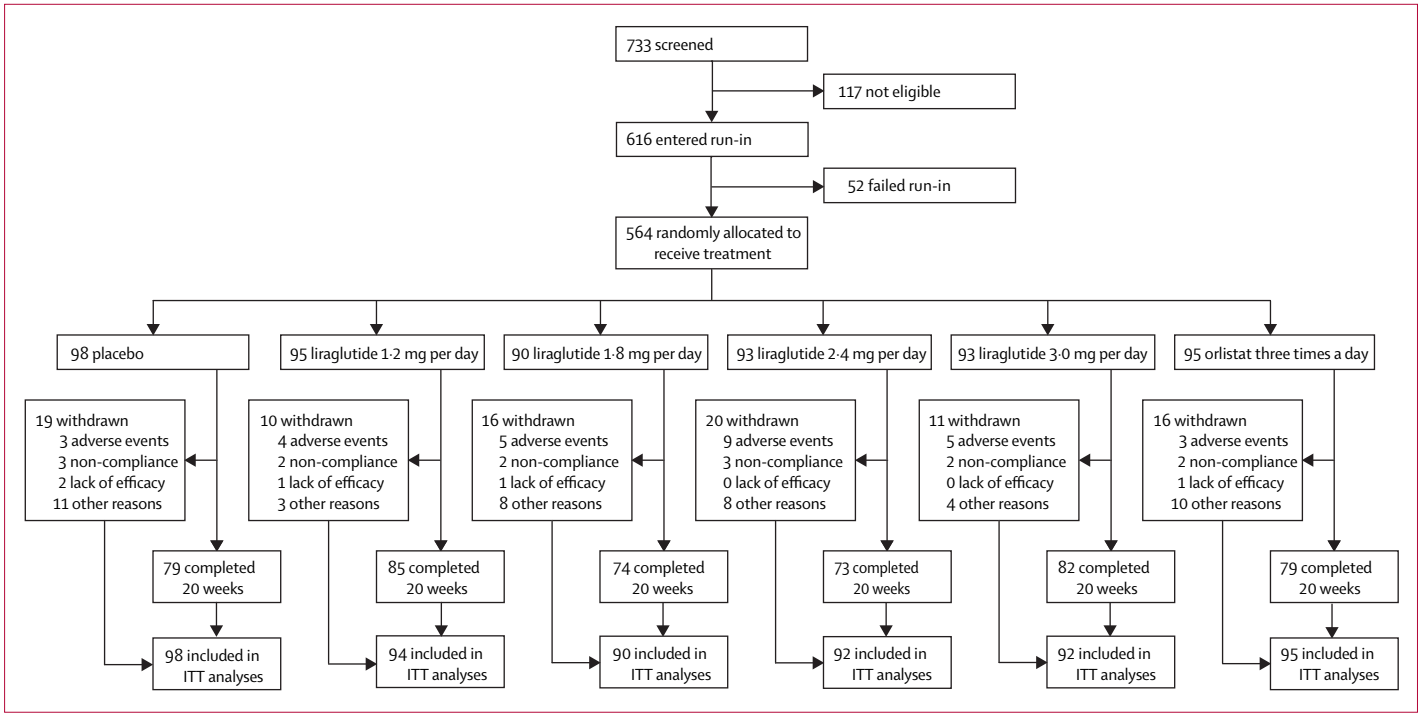

Figure 1: **Trial profile**
ITT=intention to treat.

counselling, in obese individuals. Liraglutide was compared with the approved weight-loss agent orlistat, a gastrointestinal lipase inhibitor. The safety and tolerability of doses of liraglutide higher than those previously studied in individuals with type 2 diabetes were also assessed.

Methods

Patients

Men and women aged 18–65 years, with body-mass index (BMI) of 30–40 kg/m², stable bodyweight (<5% reported change during the previous 3 months), and fasting plasma glucose of less than 7 mmol/L at run-in, were recruited from 19 clinical research sites in eight European countries. Key exclusion criteria included known type 1 or 2 diabetes mellitus, obesity induced by drug treatment, use of approved weight-lowering pharmacotherapy or participation in a clinical weight control study within the previous 3 months, previous surgical obesity treatment, and major medical conditions. There was no exclusion based on psychiatric illness. Written informed consent was obtained from all individuals. The protocol was approved by local ethics committees. The trial was done in accordance with the Declaration of Helsinki[30] and ICH Good Clinical Practice.[31]

Procedures

Obese people were randomly assigned to receive liraglutide (1·2 mg, 1·8 mg, 2·4 mg, or 3·0 mg once a day by subcutaneous injection, n=90–95), placebo (once a day by subcutaneous injection, n=98), or orlistat (120 mg three times a day orally, n=95). The trial consisted of a screening visit; a 2-week single-blind, placebo run-in period starting 1 week after screening; a 4-week dose titration period; a 16-week constant-dose period; and a post-trial follow-up visit (for those not continuing in the extension period), 4–10 days after trial completion. Visits were done once every week up to the constant-dose period, and about once every 2 weeks thereafter. During run-in and throughout treatment, all individuals were instructed to adhere to a low-fat diet (about 30% of energy from fat, 20% from protein, and 50% from carbohydrates), with about 500 kcal per day deficit below estimated 24-h energy expenditure calculated as basal metabolic rate[32] multiplied by 1·3. Individuals were encouraged to maintain or increase physical activity using pedometers. To become accustomed to the injection device, all people self-administered 100 µL vehicle once a day during run-in.

Eligible participants were randomly assigned after run-in with a central telephone or web-based system, generated by the sponsor and concealed from trial investigators. Individuals were stratified according to sex. Participants receiving liraglutide or placebo were instructed to administer subcutaneous injections once a day (liraglutide 6·0 mg/mL or vehicle in identical 3 mL cartridges) in the evening, using a pen injector. To maintain blinding, placebo treatment was subdivided into four groups with different injection volumes, corresponding to the different liraglutide doses. The trial

	Placebo (n=98)	Liraglutide				Orlistat (n=95)
		1·2 mg (n=95)	1·8 mg (n=90)	2·4 mg (n=93)	3·0 mg (n=93)	
Men:women	25%:75%	23%:77%	24%:76%	24%:76%	25%:75%	23%:77%
Age (years)	45·9 (10·3)	47·2 (9·7)	45·5 (10·9)	45·0 (11·1)	45·9 (10·7)	45·9 (9·1)
Bodyweight (kg)	97·3 (12·3)	96·2 (13·5)	98·0 (12·5)	98·4 (13·0)	97·6 (13·7)	96·0 (11·7)
BMI (kg/m²)	34·9 (2·8)	34·8 (2·6)	35·0 (2·6)	35·0 (2·8)	34·8 (2·8)	34·1 (2·6)
Male waist (cm)	116 (8·3)	118 (8·9)	116 (8·7)	115 (8·8)	115 (7·4)	114 (6·7)
Female waist (cm)	106 (9·1)	106 (9·0)	106 (8·3)	109 (10·7)	107 (7·4)	106 (9·8)
Systolic BP (mm Hg)	124 (11·1)	127 (13·1)	123 (13·0)	126 (13·9)	124 (11·3)	123 (13·5)
Diastolic BP (mm Hg)	76·8 (8·5)	79·7 (9·1)	77·9 (7·9)	78·6 (8·2)	77·8 (8·3)	76·9 (7·9)
Metabolic syndrome*	33%	25%	22%	23%	28%	24%
Glucose tolerance status						
Type 2 diabetes†	4·1%	6·3%	2·2%	1·1%	4·3%	3·2%
Prediabetes‡	32·7%	30·5%	33·3%	33·3%	29·0%	28·4%
Normal glucose tolerance§	62·2%	63·2%	64·4%	65·6%	65·6%	67·4%
Total cholesterol (mmol/L)	5·01 (1·02)	4·92 (0·89)	5·05 (1·10)	4·99 (0·95)	4·87 (0·95)	5·00 (0·87)
LDL cholesterol (mmol/L)	3·53 (0·89)	3·38 (0·77)	3·53 (0·88)	3·51 (0·86)	3·40 (0·78)	3·52 (0·77)
HDL cholesterol (mmol/L)	1·27 (0·27)	1·35 (0·40)	1·34 (0·38)	1·33 (0·28)	1·28 (0·32)	1·32 (0·31)
VLDL cholesterol (mmol/L)	0·24 (0·27)	0·23 (0·29)	0·23 (0·30)	0·19 (0·16)	0·20 (0·24)	0·19 (0·26)
Triglycerides (mmol/L)	1·56 (0·78)	1·44 (0·84)	1·43 (0·99)	1·37 (0·64)	1·42 (0·78)	1·38 (0·71)
Participants on hypertensive medication¶	27 (28%)	27 (28%)	21 (23%)	19 (20%)	11 (12%)	16 (17%)
Participants on cholesterol-lowering medication¶	4 (4%)	5 (5%)	8 (9%)	6 (6%)	7 (8%)	2 (2%)

Data are mean (SD) or n (%), unless otherwise noted. BMI=body-mass index. BP=blood pressure. LDL=low-density lipoprotein. HDL=high-density lipoprotein. VLDL=very-low-density lipoprotein. *As assessed by NCEP-ATP III criteria.[37] †Fasting plasma glucose ≥7·0 mmol/L or ≥11·1 mmol/L during oral glucose tolerance test (OGTT). ‡Either impaired fasting plasma glucose (5·6–6·9 mmol/L) or impaired glucose tolerance (7·8–11·0 mmol/L) during OGTT. §Fasting plasma glucose <5·6 mmol/L or <7·8 mmol/L during OGTT. ¶At screening.

Table 1: **Baseline characteristics at randomisation (after a diet and placebo run-in period)**

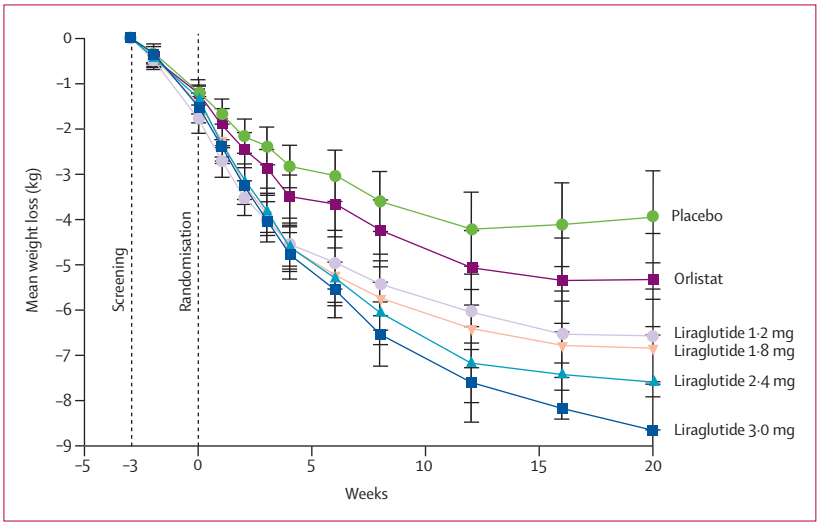

Figure 2: **Change in bodyweight**
Data are mean (95% CI) (ANCOVA estimate) for the intention-to-treat population with the last observation carried forward.

was therefore masked for liraglutide or placebo treatment, but not dose. The starting dose of 0·6 mg per day was increased during the first 2–4 weeks after randomisation (dose titration). Individuals randomly assigned to open-label orlistat treatment were instructed to take orlistat capsules (120 mg three times a day) with each main meal. The trial ran between January and September, 2007. Participants completing the study could enrol in an 84-week open-label extension period, if eligible.

The primary endpoint was change in bodyweight during the 20 weeks of the study in the intention-to-treat population. The proportion of people losing more than 5% or 10% of baseline weight was also assessed. Secondary efficacy endpoints included change in waist circumference, systolic and diastolic blood pressure, prevalence of metabolic syndrome, prediabetes status, fasting lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, and triglycerides), cardiovascular biomarkers (highly sensitive C-reactive protein, plasminogen activator inhibitor-1, fibrinogen, and adiponectin), glucose metabolism parameters (fasting plasma glucose, fasting insulin, and glycosylated haemoglobin [HbA_{1c}]), and homoeostasis model assessment (HOMA) of β-cell function and insulin resistance.[33] The change from 0 to 120 min in glucose, insulin, and C-peptide concentrations during oral glucose tolerance test (OGTT; 75-g glucose) measured at randomisation and week 20 was also a secondary endpoint. Patient-reported outcome scores of physical function, self-esteem, sexual life, public

	Placebo	Liraglutide				Orlistat
		1·2 mg	1·8 mg	2·4 mg	3·0 mg	
Weight (kg)						
Mean weight loss	−2·8 (−3·7 to −1·8)	−4·8 (−5·7 to −3·9)	−5·5 (−6·5 to −4·6)	−6·3 (−7·2 to −5·3)	−7·2 (−8·1 to −6·2)	−4·1 (−5·0 to −3·2)
Mean difference*		−2·1† (−3·6 to −0·6)	−2·8‡ (−4·3 to −1·3)	−3·5‡ (−5·0 to -2·0)	−4·4‡ (−6·0 to −2·9)	
Mean difference§		−0·7 (−2·2 to 0·9)	−1·4 (−3·0 to 0·2)	−2·1† (−3·7 to −0·6)	−3·0‡ (−4·5 to −1·4)	
Male waist (cm)						
Mean change	−5·2 (−7·3 to −3·1)	−6·4 (−8·6 to −4·2)	−6·5 (−8·8 to −4·2)	−6·3 (−8·5 to −4·1)	−6·6 (−9·0 to −4·3)	−6·5 (−8·8 to −4·3)
Mean difference*		−1·2 (−4·9 to 2·4)	−1·3 (−5·0 to 2·4)	−1·3 (−4·8 to 2·3)	−1·6 (−5·3 to 2·1)	
Mean difference§		0·11 (−3·8 to 4·0)	−0·30 (−4·1 to 3·5)	−0·17 (−4·0 to 3·6)	−0·20 (−4·0 to 3·6)	
Female waist (cm)						
Mean change	−3·6 (−4·9 to −2·3)	−5·4 (−6·7 to −4·1)	−5·2 (−6·6 to −3·9)	−6·5 (−7·8 to −5·1)	−7·3 (−8·6 to −5·9)	−5·4 (−6·7 to −4·1)
Mean difference*		−1·7 (−3·9 to 0·5)	−1·7 (−3·9 to 0·6)	−3·0¶ (−5·2 to −0·7)	−3·7‖ (−3·7 to −6·0)	
Mean difference§		−0·02 (−2·28 to 2·24)	0·18(−2·09to2·45)	−0·99 (−3·26 to 1·28)	−1·86 (−4·14 to 0·43)	
Systolic BP (mm Hg)						
Mean change	−4·0 (−6·4 to −1·6)	−5·7 (−8·2 to −3·2)	−5·6 (−8·2 to −3·1)	−8·8 (−11·3 to −6·4)	−6·9 (−9·4 to −4·3)	−5·4 (−7·9 to −2·9)
Mean difference*		−1·6 (−5·6 to 2·5)	−1·7 (−5·7 to 2·4)	−4·7** (−8·7 to −0·7)	−3·1 (−7·0 to 1·1)	
Mean difference§		−0·3 (−4·1 to 3·6)	−0·3 (−4·1 to 3·6)	−3·4 (−7·2 to 0·4)	−1·4 (−5·3 to 2·4)	
Diastolic BP (mm Hg)						
Mean change	−1·1 (−2·6 to 0·5)	−1·2 (−2·8 to 0·4)	−1·8 (−3·4 to −0·1)	−1·4 (−2·9 to 0·2)	−2·9 (−4·6 to −1·3)	−2·7 (−4·2 to −1·1)
Mean difference*		−0·05 (−2·6 to 2·5)	−0·68 (−3·3 to 1·9)	−0·29 (−2·8 to 2·3)	−1·91 (−4·5 to 0·7)	
Mean difference§		1·48 (−1·1 to 4·1)	0·93 (−1·7 to 3·6)	1·28 (−1·3 to 3·9)	−0·26 (−2·9 to 2·4)	
Prediabetes status						
Odds ratio*	..	3·0 (1·1 to 8·1)	26·1 (3·8 to 181)	10·7 (2·4 to 47)	12·5 (2·9 to 55)	..
Odds ratio§	..	3·0 (1·1 to 8·3)	26·3 (3·7 to 185)	10·8 (2·4 to 48)	12·6 (2·9 to 56)	..

Data are estimates (95% CI). Values are for the full intention-to-treat population with last observation carried forward. Odds ratio is for having normal glucose tolerance. BP=blood pressure. *Denotes mean difference to placebo. †p=0·003. ‡p<0·0001. §Mean difference to orlistat. ¶p=0·005. ||p=0·0002. **p=0·015.

Table 2: **Changes in bodyweight, waist circumference, blood pressure, and prediabetes status from randomisation (after a diet and placebo run-in period) to week 20**

distress, and work were also secondary endpoints; these were assessed with the questionnaire Impact of Weight on Quality of Life-Lite (IWQOL-Lite).[34]

Bodyweight was measured at every visit. Standardised assessments of waist circumference, blood pressure,[35,36] glucose, and insulin were made at randomisation and every 4 weeks thereafter; glucose and blood pressure were also measured at screening and follow-up, and insulin was also measured at follow-up. Diagnosis of metabolic syndrome was made according to National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria.[37] Prediabetes was defined[38] as either impaired fasting plasma glucose (5·6–6·9 mmol/L) or impaired glucose tolerance (7·8–11·0 mmol/L), measured during OGTT at randomisation and week 20. Lipid concentrations were measured at randomisation, every 4 weeks thereafter, and at follow-up. Cardiovascular biomarkers, HbA_{1c}, and C-peptide were measured at randomisation and week 20. Analyses of lipids, cardiovascular biomarkers, glucose metabolism parameters, and safety laboratory parameters were done at central laboratories (MDS Pharma Services, Hamburg, Germany), according to standard procedures. Patient-reported outcome scores were assessed during run-in, at randomisation, and week 20.

Key safety assessments were tolerability (including nausea and other gastrointestinal adverse events) and standard laboratory tests (haematological and biochemical tests, and liraglutide antibodies). Antibody data cannot be reported at this stage because analysis is affected by liraglutide in samples from individuals continuing in the trial, and will be made available once individuals have been off treatment for 5 days. Adverse events were recorded at every visit. A physical examination and electrocardiogram were done at screening and at week 20. Pulse rate and laboratory parameters were measured at screening, run-in (laboratory parameters only), randomisation, every 4 weeks thereafter, and at follow-up. A safety committee was established by the sponsor to do regular surveillance of data.

Statistical analysis

Sample size was calculated assuming that the SD of weight change at week 20 would be 5·6 kg.[39] Therefore, 547 individuals (91 in each group) would provide at least 85% confidence to detect a clinically relevant 3 kg difference (p=0·05, two-sided) in mean bodyweight

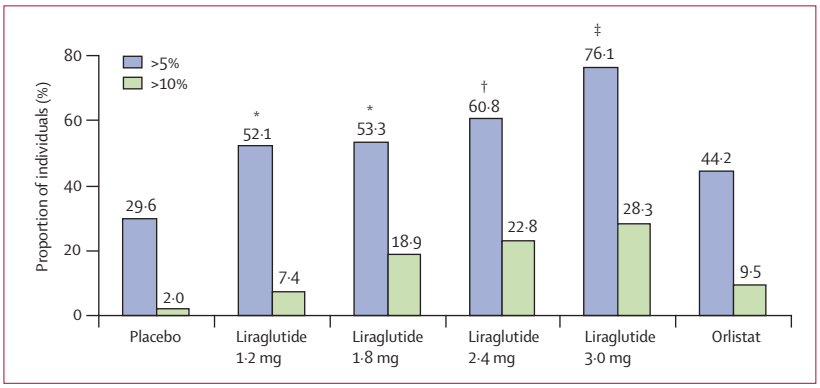

Figure 3: **Percentage of individuals who lost more than 5% and more than 10% of baseline weight at week 20 (intention-to-treat population)**
*p=0·002 *vs* placebo. †p<0·0001 *vs* placebo. ‡p≤0·0001 *vs* placebo or orlistat.

	Placebo	Liraglutide				Orlistat
		1·2 mg	1·8 mg	2·4 mg	3·0 mg	
Weight (kg)	−4·1 (3·9)	−6·7 (4·0)	−7·1 (5·8)	−7·9 (5·0)	−9·1 (5·2)	−5·5 (4·3)
SBP (mm Hg)	−7·8 (15·0)	−12·8 (14·4)	−10·7 (13·6)	−14·7 (12·0)	−13·3 (13·2)	−9·3 (11·7)
DBP (mm Hg)	−4·8 (9·0)	−4·9 (8·8)	−4·9 (9·0)	−5·1 (8·0)	−7·1 (9·8)	−4·5 (8·0)

Data are estimated mean change (SD). Values are for the full intention-to-treat population with last observation carried forward. SBP=systolic blood pressure. DBP=diastolic blood pressure.

Table 3: **Changes in bodyweight and blood pressure from screening (including a 2-week diet and placebo run-in period) to week 20**

between individuals receiving liraglutide 3·0 mg per day or placebo, based on Dunnett's test. A drop-out rate of 30% was assumed.

Data were analysed according to a pre-established analysis plan. Analyses were done on a modified intention-to-treat population, which included all randomised individuals who were exposed to at least one dose of trial product and who had at least one post-baseline bodyweight assessment. All analyses were two-sided, done at a 5% significance level and (for weight, waist circumference, blood pressure, lipids, fasting glucose, and insulin) applied to the last observation carried forward. For patient-reported outcome scores, we analysed the completer population (ie, with an actual weight measurement at week 20).

We used an analysis of covariance (ANCOVA) for the primary endpoint and for secondary endpoints waist circumference, blood pressure, and patient-reported outcome scores; this was supplemented by a repeated-measures analysis. The ANCOVA model included treatment, country, and sex as fixed effects, and bodyweight at randomisation as covariate. We aimed to assess whether data provided evidence of superiority of each liraglutide dose to placebo (primary objective) and to orlistat (secondary objective). The primary null hypothesis was no difference between treatments. We used the Dunnett's method for adjustments for multiplicity. The proportion of people losing more than 5% of baseline weight was analysed with a logistic regression model, which included the same fixed effects and covariates as for the primary analysis. We assessed superiority of each liraglutide dose to placebo (primary objective) and to orlistat (secondary objective), and made adjustments for multiplicity with Bonferroni correction. We did a post-hoc logistic regression analysis of the probability of having prediabetes status equal to normal glucose tolerance in both fasting plasma glucose and OGTT after 20 weeks. The model included sex and baseline prediabetes status as fixed effects. Analyses were done with SAS (version 8.2). This study is registered at ClinicalTrials.gov, number NCT00422058.

Role of the funding source

The sponsor participated in discussions regarding study design and protocol development, and provided logistical support during the trial. The sponsor obtained the data, which were assessed jointly by the authors and the sponsor. The authors interpreted the data, and wrote the report together with medical writing services provided by the sponsor. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

135 men and 429 women (n=564) were randomly assigned and 472 (84%) completed the trial (figure 1). Three individuals treated with liraglutide (1·2 mg, 2·4 mg, and 3·0 mg) were excluded from the intention-to-treat population because of missing post-baseline weight data. Major protocol deviations, not necessarily leading to withdrawal from study, included non-compliance with eligibility criteria (n=3), assessments at week 20 outside visit window (n=12), treatment compliance issues (n=7), and trial drug dispensing errors (n=1); these people were included in the intention-to-treat population but excluded from the completer population.

Baseline characteristics at randomisation were comparable across treatment groups (table 1). Included in the trial were 20 individuals (<4%) classified as having a glucose concentration at randomisation in the range of type 2 diabetes mellitus, which had developed since screening.

Weight loss from screening during the study is shown in figure 2. The estimated mean weight loss in the intention-to-treat population from randomisation to week 20 was significantly greater with liraglutide (all doses) than with placebo, and was dose-dependent, ranging from 4·8 kg to 7·2 kg (table 2). The completer population lost slightly more weight than did the intention-to-treat population (data not shown). Mean waist circumference at week 20 was lower with liraglutide 2·4 mg and 3·0 mg than with placebo for women but not for men (table 2). Individuals lost a mean 1·3 kg (SD 1·4) across groups between screening and randomisation, which included the 2-week diet and placebo run-in period.

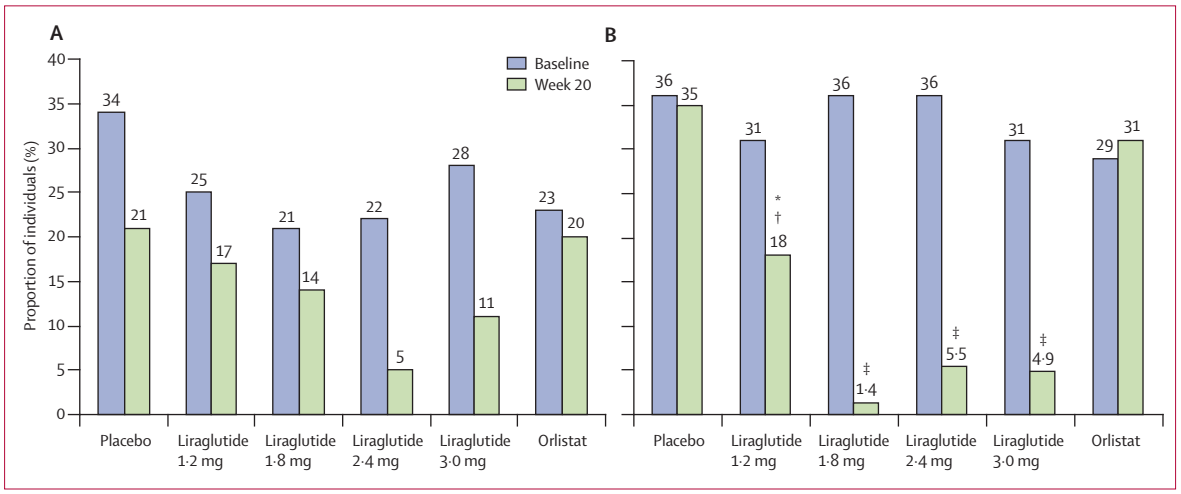

Figure 4: **Percentage of individuals with metabolic syndrome (A) and prediabetes (B) at randomisation and after 20 weeks of treatment**
Individuals included are those with valid assessment at the start and the end of the 20-week trial period. *p=0·007 *vs* placebo. †p=0·008 *vs* orlistat. ‡p≤0·0001 *vs* placebo or orlistat.

61% (n=224) of the individuals in the liraglutide treatment groups lost more than 5% weight from baseline, which was significantly more than that in the placebo group (odds ratio [OR] 2·6–7·3; figure 3). Furthermore, more individuals (76%, n=71) treated with liraglutide 3·0 mg lost more than 5% baseline weight than those treated with orlistat (44%, n=42; p<0·0001, OR 3·9). The proportion of people losing more than 10% of baseline weight was greater with liraglutide 3·0 mg (28%, n=26) than with placebo (2%, n=2), and was dose dependent. The proportion of people who lost no weight or gained weight during the trial was greater in the placebo group (22%, n=22) than in liraglutide treatment groups (2% [n=2] for 3·0 mg and 7% [n=7] for 1·2 mg). 34% (n=32) of individuals treated with liraglutide 3·0 mg moved from the obese into the overweight category, whereas only 23–25% treated with other active treatments and 11% (n=11) in the placebo group changed category.

Mean systolic and diastolic blood pressure decreased from randomisation to week 20 for all treatment groups (table 2). Changes in blood pressure from screening to week 20 are shown in table 3. Across groups, mean systolic blood pressure was reduced by 5·7 mm Hg (SD 11·0) in the 3-week period from screening to randomisation and mean diastolic blood pressure was reduced by 3·7 mm Hg (8·1).

To assess a potential bias in the results caused by the last observation carried forward approach, we did a supplementary prespecified repeated-measures analysis for changes in bodyweight, waist circumference, and blood pressure. This analysis showed similar results (data not shown).

Figure 4 shows the proportion of individuals with metabolic syndrome and prediabetes in the intention-to-treat population at randomisation and week 20. The proportion of patients with metabolic syndrome at week 20 decreased by more than 60% in those treated with liraglutide 2·4 mg and 3·0 mg. The reduction in the placebo group was 38% and in the orlistat group was 13%. The prevalence of prediabetes decreased by 84–96% with liraglutide 1·8 mg, 2·4 mg, and 3·0 mg liraglutide. In a post-hoc analysis, liraglutide-treated individuals had greater probability of having normal glucose tolerance at week 20 than did those taking placebo or orlistat (p<0·01 all doses). The estimated odds were between 4 and 38 for liraglutide, and 1·5 for placebo or orlistat.

Data for fasting lipids, cardiovascular biomarkers, and glucose parameters in non-diabetic individuals were not obtained at screening but only at randomisation 3 weeks later; therefore, data did not capture any change caused by weight loss during the 2-week run-in period. The webappendix shows changes in fasting lipid parameters and cardiovascular biomarkers. We did not see any substantial effect of liraglutide treatment on any parameter.

See **Online** for webappendix

Mean fasting plasma glucose at randomisation ranged from 5·3 to 5·4 mmol/L across groups and decreased by 7–8% at week 20 with liraglutide (mean change was –0·39 mmol/L [SD 0·45] for liraglutide 1·2 mg, –0·44 mmol/L [0·63] for 1·8 mg, –0·38 mmol/L [0·48] for 2·4 mg, and –0·44 mmol/L [0·44] for 3·0 mg), in addition to the diet and exercise programme. Placebo or orlistat treatment had no visible effect on mean fasting plasma glucose (mean change was –0·09 mmol/L [SD 0·54] and –0·10 mmol/L [0·41], respectively). Mean fasting insulin decreased with liraglutide 3·0 mg (–14·8 pmol/L [SD 49·8]), placebo (–22·1 pmol/L [119·6]), and orlistat treatment (–12·2 pmol/L [58·0]) after 20 weeks compared with that at baseline. Although insulin seemed to increase initially for all liraglutide groups, it subsequently decreased during the trial period. After 20 weeks, mean fasting insulin was almost at baseline levels for liraglutide 1·8 mg

	Placebo (n=98)	Liraglutide				Orlistat (n=95)
		1·2 mg (n=95)	1·8 mg (n=90)	2·4 mg (n=93)	3·0 mg (n=93)	
Overall withdrawal rate	19 (19%)	10 (11%)	16 (18%)	20 (22%)	11 (12%)	16 (17%)
Participants with AEs*	81 (82·7%), 221	81 (85·3%), 224	79 (87·8%), 280	84 (90·3%), 308	88 (94·6%), 314	81 (85·3%), 214
Participants with any SAE	1 (1·0%)	1 (1·0%)	4 (4·4%)	2 (2·2%)	1 (1·0%)	0
Withdrawals due to AEs	3 (3·1%)	4 (4·2%)	5 (5·6%)	9 (9·7%)	5 (5·4%)	3 (3·2%)

AE=adverse event. SAE=serious adverse event. *Presented as number of participants (%), number of events.

Table 4: **Safety data at week 20**

	Placebo (n=98)	Liraglutide				Orlistat (n=95)
		1·2 mg (n=95)	1·8 mg (n=90)	2·4 mg (n=93)	3·0 mg (n=93)	
Gastrointestinal disorders	30 (30·6%), 46	51 (53·7%), 90	54 (60·0%), 100	62 (66·7%), 133	66 (71·0%), 137	52 (54·7%), 78
Constipation	12 (12·2%), 13	14 (14·7%), 17	10 (11·1%), 10	16 (17·2%), 17	13 (14·0%), 13	6 (6·3%), 6
Diarrhoea	7 (7·1%), 7	8 (8·4%), 12	9 (10·0%), 12	12 (12·9%), 12	12 (12·9%), 13	24 (25·3%), 30
Nausea	5 (5·1%), 5	23 (24·2%), 26	28 (31·1%), 29	34 (36·6%), 43	44 (47·3%), 57	4 (4·2%), 4
Vomiting	2 (2·0%), 2	4 (4·2%), 5	8 (8·9%), 12	13 (14·0%), 16	11 (11·8%), 13	2 (2·1%), 2
General disorders and administration-site conditions	11 (11·2%), 11	16 (16·8%), 18	16 (17·8%), 16	15 (16·1%), 17	24 (25·8%), 30	4 (4·2%), 4
Fatigue	2 (2·0%), 2	3 (3·2%), 3	5 (5·6%), 5	5 (5·4%), 5	10 (10·8%), 10	1 (1·1%), 1
Infections and infestations	41 (41·8%), 62	37 (38·9%), 42	42 (46·7%), 59	36 (38·7%), 53	40 (43·0%), 53	40 (42·1%), 50
Gastroenteritis	3 (3·1%), 3	4 (4·2%), 4	11 (12·2%), 17	6 (6·5%), 6	7 (7·5%), 8	9 (9·5%), 9
Nasopharyngitis	15 (15·3%), 19	11 (11·6%), 11	10 (11·1%), 11	17 (18·3%), 21	9 (9·7%), 10	9 (9·5%), 11
Injury, poisoning, and procedural complications	8 (8·2%), 8	6 (6·3%), 6	9 (10·0%), 10	6 (6·5%), 7	6 (6·5%), 6	13 (13·7%), 14
Metabolism and nutrition disorders	11 (11·2%), 11	8 (8·4%), 8	6 (6·7%), 8	8 (8·6%), 8	11 (11·8%), 11	6 (6·3%), 8
Musculoskeletal and connective-tissue disorders	21 (21·4%), 27	11 (11·6%), 12	17 (18·9%), 23	15 (16·1%), 17	12 (12·9%), 13	14 (14·7%), 14
Nervous system disorders	21 (21·4%), 25	16 (16·8%), 19	15 (16·7%), 22	21 (22·6%), 25	19 (20·4%), 22	13 (13·7%), 17
Headache	12 (12·2%), 14	11 (11·6%), 13	7 (7·8%), 10	14 (15·1%), 17	12 (12·9%), 12	10 (10·5%), 14
Skin and subcutaneous-tissue disorders	5 (5·1%), 6	5 (5·3%), 5	9 (10·0%), 11	7 (7·5%), 8	6 (6·5%), 8	3 (3·2%), 3

Data are number of participants (%), number of adverse events.

Table 5: **Adverse events with an incidence of 10% or more in any treatment group, by system organ class and preferred term**

and 2·4 mg, and was above baseline with liraglutide 1·2 mg (+8·7 pmol/L [SD 103·2]).

Mean HbA_{1c} in individuals treated with liraglutide was slightly reduced compared with that in individuals on placebo and orlistat at week 20. The reduction seemed to be dose dependent, ranging from 0·14% (SD 0·21) with liraglutide 1·2 mg to 0·24% (0·29) with 3·0 mg. Mean change in plasma glucose during OGTT at week 20 decreased for all liraglutide groups compared with that for placebo and orlistat, but the effect did not seem to be dose dependent. Plasma insulin and C-peptide during OGTT did not substantially change with liraglutide treatment. Median β-cell function (as assessed by HOMA) decreased at week 20 with placebo and orlistat treatment by 17% and 21%, respectively (median change –21·3% and –25·8%), but increased with liraglutide treatment by 5–24% (median change 21·4% for 1·2 mg, 27·5% for 1·8 mg, 8·4% for 2·4 mg, and 6·9% for 3·0 mg). Liraglutide treatment did not have any effect on insulin resistance as assessed by HOMA.

Regarding quality of life, scores for physical function, self-esteem, and work improved more with liraglutide and orlistat treatment (in addition to diet and exercise) than with placebo after 20 weeks. Treatment with liraglutide 3·0 mg improved mean physical function by a score of 6·8 compared with placebo (95% CI 3·2–10·4; p=0·001) and by a score of 6·0 compared with orlistat (2·3–9·7; p=0·006). Mean self-esteem was also improved with liraglutide 3·0 mg by a score of 9·6 compared with placebo (5·3–14·0; p=0·0001) and by a score of 6·2 compared with orlistat (1·5–10·9; p=0·04). Liraglutide 3·0 mg also significantly improved mean work score by 5·6 compared with placebo (1·6–9·5; p=0·02). We did not see any significant effect of other liraglutide doses on physical function, self-esteem, or work, and of liraglutide on sexual life or public distress.

Adverse events include those reported from randomisation and any events worsening from screening. Overall frequency of adverse events was slightly higher

with liraglutide 1·8 mg, 2·4 mg, and 3·0 mg than with placebo, orlistat, and liraglutide 1·2 mg (table 4). Adverse events occurring in at least 10% of individuals in any group are shown in table 5. More than twice as many people reported gastrointestinal events with liraglutide doses greater than 1·2 mg than with placebo. The most common events with liraglutide treatment were nausea and vomiting, which occurred seven times more frequently with liraglutide 2·4 mg and 3·0 mg than with placebo. These events were mostly transient and of mild or moderate intensity, and event frequency increased with dose. Most nausea events (80%) developed within the first 4 weeks of the trial during dose titration (figure 5). Similarly, more than 50% of vomiting events occurred within the first 4 weeks. Vomiting was reported by 4·2–14·0% of liraglutide-treated individuals. Those taking orlistat also had more gastrointestinal side-effects than did those taking placebo; and about twice as many individuals taking orlistat reported diarrhoea events compared with those taking liraglutide 2·4 mg and 3·0 mg.

There were eight people in the liraglutide groups who withdrew (2·2%) because of nausea and five (1·3%; in the 2·4 mg and 3·0 mg groups) because of vomiting. Nobody in the placebo or orlistat groups withdrew because of such events. Nine individuals had ten serious adverse events (table 4). No specific events were more frequent in the liraglutide group than in the other groups.

Psychiatric disorders were slightly more frequent in people treated with liraglutide 2·4 mg (seven events in six people) and 3·0 mg (ten events in eight people) than in those on placebo (four events in four people)—most commonly insomnia (six events), depressed mood (three events), and nervousness (two events). Other psychiatric disorders, such as depression and anxiety, were reported by no more than two people in any group, including placebo and orlistat. Two participants withdrew from the trial because of anxiety (placebo) and food aversion (liraglutide 1·2 mg). No serious psychiatric disorders were reported.

Mean pulse rate was slightly increased with liraglutide treatment (by up to 4 beats per min) compared with placebo or orlistat. Cardiovascular adverse events were infrequent and were predominantly mild palpitations reported by 1–4% of liraglutide-treated individuals. However, one woman (aged 51 years) had atrial fibrillation after 140 days of treatment with liraglutide 3·0 mg. No serious cardiovascular events were reported.

Serum calcitonin concentrations were measured because of C-cell tumour findings in rodent carcinogenicity studies with liraglutide (Novo Nordisk, unpublished). We did not see any significant effect of liraglutide treatment. Concerns exist of a potential association between GLP-1 analogues and acute pancreatitis;[16] no events of pancreatitis were reported over the 20-week trial period.

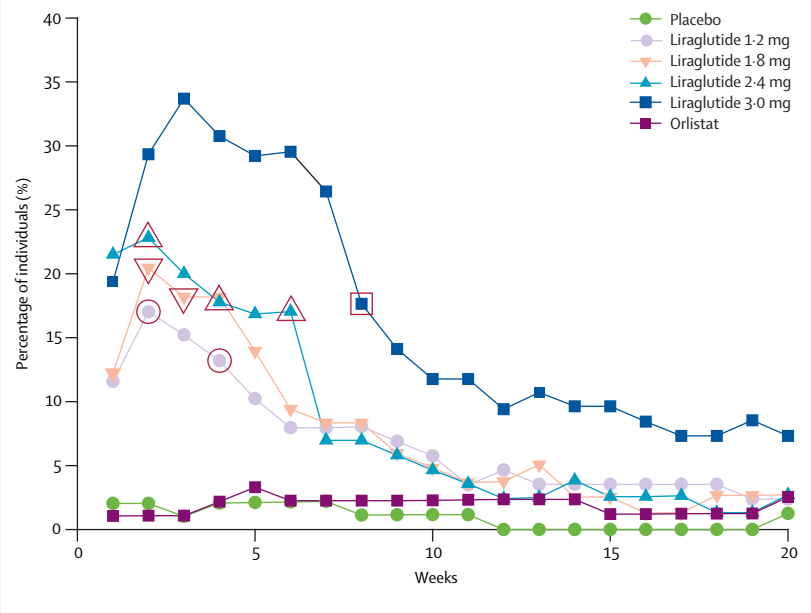

Figure 5: **Percentage of individuals with nausea during the 20-week trial period**
Each individual who withdrew because of nausea is shown by a red symbol.

Discussion

Treatment with liraglutide, in addition to an energy-deficit diet and exercise programme, led to a sustained, clinically relevant, dose-dependent weight loss that was significantly greater than that with placebo (all doses) and orlistat (*vs* liraglutide 2·4 mg and 3·0 mg). Mean weight loss with liraglutide 3·0 mg was 7·2 kg. Weight loss was accompanied by reductions in waist circumference, systolic and diastolic blood pressure, and frequency of both metabolic syndrome and prediabetes. Liraglutide was generally well tolerated. However, nausea and vomiting were more frequent with liraglutide than with the other treatments, although these events were mostly transient and of mild or moderate intensity.

76% of individuals treated with liraglutide 3·0 mg lost more than 5% weight, and almost 30% lost more than 10% weight after 20 weeks of treatment. More than 50% of participants treated with liraglutide achieved the target of 5–10% weight reduction (moderate weight loss), which might have a beneficial effect on cardiovascular risk factors and mortality.[40,41] The result of the repeated-measures analysis was very similar to that of the last observation carried forward approach, probably because a similar pattern of withdrawals was seen in all groups. Similarly, weight loss was also indicated by the fact that weight loss in the completer population was only slightly (between 0·3 kg and 1·1 kg) greater than in the intention-to-treat population. Although individuals were not selected for hypertension, mean systolic blood pressure decreased by up to 8·8 mm Hg from randomisation and diastolic blood pressure also decreased. We did not see any effects on

fasting lipid concentrations. This finding could be explained by the fact that lipid concentrations were not measured at screening but only at randomisation 3 weeks later, so changes in lipid parameters do not take into account the introduction of diet and a mean weight loss during the run-in period of 1·3 kg. The weight loss most likely affected fasting lipids and other metabolic parameters; both systolic and diastolic blood pressure were reduced substantially (by 5·7 and 3·7 mm Hg, respectively) in the 3-week period. Previous trials have shown no consistent changes in lipid parameters with liraglutide in patients with type 2 diabetes, although triglycerides decreased significantly with liraglutide 1·9 mg over 14 weeks.[11] Furthermore, in the trial with exenatide over 26 weeks, both triglycerides and free fatty acids significantly decreased with 1·8 mg liraglutide.[16] Lipid results for other weight-reducing agents have been variable.[42]

Rates of prediabetes—a strong predictor of type 2 diabetes—and metabolic syndrome decreased greatly with liraglutide 2·4 mg and 3·0 mg. The reduction in prediabetes rate was accompanied by reductions in mean fasting plasma glucose concentration, glucose concentration during OGTT, and HbA_{1c}. However, these reductions do not account for any changes in glucose parameters during the 2-week run-in period. Fasting insulin concentrations initially increased from randomisation, but as glucose concentrations and body-weight decreased, insulin gradually decreased, indicating the glucose-dependent effect of liraglutide in increasing insulin secretion. Liraglutide treatment had a positive effect on several risk factors for cardiovascular disease, including obesity, prediabetes, and metabolic syndrome, as well as its associated parameters such as waist circumference and blood pressure. In the current trial, orlistat had no substantial effect on the rate of either metabolic syndrome or prediabetes, possibly because of a lack of power of the study to detect such an effect, although in the XENDOS study[42] it reduced the incidence of type 2 diabetes over 4 years.

Liraglutide was generally well tolerated. The injection regimen did not seem to impair adherence, and compliance was similar across treatment groups. Overall, injection-site symptoms occurred in less than 7% of participants, notably less than those observed with recombinant leptin administration.[43] Gastrointestinal adverse events, especially nausea and vomiting, were more frequent with liraglutide than with placebo. These events were mostly transient, and most of the people withdrawing (n=8) because of nausea did so within the first 4–5 weeks of the trial. These withdrawals were not the reason for the decline in nausea over time (figure 5). Gastrointestinal adverse events are also commonly reported with other weight-loss agents.[42] Although liraglutide treatment increased pulse rate, as observed previously,[10] the clinical relevance of this effect is unclear. Some evidence shows that GLP-1 might have beneficial effects on the myocardium and on endothelial function.[44] Although liraglutide might increase heart rate through a thermogenic effect, this effect has not been supported by a short-term study in type 2 diabetics,[45] which did not show any effect of liraglutide on 24-h energy expenditure. However, liraglutide might cause vasodilation mediated by the stimulation of postprandial insulin; the increase in heart rate might be a secondary effect. Also, liraglutide treatment has not led to an increase in cardiovascular events in patients with type 2 diabetes; rather, improvements in certain cardiovascular risk markers (the inflammatory biomarker plasminogen activator inhibitor-1 and B-type natriuretic peptide, a marker of left ventricular dysfunction) have previously been observed,[44] in addition to the blood pressure lowering effects. Liraglutide did not have substantial effects on cardiovascular risk markers in the non-diabetic obese participants in this study, although changes in these parameters during run-in were not taken into account.

A limitation with the current study is that, for obvious drug-administration reasons, the orlistat treatment was open-label, thus introducing a potential for bias. The long-term effects of liraglutide on bodyweight, lipids, cardiovascular risk factors, and mortality, and its potential for prevention of diabetes, need to be addressed in future long-term clinical studies, including the 84-week extension follow-up of this study, and in obese diabetic individuals. In patients with type 2 diabetes, a weight loss of 2·4 kg and 2·7 kg was maintained over 52 weeks and 2 years, respectively, with liraglutide 1·8 mg.[10,46] Phase 3 studies with liraglutide at a dose of 3·0 mg are currently planned or underway.

Overall, the results of this study indicate the potential benefit of liraglutide, in conjunction with an energy-deficit diet, in the treatment of obesity and associated risk factors. Liraglutide offers a new mode of action for the treatment of obesity and improved efficacy compared with currently available therapies. Its effect on prediabetes suggests that it might be important for treating obese prediabetic individuals. Although liraglutide improved several factors associated with cardiovascular events over 20 weeks, which are regarded as more clinically relevant than weight loss per se,[42] the long-term risk–benefit profile for liraglutide, as well as its weight maintenance capabilities, remain to be established.

Contributors

AA, LVG, MFR, and MEJL participated in the concept and design of the study. AA, SR, LVG, AR, LN, MAH, and MEJL were major contributors of clinical data and patients. AA, SR, LVG, AR, LN, JM, MFR, and MEJL contributed to the analysis and interpretation of data. All authors participated in the revision of the report and approved the final version.

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Conflicts of interest

Liraglutide is a Novo Nordisk proprietary compound under development. AA has held paid lectures and commercially-sponsored research for Novo Nordisk and Neurosearch, and is an advisory board member for both. SR has held paid lectures and commercially-sponsored research for Novo Nordisk. LVG is an advisory board member for Novo Nordisk and Eli Lilly. AR is an advisory board member and has done commercially-sponsored research for Novo Nordisk. LN has held paid lectures and commercially-sponsored research for Eli Lilly, Merck, Novo Nordisk, Boehringer Ingelheim, AstraZeneca, Sanofiaventis, Bristol-Myers Squibb, Pfizer, and Janssen-Cilag, and is an advisory board member for Novo Nordisk, Novartis, and AstraZeneca. MAH and MEJL have done commercially-sponsored research for Novo Nordisk. JM and MFR are employees of Novo Nordisk and MFR owns stock in Novo Nordisk.

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