2 Synopsis

Trial Registration ID-number	**EudraCT number**
NCT00422058	2006-004481-13

Title of Trial

Effect of liraglutide on body weight in obese subjects without diabetes: a 20-week randomised, double-blind, placebo-controlled, six-armed parallel-group, multi-centre, multinational trial with an open label orlistat comparator arm.

Investigators

[redacted] (signatory investigator) and 18 other principal investigators.

Trial Sites

19 sites in 8 countries: Denmark (3), Sweden (2), Finland (3), UK (3), Netherlands (1), Belgium (1), Spain (4) and Czech Republic (2).

Publications

None.

Trial Period	**Development Phase**
10 January 2007 to 13 September 2007	Phase 2b

Objectives

Primary Objective:

- To investigate the efficacy of liraglutide to induce weight loss

Secondary Objectives:

Efficacy

- To establish the dose-response relationship of 4 doses of liraglutide and placebo on weight loss
- To compare the weight-lowering effect of liraglutide to orlistat
- To investigate the effects induced by liraglutide on:
  - Body composition
  - Cardiovascular risk factors
  - Glucose metabolism including β-cell function
  - Presence of the metabolic syndrome
  - Patient reported quality of life

Safety

- To evaluate the safety and tolerability of 4 doses of liraglutide

In a Subset of Subjects

- To investigate the effect of liraglutide on body composition assessed by dual energy x-ray absorptiometry (DEXA) and computerised axial tomography (CT) scan slices
- To investigate the effect of liraglutide on appetite sensations

Methodology

This was a 20-week, randomised, double-blind, placebo-controlled, six-armed parallel-group, multi-centre, multi-national trial including a parallel open-label orlistat comparator arm. Obese subjects without type 2 diabetes were selected as the trial population, since there is recognised need for new and effective therapeutic strategies to combat the obesity epidemic.

The duration of the trial from screening until completion of follow-up was up to 24 weeks for each subject, with a liraglutide/placebo/orlistat treatment duration of 20 weeks. The trial consisted of a screening visit (Visit 1), a 2-week single-blind placebo run-in period (Visit 2 to Visit 3), a 4-week dose escalation period (Visit 3 to Visit 7), a 16-week maintenance period (Visit 7 to Visit 12) and a post-trial follow-up visit (Visit 13), 4 to 10 days after Visit 12.

A planned total of 547 obese subjects without type 2 diabetes were to be randomised in a 1:1:1:1:1:1 manner to receive 1 of 4 doses of liraglutide (1.2, 1.8, 2.4 or 3.0 mg once daily), liraglutide placebo or orlistat (120 mg 3 times daily). Eligible subjects, according to inclusion and exclusion criteria, and those able to comply with the protocol

procedures, were randomised at Visit 3 into 1 of the 6 treatment arms using a telephone or web-based randomisation system. The starting dose of liraglutide was 0.6 mg/day; this was increased during the first 2-4 weeks after randomisation, by 0.6 mg increments, to the dose to be administered for the rest of the trial. At the time of randomisation, the subjects were also stratified according to gender. An open-label orlistat arm, representing an accepted obesity treatment, was included as reference treatment.

Laboratory samples for efficacy and safety analyses were taken at Visits 3, 7, 9, 10, 11, 12 and 13.

A planned total of 102 subjects (17 subjects per treatment arm) were to be enrolled in a sub-study, where body composition was measured using DEXA and CT scan at Visit 3 and Visit 12. Appetite sensations after intake of a standardised breakfast meal were also assessed by performing a meal test at Visit 3 and Visit 11.

Number of Subjects Planned and Analysed

It was planned to enrol a total of 547 obese subjects without type 2 diabetes. Subject disposition is given below:

	Placebo	**1.2 mg liraglutide**	**1.8 mg liraglutide**	**2.4 mg liraglutide**	**3.0 mg liraglutide**	**Orlistat**	**Total**
Screened							733
Randomised/exposed	98	95	90	93	93	95	564
Withdrawn	19	10	16	20	11	16	92
Adverse Events	3	4	5	9	5	3	29
Non-compliance	3	2	2	3	2	2	14
Ineffective therapy	2	1	1	0	0	1	5
Other	11	3	8	8	4	10	44
Completed	79	85	74	73	82	79	472
ITT analysis set	98	94	90	92	92	95	561
PP analysis set	96	91	87	88	88	88	538
Safety analysis set	98	95	90	93	93	95	564
Substudy analysis set	21	18	17	20	16	21	113

Diagnosis and Main Criteria for Inclusion

Main inclusion criteria: body mass index ≥ 30.0 and ≤ 40.0 kg/m^2; stable body weight; age between 18 and 65 yrs; fasting plasma glucose < 7.0 mmol/L.

Main exclusion criteria: untreated thyroid disease; obesity induced by drug treatment; use of approved weight-lowering pharmacotherapy within 3 months; participation in a weight control clinical trial within 3 months; previous surgical treatment of obesity; chronic malabsorption syndrome or cholestasis; known type 1 or type 2 diabetes; impaired liver or renal function; clinically significant active cardiovascular disease; uncontrolled treated/untreated hypertension; cancer.

Main withdrawal criteria on dosing day: non-compliance with protocol run-in period procedures.

Test Product, Dose and Mode of Administration, Batch Number

Active product liraglutide (6.0 mg/mL solution for injection) was administered by a daily subcutaneous injection in the abdomen or thigh in the evening before bedtime, using a 3 mL FlexPen® and Novofine® disposable needles. The doses of liraglutide after the 2-4 week dose-escalation period were 1.2, 1.8, 2.4 and 3.0 mg/day.

Batch numbers used in the trial were: SP51134 and SP51680.

Duration of Treatment

The planned duration of treatment was 20 weeks, consisting of a 2-4 week dose escalation period and a 16-week maintenance period. Mean actual duration of treatment ranged from 127 to 130 days across treatment arms.

Reference Therapy, Dose and Mode of Administration, Batch Number

Vehicle only placebo (solution for injection) was administered in the same way as active product. Batch numbers used in the trial were: SP51130 and TP50220 (vehicle only). Orlistat was provided as 120 mg capsules, to be taken 3 times daily with main meals. Batch numbers used were: M1360 and B2616.

Criteria for Evaluation – Efficacy

- Body measurements: weight, height and waist circumference
- Plasma glucose, insulin, C-peptide and liraglutide concentration during oral glucose tolerance test
- Fasting plasma glucose and HbA_{1c}
- Blood samples for assessment of fasting lipid profile
- Blood pressure
- Blood samples for assessment of biomarkers for cardiovascular risk
- Patient reported outcome (PRO) with the questionnaire Impact of Weight on Quality of Life-Lite

Sub-study Subjects

- Body composition using dual energy x-ray absorptiometry and computerised axial tomography scans
- Blood samples for the analysis of glucose and insulin during a meal test
- Appetite sensations determined by visual analogue scales after a standardised breakfast meal

Criteria for Evaluation – Safety

- Adverse events
- Clinical laboratory tests (haematology, biochemistry and liraglutide antibodies)
- Physical examination
- Vital signs
- ECG

Statistical Methods

Three population data sets were analysed. The modified intention to treat (ITT) analysis set included all randomised subjects exposed to at least one dose of trial product and with at least one post-baseline assessment of body weight (561 subjects in total). The per protocol (PP) analysis set included all exposed subjects who completed the 20-week treatment period without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy results, as well as non-violating early withdrawals (538 subjects in total). The safety analysis set included all randomised and exposed subjects (564 subjects in total).

All statistical tests carried out were two-sided and conducted at a 5% significance level unless otherwise stated.

The primary endpoint was change from baseline in body weight after 20 weeks of treatment. The statistical analysis of the primary endpoint was carried out by:

1. An analysis of covariance (ANCOVA) analysis applied to the last observation carried forward (LOCF) in the ITT population. Treatment, country and sex were included as fixed effects and baseline body weight as a covariate. The objective was to investigate whether the data gave evidence of superiority of each liraglutide dose to placebo (primary objective), and to orlistat (secondary objective).
2. An analysis of responder rates of subjects losing more than 5% compared to baseline weight using the LOCF in the ITT population. The analysis was carried out as a logistic regression model, including treatment, country, and sex as fixed effects, and baseline body weight as a covariate:
3. An ANCOVA analysis similar to analysis 1 above applied to the observed weight loss after 20 weeks of treatment in the PP population with a valid assessment of weight loss (an actual weight measurement) after 20 weeks.
4. Analysis of responder rates of subjects losing more than 5% compared to baseline weight in the PP population with a valid assessment of weight loss after 20 weeks of treatment, carried out as analysis 2 above.
5. A repeated measures analysis including all available data of body weight as dependent variables. Interactions between visits and the fixed effects 'treatment', 'sex' and 'country' were included in the model.

Secondary endpoints were change from baseline in the following measurements after 20 weeks of treatment:

- Waist circumference
- Cardiovascular risk markers (highly sensitive C-reactive protein, plasminogen activator inhibitor-1, fibrinogen and adiponectin)
- Fasting lipid profile (total cholesterol, low density lipoprotein, very low density lipoprotein and high density lipoprotein cholesterol, triglycerides, free fatty acids and apolipoprotein B)
- Blood pressure (systolic and diastolic)
- Fasting plasma glucose, insulin and HbA_{1c}
- Beta cell function and insulin resistance derived from the homeostasis model assessment method

- Change from 0 to 120 minutes in glucose, insulin and C-peptide, respectively, during oral glucose tolerance test
- Presence of the metabolic syndrome (ATP III criteria)
- Pre-diabetes status
- PRO scores of physical function, self-esteem, sexual life, public distress and work, assessed by means of the questionnaire Impact of Weight on Quality of Life-Lite

Change from baseline in waist circumference and blood pressure was analysed using the type of analyses 1, 3 and 5, described above for the primary analysis. The remaining endpoints were summarised by descriptive statistics only, except for pre-diabetes status (see **unplanned post-hoc analyses** below).

The analysis of overall PRO scores in each category were analysed as for analysis 3. For supportive evidence, a repeated measures analysis of the PRO scores was also carried out.

Secondary endpoints in a subset of subjects were change from baseline in the following after 20 weeks:

- Measurements from dual energy x-ray absorptiometry scan: whole body fat/lean mass, trunk fat/lean mass and calculated whole body/trunk fat percentage
- Measurements from computerised axial tomography scan: visceral/subcutaneous adipose tissue area, calculated visceral/subcutaneous adipose tissue ratio, liver/spleen attenuation ratio
- Measurements from the meal test (performed at Week 16): the area under the curve (AUC) from 0 to 240 minutes after initiation of the breakfast meal determined from the glucose and insulin concentration curves
- Weighted mean ratings (calculated as the AUC from 0 to 240 minutes after initiation of the breakfast meal divided by 240 min) for hunger, fullness, satiety, prospective food consumption, thirst, well being and nausea

For all sub-study endpoints, statistical analyses similar to those of the PRO scores, described above, were carried out.

Safety endpoints included:

- Adverse events
- Physical examination, pulse and ECG
- Clinical laboratory tests (haematology, biochemistry and liraglutide antibodies)

All of the safety endpoints, except calcitonin, were evaluated descriptively and no formal statistics were applied. For calcitonin, a repeated measures model was conducted.

Unplanned post-hoc analyses

A logistic regression analysis of the odds of having pre-diabetes status (normal glucose tolerance in both fasting plasma glucose and oral glucose tolerance test) after 20 weeks of treatment for subjects in the PP analysis set completing the trial was performed.

Demography of Trial Population

	Placebo n=98	1.2 mg liraglutide n=95	1.8 mg liraglutide n=90	2.4 mg liraglutide n=93	3.0 mg liraglutide n=93	Orlistat n=95
Sex, N (%)						
Male	24 (24.5)	22 (23.2)	22 (24.4)	22 (23.7)	23 (24.7)	22 (23.2)
Female	74 (75.5)	73 (76.8)	68 (75.6)	71 (76.3)	70 (75.3)	73 (76.8)
Age, yr; mean (SD)	45.9 (10.3)	47.2 (9.7)	45.5 (10.9)	45.0 (11.1)	45.9 (10.7)	45.9 (9.1)
Race, N (%)						
White	97 (99.0)	94 (98.9)	88 (97.8)	91 (97.8)	92 (98.9)	93 (97.9)
American Indian / Alaska Native	0	0	0	0	0	1 (1.1)
Black / African American	1 (1.0)	0	2 (2.2)	1 (1.1)	1 (1.1)	1 (1.1)
Other	0	1 (1.1)	0	1 (1.1)	0	0
Body mass index, kg/m^2; mean (SD)	34.9 (2.8)	34.8 (2.6)	35.0 (2.6)	35.0 (2.8)	34.8 (2.8)	34.1 (2.6)
Weight, kg; mean (SD)	97.3 (12.3)	96.2 (13.5)	98.0 (12.5)	98.4 (13.0)	97.6 (13.7)	96.0 (11.7)
Waist circumference (cm); mean (SD)	108.3 (10.0)	108.8 (10.4)	108.2 (9.5)	110.2 (10.7)	108.9 (8.3)	107.6 (9.7)
Blood pressure systolic (mmHg); mean (SD)	123.6 (11.1)	127.0 (13.1)	123.4 (13.0)	126.2 (13.9)	124.3 (11.3)	122.7 (13.5)
Blood pressure diastolic (mmHg); mean (SD)	76.8 (8.5)	79.7 (9.1)	77.9 (7.9)	78.6 (8.2)	77.8 (8.3)	76.9 (7.9)
HbA_{1c} (%);mean (SD)	5.60 (0.38)	5.58 (0.33)	5.60 (0.40)	5.54 (0.33)	5.57 (0.40)	5.55 (0.32)

Efficacy Results

- Results for the PP population were generally in agreement with those for the ITT population when statistical analyses were performed.

Primary Endpoint

Body Weight

- Treatment with liraglutide led in all 4 treatment arms to a significantly higher weight loss compared to placebo ($p<0.005$). The estimated mean weight loss appeared to be dose-dependent, ranging from 4.8 (1.2 mg liraglutide) to 7.2 kg (3.0 mg liraglutide) at Week 20 (ITT analysis set). This gave an additional estimated mean weight loss above placebo of between 2.1 kg (95% CI: -3.56; -0.56) and 4.4 kg (-5.95; -2.92).
- Treatment with liraglutide doses 2.4 and 3.0 mg led to a significantly greater mean weight loss compared to orlistat ($p<0.005$; estimated difference of 2.1 and 3.0 kg, respectively).
- Significantly more subjects lost >5% baseline weight during treatment with liraglutide (all doses) compared with placebo ($p<0.003$; odds ratio between 2.6 and 7.3). With the 2.4 mg liraglutide dose, about 60% subjects lost >5% baseline weight compared with about 76% subjects in the 3.0 mg group, 30% in placebo and 44% with orlistat treatment. Weight loss of >10% baseline occurred in about 23% subjects with 2.4 mg liraglutide, 28% with 3.0 mg, 2% in placebo and almost 10% in the orlistat treatment group.

Secondary Endpoints

Waist Circumference and Blood Pressure

- Treatment with 2.4 and 3.0 mg liraglutide led to a significant reduction in mean waist circumference compared with placebo ($p<0.005$) of 2.5 cm (95% CI: -4.49; -0.63) and 3.1 cm (-5.0; -1.23), respectively.
- Treatment with 2.4 mg liraglutide significantly reduced mean systolic blood pressure by 4.71 mmHg (95% CI:

-8.71; -0.70) compared with placebo after 20 weeks of treatment (p=0.015). Mean systolic blood pressure was reduced by 2.92 mmHg (95% CI: -6.95; 1.11) for 3.0 mg liraglutide compared with placebo, but the reduction was not significant (p=0.23). Mean systolic blood pressure reductions at Week 20 compared to baseline were greater across all liraglutide arms (range -5.63 to -8.84 mmHg) compared with both placebo (-4.04 mmHg) and orlistat (-5.40 mmHg).

- No significant effect of liraglutide treatment on mean diastolic blood pressure was observed.

Cardiovascular Biomarkers and Fasting Lipid Profile

- No effect of liraglutide treatment on cardiovascular biomarkers (highly sensitive C-reactive protein, plasminogen activator inhibitor-1, fibrinogen and adiponectin) or fasting lipid profile was apparent.

Glucose Metabolism Parameters, Beta Cell Function and Insulin Resistance

- Mean fasting plasma glucose was reduced by 7-9% at Week 20 compared to baseline for all liraglutide arms (LOCF); placebo or orlistat treatment had no apparent effect on mean fasting plasma glucose. Mean HbA_{1c} appeared to be slightly reduced compared to placebo at Week 20 for all liraglutide arms and the reduction seemed to be dose-dependent, ranging from 0.14% (1.2 mg liraglutide) to 0.24% (3.0 mg).
- Mean change in plasma glucose during OGTT at Week 20 appeared to be reduced for all liraglutide treatment groups compared to placebo and orlistat; there was no clear effect of liraglutide dose. No effect of liraglutide treatment was apparent with respect to mean changes in plasma insulin and C-peptide during oral glucose tolerance test at Week 20 compared to baseline.
- Median β-cell function (HOMA) was reduced at Week 20 with placebo and orlistat treatment by 17% and 21%, respectively, but was increased with liraglutide treatment by 5-24%; no dose effect was apparent. There was no apparent effect of liraglutide treatment on insulin resistance.

Pre-Diabetes and Metabolic Syndrome Status

- The percentage of subjects with pre-diabetes or diabetes at baseline who had shifted to normal at Week 20 was about double for subjects treated with 2.4 mg and 3.0 mg liraglutide (more than 85%) compared with both placebo and orlistat (about 45%). The odds of having normal glucose tolerance after 20 weeks of treatment was estimated to be between 4.2 and 37 for liraglutide compared to 1.5 for both placebo and orlistat; p<0.0125 in a post-hoc analysis.
- The percentage of subjects with metabolic syndrome status at baseline who had shifted to normal at Week 20 was more than 1½ greater with 2.4 and 3.0 mg liraglutide treatment (77 and 76%, respectively) compared with placebo (39%) and orlistat (47%).

Patient Reported Outcomes on Quality of Life

- With regard to quality of life, mean scores for physical function, self esteem and work tended to be increased to a greater extent with liraglutide and orlistat treatment compared with placebo after 20 weeks, corresponding to apparent improvements in these parameters. Treatment with 3.0 mg liraglutide significantly improved mean physical function score compared with both placebo (p=0.001) and orlistat (p=0.006). Treatment with 3.0 mg liraglutide significantly improved mean self esteem score compared with both placebo (p=0.0001) and orlistat (p=0.04). Treatment with 3.0 mg liraglutide also significantly improved mean work score compared with placebo (p=0.02). No statistically significant effect of other liraglutide doses on physical function, self esteem or work was observed and no significant effect of any dose on sexual life or public distress was noted.

In the Sub-study

Weight loss in the sub-study participants appeared greater than that observed in the overall trial population. This may impact the interpretation of the following results:

Body Composition

- Mean whole body fat mass, mean trunk fat mass and mean trunk fat percentage was reduced for all treatment groups compared to baseline and appeared to be reduced to a greater extent with liraglutide (and orlistat) treatment compared with placebo after 20 weeks of treatment. Mean whole body fat percentage also tended to be reduced for most liraglutide arms (and orlistat) compared with placebo. The observed differences were not statistically significant. Treatment with 1.8 mg and 2.4 mg liraglutide significantly reduced mean whole body lean mass compared with orlistat (estimated differences 1886 and 1662 g; p=0.015 and 0.029, respectively). Weight loss was predominantly from fat mass rather than from lean body mass for all treatment arms.
- Mean visceral and subcutaneous adipose tissue area was reduced for all treatment groups after 20 weeks of

treatment compared to baseline. Treatment with 2.4 mg liraglutide significantly reduced mean visceral adipose tissue area compared with placebo (p=0.046; estimated difference 18.7 cm^2; 95% CI: -37.05; -0.38). No other significant effects on mean visceral and subcutaneous adipose tissue area or on mean calculated visceral/subcutaneous adipose tissue ratio compared with placebo or orlistat treatment were observed. Mean liver/spleen attenuation ratio tended to increase from baseline to Week 20 for all treatment groups. Treatment with 1.8 mg liraglutide significantly increased mean liver/spleen attenuation ratio at Week 20 compared with both placebo (p=0.028; estimated difference 0.113; 95% CI: 0.0124; 0.2143) and orlistat (p=0.024; estimated difference 0.122; 95% CI: 0.0165; 0.2265). There was no significant effect of other liraglutide doses on mean liver/spleen attenuation ratio.

Meal Test and Appetite Sensations

- Treatment with 2.4, 1.8 and 1.2 mg liraglutide significantly reduced mean glucose $AUC_{0\text{-}240min}$ during meal test compared with placebo ($p<0.03$), by between 12 and 14%. Treatment with 3.0 mg liraglutide significantly reduced mean insulin $AUC_{0\text{-}240min}$ by approximately 25% compared with orlistat treatment (p=0.05). No other significant effects of liraglutide treatment on glucose or insulin $AUC_{0\text{-}240min}$ compared with placebo or orlistat were noted.
- In general, treatment differences for each subjective appetite parameter during the breakfast meal test at Week 16 compared to baseline were not great. No effect of liraglutide treatment on appetite parameters or nausea at Week 16 compared to either placebo or orlistat was observed.

Safety Results

Adverse Events

- Approximately 16% (92/564) subjects withdrew from the trial. Withdrawals due to treatment-emergent adverse events (29 subjects) were mostly due to gastrointestinal adverse events. Of these, the number of withdrawals in liraglutide arms was slightly greater (between 4 and 9 subjects) compared with placebo and orlistat (3 in each).
- The most common treatment-emergent adverse events were gastrointestinal disorders (584 events in 315 subjects); infections and infestations (319 events in 236 subjects); nervous system disorders (130 events in 105 subjects); and musculoskeletal and connective tissue disorders (106 events in 90 subjects). Of these, only gastrointestinal disorders appeared to be affected by liraglutide treatment. More subjects experienced gastrointestinal disorders across all active treatment groups compared with placebo.
- Approximately 50% of all treatment-emergent adverse events were rated probably or possibly related to trial drug.
- There were 10 treatment-emergent serious adverse events during the trial, for 9 subjects. Most of the serious adverse events (7/10) were considered unlikely to be related to treatment; all were of moderate or severe intensity. Of the 3 serious adverse events rated probably or possibly related to treatment, 2 occurred [redacted] in the 2.4 mg liraglutide arm (gastrointestinal disorders upper abdominal pain and vomiting, probably related) and 1 occurred in the 1.8 mg liraglutide arm (prostate cancer, possibly related). There were no serious adverse events in the orlistat treatment arm. There were no deaths during the trial.
- The most common gastrointestinal events were nausea, diarrhoea, constipation and vomiting. More events of nausea and vomiting occurred in liraglutide-treated subjects compared with placebo and orlistat. Event frequency tended to increase with dose, from 26 events in 23 subjects (1.2 mg liraglutide) to 57 events in 44 subjects (3.0 mg), compared with 5 events in 5 subjects (placebo).
- Most nausea events (80%) developed within the first 4 weeks of the trial during dose-escalation and all except 3 were of mild or moderate intensity. The majority (159/164 events) were possibly or probably related to treatment.
- The frequency of vomiting events with liraglutide treatment ranged from 5 events in 4 subjects (1.2 mg) to 16 events in 13 subjects (2.4 mg); there were 2 events for 2 subjects in placebo and orlistat groups. More than 50% events occurred within the first 4 weeks and all but 4 were of mild/moderate intensity. Most (45/50 events) were probably/possibly related to treatment.
- Diarrhoea events occurred with greatest frequency (30 events in 24 subjects) in the orlistat treatment arm, but were also slightly more frequent for subjects treated with liraglutide (up to 13 events in 12 subjects; 3.0 mg) compared with placebo (7 events in 7 subjects). All but 2 events were of mild/moderate intensity and most (73/86) were possibly/probably related to treatment.
- There were 7 treatment-emergent events of hypoglycaemia (symptoms only) in 7 subjects during the trial. One was in placebo, the remainder in subjects treated with liraglutide (3 in the 3.0 mg group). All hypoglycaemia events were rated as possibly/probably related to treatment. One event (1.8 mg liraglutide) was rated as severe; the

rest were mild or moderate.

- Two fasting plasma glucose values in the hypoglycaemic range (below 3.1 mmol/L) were recorded during the trial, in subjects treated with liraglutide 2.4 and 3.0 mg, respectively.

Clinical Laboratory Tests, Including Calcitonin

- No clinically relevant changes in haematology parameters were observed.
- There were 5 clinically significant abnormalities for biochemistry parameters related to clinical laboratory treatment-emergent adverse events possibly related to treatment, 3 in liraglutide-treated subjects. One subject (2.4 mg liraglutide) had abnormally high bilirubin concentrations [redacted]. Another (2.4 mg liraglutide) had abnormally high creatinine phosphokinase concentration at Visit only. One subject (3.0 mg liraglutide) had abnormally high creatinine phosphokinase concentration at Visits [redacted] No subjects were withdrawn from the trial as a result of the described abnormalities.
- Mean calcitonin concentration was reduced in all groups at Weeks 8 and 20 compared to baseline. No significant effect on calcitonin concentration of liraglutide treatment compared with placebo was observed.

Physical Examination, Pulse and ECG

- No marked treatment effects on physical examination or ECG were observed. Mean pulse-rate was slightly increased with liraglutide treatment (by up to 4 beats/minute) compared with placebo/orlistat.

Liraglutide Antibodies

- Two subjects had positive samples for liraglutide antibodies one week after end of trial; all tested negative for neutralising effects and cross-reactivity.

Conclusions

- Liraglutide exhibited a significantly greater weight loss compared with placebo at all doses (1.2, 1.8, 2.4 and 3.0 mg) over the 20-week period. The effect of liraglutide appeared to be dose-dependent, with mean weight loss ranging from 4.8 to 7.2 kg, which was between 2.1 and 4.4 kg more than that achieved in placebo. Liraglutide at 2.4 and 3.0 mg led to a significantly greater mean weight loss of 2.1 and 3.0 kg, respectively, compared to that observed with orlistat treatment. Significantly more liraglutide-treated subjects (60% and 76% for liraglutide doses 2.4 and 3.0 mg, respectively) lost >5% baseline weight compared with placebo (30%) and orlistat treatment (44%).
- Treatment with 2.4 and 3.0 mg liraglutide led to a significant reduction in waist circumference compared with placebo and, in a subset of subjects, visceral adipose tissue area was significantly reduced with 2.4 mg liraglutide compared with placebo.
- Treatment with 2.4 mg liraglutide significantly reduced systolic blood pressure compared with placebo. No effect of liraglutide treatment on cardiovascular risk markers was apparent.
- Mean fasting plasma glucose was reduced by 7-9% compared to baseline for all liraglutide arms; treatment with placebo or orlistat had no apparent effect. Beta-cell function was reduced with placebo and orlistat treatment by 17 and 21%, respectively, but was increased with liraglutide treatment by 5-24%; no obvious dose effect was apparent.
- A significantly greater number of subjects treated with liraglutide (more than 85% of subjects with pre-diabetes status at baseline dosed with 2.4 mg or higher) had an improvement in the chance of having normal glucose tolerance at Week 20 compared with placebo and orlistat (about 45%), in a post-hoc analysis. Conversely, approximately 20% of subjects dosed with orlistat or placebo developed pre-diabetes during the trial, compared with less than 5% for subjects treated with 2.4 or 3.0 mg liraglutide.
- The percentage of subjects with metabolic syndrome status at baseline who had shifted to normal at Week 20 appeared to be greater with 2.4 and 3.0 mg liraglutide treatment compared with placebo and orlistat treatment.
- Treatment with 3.0 mg liraglutide significantly improved patient reported physical function, self esteem and work scores compared with placebo.
- In the sub-study, no consistent effects of liraglutide treatment on appetite parameters or nausea during meal test compared with placebo or orlistat treatment were observed.
- Approximately 16% subjects withdrew from the trial in total, slightly more in liraglutide treatment arms compared with placebo and orlistat.
- More subjects experienced gastrointestinal disorders across all active treatment groups compared with placebo,

particularly nausea, diarrhoea, constipation and vomiting. More events of nausea and vomiting occurred in liraglutide-treated subjects compared with placebo and orlistat, and were possibly/probably related to treatment; frequency tended to increase with dose. Most nausea and vomiting events developed within the first 4 weeks of the trial, were transient in nature for doses up to and including 2.4 mg liraglutide and were of mild/moderate intensity.

- Of the 3 moderate/severe treatment-emergent serious adverse events rated probably or possibly related to treatment, 2 occurred [redacted] in the 2.4 mg liraglutide arm (upper abdominal pain and vomiting, probably related) and 1 occurred in the 1.8 mg arm (prostate cancer, possibly related).
- There were no apparent clinically relevant changes in haematology parameters and no marked treatment effects on physical examination or ECG. Mean pulse-rate was slightly increased with liraglutide treatment compared to treatment with placebo/orlistat. No obvious treatment-related change in calcitonin was observed during the trial.
- No major safety concerns were raised with this trial.

The trial was conducted in accordance with the Declaration of Helsinki (2000) and ICH Good Clinical Practice (1996).