2 Synopsis

Trial Registration ID-number NCT00480909 (extension to NCT00422058)	**EudraCT number** 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 with an 84 week extension period. *This synopsis covers the 52-week and 104-week periods*	
Investigators Professor [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 A manuscript based on the main trial has been published: Astrup et al., 2009 'Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study'. The Lancet 374: 1606-1616.	
Trial Period 20 June 2007 to 30 April 2009 (84-week extension period) 10 January 2007 to 30 April 2009 (104-week period) 10 January 2007 to 23 April 2008 (52-week period) 10 January 2007 to 13 September 2007 (20-week main period, reported separately)	**Development Phase** Phase 2b

Objectives (Extension)

As stated in the protocol and protocol amendments, the objectives relevant to the 84-week extension were as follows:

Primary Objective of the Extension (Week 21-104)

- To evaluate the long term safety and tolerability of liraglutide

Secondary Objectives of the Extension (Week 21-104)

- To summarise the long term efficacy of liraglutide to induce and maintain weight loss
- To summarise the effects induced by liraglutide on:
  - Waist circumference
  - Cardiovascular risk markers as assessed by blood pressure, lipids, cardiovascular biomarkers, Metabolic Syndrome status (ATP-III) and glucose metabolism (OGTT, insulin and HOMA).
  - Patient reported quality of life
  - Pre-diabetes status

Objectives (52-week Interim Analysis)

The following objectives were to be evaluated in the interim analysis:

Primary Objectives of the Interim Analysis (Week 21-52)

- To investigate the efficacy of liraglutide to induce weight loss

Secondary Objectives of the Interim Analysis (Week 21-52)

- To compare the weight lowering effect of liraglutide to orlistat
- To investigate the long term efficacy of liraglutide to induce and maintain weight loss
- To investigate the effects induced by liraglutide on:
  - Body composition as assessed by waist circumference
  - Cardiovascular risk factors as assessed by systolic and diastolic blood pressures and fasting lipid profile
  - Glucose metabolism, including beta-cell function, as assessed by pre-diabetes status
  - Presence of the metabolic syndrome as assessed using the criteria introduced by the Adult Treatment Panel III (ATP III) under the National Cholesterol Education Program (NCEP)

Safety Objectives of the Interim Analysis

To evaluate the long-term safety and tolerability of liraglutide

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 with an 84-week extension period. 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 obesity and its associated co-morbidities.

The duration of the trial from screening until completion of follow-up was up to 24 weeks for subjects completing the main trial with liraglutide, placebo or orlistat treatment (treatment duration of 20 weeks). For subjects participating in the extension period the total trial duration was up to 108 weeks (including the main trial). The main trial consisted of a screening visit (Visit 1), 2 weeks single-blind placebo run-in period (Visit 2 to Visit 3), 4 weeks dose escalation period (Visit 3 to Visit 7), 16 weeks maintenance period (Visit 7 to Visit 12) and a post-trial follow-up visit (Visit 13) four to ten days after Visit 12 for subjects not wishing to enter the extension period.

From 20–52 weeks, subjects and investigators remained blinded to liraglutide/placebo treatment but the sponsor was unblinded; after 52 weeks, all were unblinded. The extension period initially consisted of a further 32-week maintenance period on the medication to which the subjects were randomised (Visits 13a to 20) after which an interim analysis was made. This was followed by up to 4 weeks of unblinded dose escalation (Visits 20 to 22), 48 weeks of open-label treatment (Visits 23-34) and a post-trial follow-up visit (Visit 35). After Visit 20 (52 weeks), all subjects treated with liraglutide or placebo in the main trial and extension period were initially treated with liraglutide 2.4 mg in the open-label extension period, but were all gradually changed to treatment with liraglutide 3.0 mg as decided following discussion of the results of the 52-week interim analysis. Subjects treated with orlistat in the main trial continued unchanged during the extension period.

For the main trial, 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 (once daily) or orlistat (120 mg 3 times daily). The placebo arm was further subdivided into 4 arms with different injection volumes corresponding to the different doses of liraglutide. 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, Interactive Voice/Web Response System. In order to avoid bias, the trial was conducted as a double-blind trial; both investigator and subject knew the dose of trial drug, but not whether it was active (liraglutide) or placebo. 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. All subjects completing the main trial were offered to participate in an 84-week extension period.

Laboratory samples for efficacy and safety analyses were taken at Visits 3, 7, 9, 10, 11, 12 (main trial) and Visits 15, 18, 20, 24, 27, 30, 33, 34, and 35 (Extension period).

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
Enrolled in the extension	67	68	59	65	72	67	398
Exposed in the extension	67	68	59	65	72	67	398
Completed 52 weeks	62	61	55	58	65	55	356
Completed 104 weeks	47	46	38	45	47	45	268
Modified ITT analysis set (Interim)	98	94	90	92	92	95	561
PP analysis set (Interim)	96	91	87	88	88	88	538
Safety analysis set (Interim	98	95	90	93	93	95	564
Withdrawals until 20 weeks	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
Withdrawals until 52 weeks	24	17	20	27	18	28	134
Adverse Events	3	5	6	12	7	3	36
Non-compliance	3	2	3	3	2	3	16
Ineffective therapy	4	1	2	1	0	1	9
Other	14	9	9	11	9	21	73
Withdrawn in Extension period	20	22	21	20	25	22	130
Adverse Events	3	4	7	4	4	0	22
Non-compliance	1	2	3	1	5	3	15
Ineffective therapy	3	2	5	2	0	1	13
Other	13	14	6	13	16	18	80
Withdrawn (until 104 weeks)	39	32	37	40	36	38	222
Adverse Events	6	8	12	13	9	3	51
Non-compliance	4	4	5	4	7	5	29
Ineffective therapy	5	3	6	2	0	2	18
Other	24	17	14	21	20	28	124
Safety Analysis Set (Extension)	98	95	90	93	93	95	564
ITT Analysis Set (Extension)	98	94	90	92	92	95	561
PP Analysis Set (Extension)	97	93	87	88	89	83	537
PP Extension Completers	46	46	35	43	44	36	250

Diagnosis and Main Criteria for Inclusion

Main inclusion criteria: body mass index ≥ 30.0 and ≤ 40.0 kg/m2; stable body weight; age between 18 and 65 yrs; fasting plasma glucose < 7.0 mmol/L.

Main exclusion criteria: known type 1 or type 2 diabetes; 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; 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 FlexPen® (3 mL) 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 were: SP51134, SP51680, SP51466, TP51561 and VP50393

Duration of Treatment

The planned duration of treatment was 20 weeks in the main trial and up to a total of 104 weeks including the extension period.

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 (Tradenames: Xenical® and Alli®) was provided as 120 mg capsules, to be taken 3 times daily with main meals. Batch numbers used were: M1360, B2616, B2633, M1437, M1449, M1475 and B2626A.

Criteria for Evaluation – Efficacy

- Body measurements: weight 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

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 randomised and exposed subjects, who had signed informed consent, who had at least one assessment of efficacy results, and who did not significantly violate any of the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy results (537 subjects in total). Early withdrawals were included in the PP analysis if they were exposed, had at least one assessment of body weight and they – until time of discontinuation – did not significantly violate the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy results. The safety analysis set included all randomised and exposed subjects (564 subjects in total). For body weight, responders were defined as subjects with >5% body weight loss.

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

Safety Endpoints:

- 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 analyses of calcitonin levels, a repeated measures analysis after 52-weeks and a logistic regression testing after 104 weeks were applied.

Efficacy Endpoints:

Change in body weight, change in waist circumference and change in diastolic and systolic blood pressure was analysed by an ANCOVA applied to the last observation carried forward (LOCF) in the ITT population. The model included treatment, country, and gender as fixed effects, and baseline value of the variable in question as a covariate. For the end of 104 weeks statistical testing, only subjects randomised to liraglutide 2.4 mg, liraglutide 3.0 mg and orlistat were included and the two groups of liraglutide treated subjects were pooled into one treatment group. For each variable, the difference between treatment with liraglutide and orlistat in the mean change after 104 weeks of treatment was estimated and presented together with 95% confidence intervals and p-values.

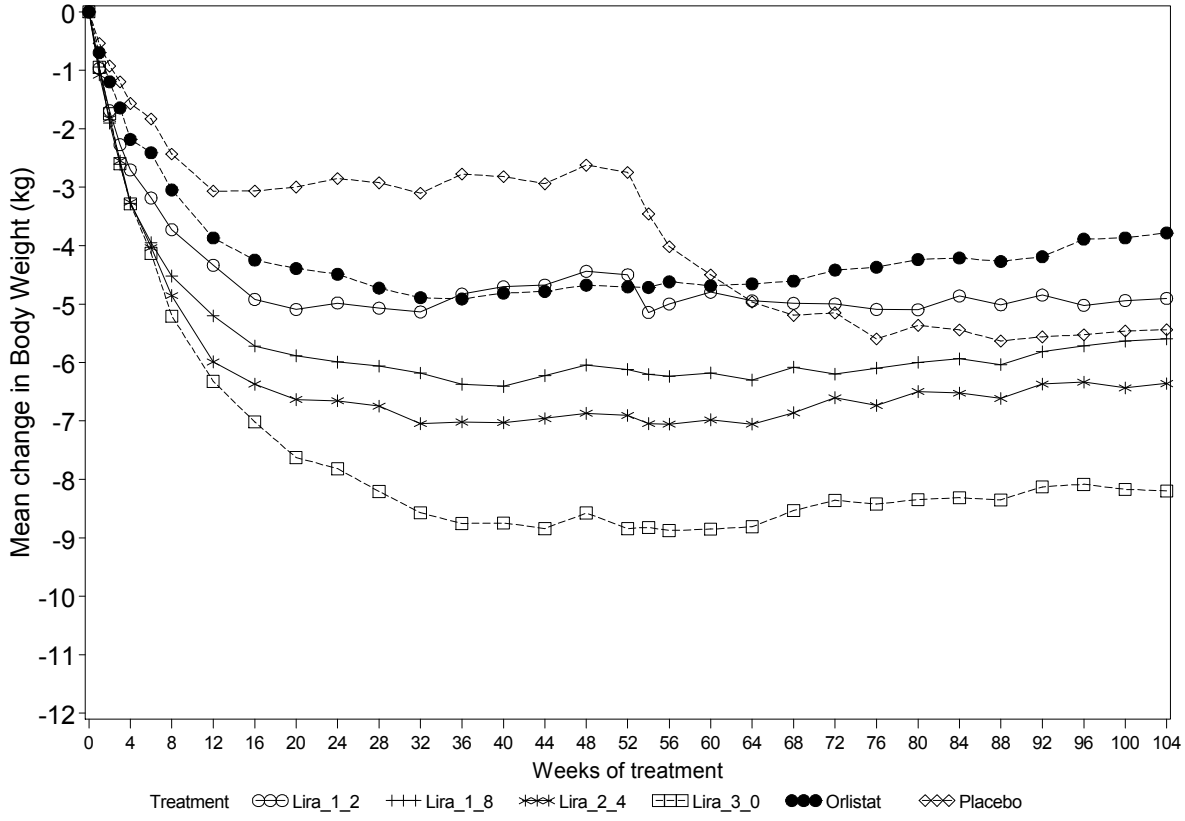
Demography of Trial Population at Baseline

	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

***Body Composition – Change in Body Weight*:**

- After 52 weeks, treatment with liraglutide (1.8-3.0 mg) led to a significantly greater weight loss compared to placebo. This gave an additional estimated mean weight loss with liraglutide compared to placebo of between 3.4 kg and 5.8 kg.
- After 52 weeks, treatment with liraglutide doses 2.4 and 3.0 mg led to a significantly greater mean weight loss compared to orlistat, estimated difference of 2.2 and 3.8 kg, respectively.
- After 52 weeks, estimated mean weight loss with liraglutide treatment appeared to be dose-dependent, ranging from 3.8 (1.2 mg liraglutide) to 7.8 kg (3.0 mg liraglutide).
- After 104 weeks, estimated treatment difference in body weight change for the high doses of liraglutide (subjects randomised to 2.4 and 3.0 mg liraglutide pooled) compared with orlistat was maintained at 3.0 kg after 104 weeks of treatment and an ANCOVA of change in body weight demonstrated a statistically significantly greater weight loss in subjects treated with the high doses of liraglutide (-5.32 kg) than subjects treated with orlistat (-2.33 kg). The results provided evidence of superiority of liraglutide over orlistat after 104 weeks of treatment. Change in body weight during the 104-week trial is presented below.



Note: Subjects randomised to placebo were transferred to treatment with liraglutide after week 52

Change in Body Weight, ITT (LOCF)

Body Composition - Responders

- After 52 weeks, significantly more subjects lost >5% baseline weight during treatment with liraglutide (1.8-3.0 mg) compared with placebo ($p<0.001$; odds ratio range from 3.0 to 7.8). With 3.0 mg liraglutide, 75% subjects lost >5% of their baseline weight, compared with 53% in the 2.4 mg group, 28% in placebo and 45% in the orlistat arm. Weight loss of >10% of baseline occurred in 37% subjects treated with 3.0 mg liraglutide and 29% subjects in the 2.4 mg group, compared with 10% in placebo and 16% in the orlistat group. Significantly more subjects in the 3.0 mg liraglutide group had lost 5% or more of their baseline weight and maintained this weight loss compared with those treated with orlistat ($p=0.0001$; odds ratio 3.7).
- After 104 weeks, between 44.7% and 64.1% of the subjects had lost and maintained 5% or more of their body weight at baseline with liraglutide compared with 32.6% of the subjects with orlistat and the odds ratio of losing more than 5% of the body weight at baseline with a high dose of liraglutide versus orlistat was more than 2.5. The results provided evidence of superiority of liraglutide (pooled group of subjects randomised to liraglutide 2.4 and 3.0 mg) over orlistat

Body Composition - Waist Circumference

- After 52 weeks, treatment with 2.4 and 3.0 mg liraglutide led to a significant reduction in estimated mean waist circumference compared with placebo ($p<0.001$) of 3.6 and 4.7 cm, respectively. Estimated mean waist circumference was reduced by >6 cm with 2.4 and 3.0 mg liraglutide
- After 104 weeks, estimated mean reduction in waist circumference was 6.2 cm for the subjects randomised to liraglutide 2.4 and 3.0 mg (pooled group) compared with subjects treated with orlistat with an estimated mean reduction of 4.5 cm; however no statistical significant treatment difference was observed

Cardiovascular Risk Factors

- At Week 52, mean systolic BP was reduced compared to baseline for all treatment groups. Treatment with 2.4 mg liraglutide significantly reduced mean systolic BP by 5.3 mmHg compared with placebo after 52 weeks of treatment ($p=0.005$). Treatment with 2.4 mg liraglutide also significantly reduced mean systolic BP by 4.7 mmHg compared with orlistat treatment. No significant effect of treatment was observed for other liraglutide doses compared with placebo or orlistat
- At Week 104, the estimated mean reduction in systolic blood pressure was 4.60 mmHg with liraglutide and 1.52 mmHg with orlistat, this difference was statistically significant ($p = 0.02$)
- No significant effect of liraglutide treatment on mean diastolic blood pressure was observed at either 52 or 104 weeks.
- No significant effects of treatment on fasting lipid profile for TC, LDL-C, HDL-C, VLDL-C, TG, FFA and ApoB compared to baseline was apparent at either 52 or 104 weeks
- No effect of liraglutide treatment on cardiovascular risk markers highly sensitive C-reactive protein, plasminogen activator inhibitor-1, fibrinogen or adiponectin compared to baseline was apparent at 104 weeks
- At week 104, during Oral Glucose Tolerance Test (OGTT), mean change in plasma insulin was increased from baseline in the liraglutide 1.8 mg group, while for all other groups mean change in plasma insulin was reduced compared to baseline. Mean change in plasma glucose was reduced in all treatment groups
- At Week 52 (and with the last observation carried forward), the percentage of subjects with metabolic syndrome at baseline who had shifted to normal was approximately 2 times greater with 2.4 and 3.0 mg liraglutide treatment (22/31 (71%) and 25/37 (68%), respectively) compared with placebo (15/46 (33%)), and was about 1.5 times greater than with orlistat treatment (16/34 (47%)).
- At Week 104 (with the last observation carried forward), the percentage of subjects who had metabolic syndrome at baseline but who had shifted to normal was 66 and 70% in subjects randomised to liraglutide 2.4 and 3.0 mg, respectively, and was similar with orlistat at 65%. The percentage was 67% in subjects randomised to placebo (treated with liraglutide after 52 weeks). Almost 6% of subjects randomised to the high dose liraglutide groups compared with 11% in the orlistat group developed metabolic syndrome over the 104-week period.

Pre-Diabetes Status

- At week 52, using ADA 2003 criteria with LOCF, the percentage of subjects who shifted from pre-diabetes status at baseline to normal status after 52 weeks was 70-80% with 1.8-3.0 mg liraglutide, more than double the percentage observed in the placebo (29%) and orlistat (32%) treatment arms. Subjects treated with liraglutide doses 1.8-3.0 mg had significantly improved odds of having normal glucose tolerance compared to both placebo and orlistat arms (estimated odds for liraglutide between 7 and 10 compared to 1 for both placebo and orlistat; $p<0.001$).
- At week 52, using WHO criteria, superiority of liraglutide doses 1.8-3.0 mg to both placebo and orlistat treatment groups was also demonstrated
- At week 104 week, with LOCF, the percentage of subjects with pre-diabetes at baseline who improved in pre-diabetes status (change from impaired glucose tolerance to normal glucose tolerance using the ADA 2003 criteria) was highest in the liraglutide 2.4 and 3.0 mg dose groups (16/26, 62% and 16/24, 67%, respectively) and placebo group (14/28, 50%, treated with liraglutide after 52 weeks) and lowest in the orlistat group (7/22, 32%).

Quality of Life

- At week 104, increases across all treatments were observed in patient reported outcome scores of physical function (11 items), self-esteem (7 items), sexual life (4 items), public distress (5 items), work (4 items) and total scores, indicating improvements in quality of life.

Safety Results

- Conclusions from the safety results after 52 weeks did not differ from the results after 104 weeks. A summary of adverse events from the entire treatment period (week 0 to week 104) is presented in the table below:

Summary of Treatment Emergent Adverse Events (Week 0 to Week 104) - Safety Analysis Set

	Placebo N (%) E	Liraglutide 1.2 mg N (%) E	Liraglutide 1.8 mg N (%) E	Liraglutide 2.4 mg N (%) E	Liraglutide 3.0 mg N (%) E	Orlistat N (%) E
Safety analysis set	98	95	90	93	93	95
Adverse events	90 (91.8) 684	90 (94.7) 642	87 (96.7) 682	89 (95.7) 763	90 (96.8) 755	89 (93.7) 624
Serious Adverse Events	6 (6.1) 6	9 (9.5) 9	10 (11.1) 11	7 (7.5) 10	10 (10.8) 15	6 (6.3) 6
Relation to Treatment						
Probable	33 (33.7) 67	35 (36.8) 57	25 (27.8) 44	33 (35.5) 68	38 (40.9) 58	39 (41.1) 51
Possible	63 (64.3) 153	57 (60.0) 142	68 (75.6) 175	67 (72.0) 187	78 (83.9) 219	52 (54.7) 103
Unlikely	83 (84.7) 464	82 (86.3) 443	76 (84.4) 463	72 (77.4) 508	82 (88.2) 478	78 (82.1) 469
Severity						
Mild	85 (86.7) 490	82 (86.3) 424	79 (87.8) 414	82 (88.2) 499	87 (93.5) 516	83 (87.4) 414
Moderate	64 (65.3) 183	68 (71.6) 199	67 (74.4) 253	70 (75.3) 243	76 (81.7) 216	62 (65.3) 196
Severe	11 (11.2) 11	15 (15.8) 19	11 (12.2) 15	17 (18.3) 20	15 (16.1) 23	10 (10.5) 13
Adverse Events Withdrawals	6 (6.1) 10	8 (8.4) 15	12 (13.3) 21	13 (14.0) 21	9 (9.7) 14	3 (3.2) 3

Adverse Events During the 104 Week Period

- The proportion of subjects reporting adverse events was comparable between liraglutide and orlistat and evenly distributed between the treatment groups with between 91.8% and 96.8% of the subjects reporting one or more adverse event across the groups. The most commonly reported adverse events across all groups were within the system organ classes of gastrointestinal disorders (mainly nausea in subjects randomised to liraglutide and diarrhoea in subjects randomised to orlistat), infections and infestations (mainly nasopharyngitis), musculoskeletal and connective tissue disorders (mainly back pain) and nervous system disorders (mainly headache). Adverse events with a possible or probable relation to trial drug were mainly nausea for subjects randomised to liraglutide and diarrhoea in subjects randomised to orlistat.
- The proportion of subjects with severe adverse events was slightly higher in subjects randomised to treatment with liraglutide (12.2% to 18.3%) than subjects randomised orlistat (10.5%) with no relation to dose.
- The proportion of subjects reporting serious adverse events was slightly higher in subjects randomised to treatment with liraglutide (7.5% to 11.1%) than in subjects randomised to orlistat (6.3%). Eight (8) serious adverse events were assessed as possibly or probably related to liraglutide treatment (diverticulitis, prostate cancer, non-cardiac chest pain, thyroglossal cyst, upper abdominal pain, abdominal pain, acute cholecystitis) and 1 serious adverse event was assessed as possibly related to orlistat treatment (cholelithiasis).
- A total of 51 subjects withdrew from the trial due to adverse events including SAEs (8 to 13 subjects in each liraglutide group, 6 subjects randomised to placebo and 3 subjects randomised to orlistat). This corresponds to 9% of all subjects randomised to treatment. Of these, 22 subjects (5.5%) withdrew due to adverse events during the extension. Four (4) subjects were withdrawn due to serious adverse events, all randomised to treatment with liraglutide.
- Medical events of special interest were defined as thyroid, pancreatitis, immunogenic, cardiovascular, neoplasm, psyciatric and hepatobiliary adverse events. Of these 7 were reported as SAEs: 1 event of acute pancreatitis, 1 event of anaphylactic reaction, 1 event of atrial fibrillation, 1 event of uterine leiomyoma, 1 event of adenocarcinoma (all during treatment with liraglutide and assessed as unlikely related to treatment). One (1) event

of prostate cancer and 1 event of breast cancer were assessed as probably related to liraglutide treatment.

- The percentage of subjects reporting psychiatric disorders were slightly higher in the liraglutide 2.4 and 3.0 mg groups (15.1 and 14.0 % of subjects, respectively compared with 8.4 to 11.2% of subjects across the other groups), while the number of events per reporting subject in these groups were comparable to the placebo and orlistat groups (approximately 1.3-1.5 event per subject). The majority of psychiatric disorders reported were stress, depression, depressed mood, insomnia and anxiety. All of the psychiatric disorder-TEAEs were non-serious, all were mild to moderate in severity, and the majority was assessed as unlikely related to treatment. In total 15 of the psychiatric TEAEs were assessed as probably or possibly related to treatment (treatment at the time of the event: 1 with placebo, 4 with orlistat, 1 with liraglutide 1.2 mg, 2 with liraglutide 1.8 mg, 6 with liraglutide 2.4 mg and 1 with liraglutide 3.0 mg).

Liraglutide Antibodies

- Positive liraglutide antibodies were reported by 7 subjects during the trial (6 randomised to liraglutide and 1 to orlistat). One subject randomised to liraglutide 1.2 mg showed liraglutide antibodies with a cross-reacting effect at the end of the trial (the subject was exposed to both liraglutide 2.4 mg and 3.0 mg during the open-label extension period).

Haematology and Biochemistry

- No obvious effect of liraglutide treatment was apparent for any haematology or biochemistry parameter during treatment.
- The majority of calcitonin assessments were below the upper normal limit during the 104-week trial period and no difference was observed between subjects randomised to orlistat and liraglutide (a pooled group of subjects randomised to liraglutide 2.4 mg and liraglutide 3.0 mg) from the logistic regression of change in calcitonin category.

Physical Findings, Pulse, ECG and Other Safety Parameters

- Mean pulse-rate ranged from 67 to 73 beats/minute across groups and was slightly increased with liraglutide treatment (by up to 6 beats/minute) compared to treatment with orlistat.
- The majority of subjects across treatment arms had normal ECGs at both screening and end of trial. A number of subjects in each group had abnormal, not clinically significant evaluations during the trial. No obvious treatment effect on ECG was apparent.
- Hypoglycaemic episodes were reported by 2 subjects randomised to placebo (of which 1 subject was treated with liraglutide at the time of the event) and 8 subjects randomised to liraglutide (1 episode each). None of the hypoglycaemic episodes fulfilled the criteria for a serious adverse event. Four FPG values below 3.1 mmol/L were recorded during treatment with liraglutide 2.4 mg and 1 during treatment with liraglutide 3.0 mg.

Conclusions

With this extension trial, long term safety and tolerability of liraglutide was examined in obese subjects without diabetes. As for the main double-blind period of this trial, no major safety concerns were raised with this extension period. The proportion of subjects with severe and serious adverse events and with psychiatric disorders was slightly higher with liraglutide than orlistat. At end of the trial pulse was slightly higher with liraglutide than orlistat, probably due to a slight decrease in the orlistat group during the trial. Liraglutide demonstrated a greater weight loss than orlistat and the odds of losing more than 5% of the body weight at baseline was more than 2.5 higher with liraglutide than orlistat, no difference was observed in change in waist circumference between liraglutide and orlistat. Systolic blood pressure was reduced to a greater extent with liraglutide compared with orlistat. The proportion of subjects with metabolic syndrome at randomisation who had shifted to normal by Week 104 was similar across all treatments, whilst a relatively low proportion of subjects developed the condition, indicating an overall decrease in the prevalence of metabolic syndrome across treatments. The proportion of subjects with an improvement in pre-diabetes status from baseline was larger with liraglutide than orlistat, whereas patient reported outcome in quality of life was improved with all treatments.

The trial was conducted in accordance with the Declaration of Helsinki (2000, amended 2002, and clarified on Paragraph 30 in 2004) and ICH Good Clinical Practice (1996).

The results presented reflect data available in the clinical database as of 08 April 2010.