# 2 Synopsis – Including CTR Amendment 1, Dated 28 May 2009

| **Trial Registration ID-number** | **EudraCT number** |
|---|---|
| NCT00318461 | 2005-003417-32 |

**Title of Trial**

Liraglutide Effect and Action in Diabetes (LEAD-2): Effect on glycaemic control after once daily administration of liraglutide in combination with metformin versus metformin monotherapy versus metformin and glimepiride combination therapy in subjects with type 2 diabetes. A six-month double-blind, double-dummy, randomised, active control, parallel-group, multi-centre, multi-national trial with an 18 months extension period.

*This report covers the 6-month double-blind confirmatory part of the trial.*

**Investigators**

A total of 171 principal investigators in 21 countries. Prof. Dr. [redacted]

**Trial Sites**

A total of 170 centres in 21 countries participated: AR (4), AU (19), BE (6), BG (1), DE (33), DK (9), ES (14), GB (11), HR (2), HU (5), IE (4), IN (5), IT (10), NL (5), NZ (3), NO (8), RO (3), RU (6), SE (8), SK (7), ZA (7)

**Publications**

None

| **Trial Period** | **Development Phase** |
|---|---|
| 30 May 2006 to 04 May 2007 | Phase 3a |

**Objectives**

**Primary Objective:**

- To assess and compare the effect on glycaemic control (as measured by $HbA_{1c}$) of once daily administration of three doses of liraglutide in combination with metformin versus metformin monotherapy versus metformin and glimepiride combination therapy in subjects with type 2 diabetes.

**Secondary Objectives:**

- To assess and compare the effect on body weight.
- To assess and compare the effect on glycaemic control (fasting plasma glucose [FPG] and 7-point plasma glucose profiles [self-measured]).
- To assess and compare β-cell function (fasting insulin, fasting pro-insulin, fasting C-peptide) and fasting glucagon. The homeostasis model assessment (HOMA) (Matthews et al. Diabetologia. 1985;28:412-9) will be used.
- To assess and compare lipid profiles (total cholesterol [TC], low density lipoprotein cholesterol [LDL-C], very low density lipoprotein cholesterol [VLDL-C], high density lipoprotein cholesterol [HDL-C], triglyceride [TG], free fatty acid [FFA], apolipoprotein B [ApoB]).
- To assess and compare the effect on blood pressure (BP).

**Safety Objectives:**

- To assess and compare incidences of hypoglycaemic episodes.
- To assess the safety and tolerability of liraglutide in combination with metformin.
- To assess the formation of liraglutide antibodies.

**Other Objectives:**

- To assess and compare cardiovascular effects (highly sensitive C reactive protein [hsCRP], plasminogen activator inhibitor-1 [PAI-1] and N-terminal B-type natriuretic peptide [NT-proBNP]).
- To assess and compare waist and hip circumference and waist-to-hip ratio.
- Additionally, for the subjects entering the extension treatment period the β-cell sparing effect will be assessed as the slope of increase in HbA1c per year after nadir and compared.

**Objectives (Continued)**

**In a Subset of Subjects:**

- Patient reported outcomes assessed by Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Impact of Weight on Quality of Life Questionnaire – Lite Version (IWQOL-Lite).
- To assess and compare body composition (including fat distribution assessed by DEXA and abdominal CT scan slices).

**Methodology**

This was a 6-month double-blind, double-dummy, randomised, active control, parallel-group, multi-centre, multi-national trial with an 18 months extension period investigating the safety and efficacy of liraglutide as add-on to metformin. This report covers the 6-month double-blind confirmatory part of the trial.

Subjects were randomised in 5 groups (2:2:2:1:2) to receive 0.6 mg once-daily liraglutide plus metformin (liraglutide 0.6 mg+metformin), 1.2 mg once-daily liraglutide plus metformin (liraglutide 1.2 mg+metformin), 1.8 mg once-daily liraglutide plus metformin (liraglutide 1.8 mg+metformin), metformin monotherapy (metformin) or glimepiride plus metformin combination therapy (glimepiride+metformin). At randomisation, subjects were stratified with respect to their previous treatment (oral antidiabetic drug [OAD] monotherapy or combination therapy). Randomisation took place after a metformin run-in period of 3 weeks followed by a metformin maintenance period of 3 weeks. During the run-in period, the dose level of metformin was increased up to 2000 mg/day. Subjects already on metformin therapy at enrolment could go through a modified titration period or advance directly to the metformin maintenance period at the discretion of the investigator.

After randomisation, subjects in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups underwent a 1-2 week period of forced titration with liraglutide for reaching the intended daily dose level. All subjects underwent a 3 week period of forced titration with glimepiride. After the titration period, a 23 week maintenance treatment period commenced, during which dose levels of liraglutide and glimepiride were fixed while the metformin dose level could be adjusted to between 1500 and 2000 mg/day at the discretion of the investigator in case of unacceptable hypoglycaemia or other adverse events. Liraglutide was administered as subcutaneous (s.c.) injections once daily (active or placebo). Glimepiride was to be taken orally once daily (active or placebo). Metformin was to be taken orally twice daily (open-label). For subjects not participating in the extension period, the 26 weeks of treatment were followed by a 1-week follow-up period and a follow-up visit.

**Number of Subjects Planned and Analysed**

A total of 1865 subjects with type 2 diabetes were planned to be screened in order to include 1118 subjects in the run-in period and to be able to randomise 1026 subjects. It was anticipated to reach 770 evaluable subjects after 6 months of treatment based on an estimated drop-out rate of 25%.

The actual subject disposition (including analysis sets) was as follows:

| | LIRA 0.6 + Met N (%) | LIRA 1.2 + Met N (%) | LIRA 1.8 + Met N (%) | Met N (%) | Met + Glim N (%) | Total N (%) |
|---|---|---|---|---|---|---|
| Screened | | | | | | 1662 |
| Screening failures | | | | | | 571 |
| Randomized | 242 (100) | 241 (100) | 242 (100) | 122 (100) | 244 (100) | 1091 (100) |
| Exposed | 242 (100) | 240 (99.6) | 242 (100) | 121 (99.2) | 242 (99.2) | 1087 (99.6) |
| Withdrawals | 34 (14.0) | 44 (18.3) | 51 (21.1) | 48 (39.3) | 34 (13.9) | 211 (19.3) |
| Adverse Events | 11 ( 4.5) | 23 ( 9.5) | 29 (12.0) | 2 ( 1.6) | 8 ( 3.3) | 73 ( 6.7) |
| Ineffective therapy | 19 ( 7.9) | 8 ( 3.3) | 13 ( 5.4) | 29 (23.8) | 9 ( 3.7) | 78 ( 7.1) |
| Non-compliance with protocol | 2 ( 0.8) | 4 ( 1.7) | 4 ( 1.7) | 4 ( 3.3) | 5 ( 2.0) | 19 ( 1.7) |
| Other | 2 ( 0.8) | 9 ( 3.7) | 5 ( 2.1) | 13 (10.7) | 12 ( 4.9) | 41 ( 3.8) |
| Completers | 208 (86.0) | 197 (81.7) | 191 (78.9) | 74 (60.7) | 210 (86.1) | 880 (80.7) |
| ITT analysis set | 242 ( 100) | 240 (99.6) | 242 ( 100) | 121 (99.2) | 242 (99.2) | 1087 (99.6) |
| PP analysis set | 194 (80.2) | 187 (77.6) | 181 (74.8) | 71 (58.2) | 202 (82.8) | 835 (76.5) |
| Safety analysis set | 242 ( 100) | 240 (99.6) | 242 ( 100) | 121 (99.2) | 242 (99.2) | 1087 (99.6) |

**Diagnosis and Main Criteria for Inclusion**

Male and female subjects diagnosed with type 2 diabetes, treated with OAD(s) for at least 3 months, aged 18-80 years inclusive (as allowed according to local guidelines for metformin and glimepiride treatment), body mass index (BMI) ≤ 40.0 kg/m$^2$ and $HbA_{1c}$ values of 7.0-10.0% (incl.) in subjects on OAD combination therapy and 7.0-11.0% (incl.) in subjects on OAD monotherapy.

**Test Product, Dose and Mode of Administration, Batch Number**

Liraglutide (6.0 mg/mL) in 3 mL FlexPen® (Batch nos. RP52008, SP51132 and SP52281) to be injected s.c. in the upper arm, abdomen or thigh. Daily liraglutide doses were 0.6 mg, 1.2 mg and 1.8 mg in the 3 liraglutide groups.
Glimepiride placebo capsules (Batch nos. PBBK034, PBBK035, PBBK036, PBBK037, PBBK038, PBBK041, PBBK042, PBBK071 and SBBK048) for once-daily oral administration.
Metformin tablets (500 mg) (Batch nos. 102525, 102526, 102602, 102803 and 102804) for oral administration. Daily metformin dose was 1500-2000 mg.

**Duration of Treatment**

A metformin run-in period of 3 weeks and a metformin maintenance period of 3 weeks followed by a 26-weeks treatment period during which all subjects underwent a 3 week period of forced titration with glimepiride and subjects in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups started with a 1-2 week period of forced titration with liraglutide for reaching the intended daily dose.

**Reference Therapy, Dose and Mode of Administration, Batch Number**

Liraglutide placebo in 3 mL FlexPen® (Batch nos. RP51969, SP51129, SP51130 and TP50221) to be injected s.c. in the upper arm, abdomen or thigh. Daily liraglutide placebo injection volumes were similar to the volumes of active liraglutide.
Glimepiride tablets (1 and 2 mg) in blinded capsules (Batch nos. E479, E407 and 40E524) for oral administration. Daily glimepiride dose was 1-4 mg during the 3-week titration period and 4 mg during the rest of the trial.
Metformin tablets (500 mg) (Batch nos. 102525, 102526, 102602, 102803, 102804) for oral administration. Daily metformin dose was 1500-2000 mg.

**Criteria for Evaluation – Efficacy**

$HbA_{1c}$, body weight, FPG, self-measured 7-point plasma glucose profiles, β-cell function (fasting insulin, fasting pro-insulin, fasting C-peptide), fasting glucagon, systolic and diastolic blood pressure, fasting lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, FFA and ApoB), cardiovascular biomarkers (hsCRP, PAI-1 and NT-proBNP), waist and hip circumference, patient reported outcome (in a subset of subjects), dual-energy X-ray absorptiometry (DEXA) scan (in a subset of subjects) and computerised tomography (CT) scan (in a subset of subjects).

**Criteria for Evaluation – Safety**

Adverse events, physical examination, pulse, electrocardiogram (ECG), opthalmoscopy, hypoglycaemic episodes and CT scan. Laboratory analyses of standard haematology, biochemistry and urine parameters, calcitonin, liraglutide antibody levels and pregnancy test.

**Statistical Methods**

**Analysis Sets**

- The intention to treat (ITT) analysis set was used for analyses of all efficacy endpoints and included all randomised subjects who had been exposed to at least one dose of the trial products.
- The per protocol (PP) analysis set was used for analysis of the primary endpoint and included all subjects who
  - had at least 151 days between first and last dose on randomised treatment.
  - had no protocol deviations with potential impact on the primary efficacy assessment
  - fulfilled the first three inclusion criteria (for $HbA_{1c}$ an extended range of ±0.25% was allowed)
  - fulfilled all randomisation criteria (for FPG an extended range of ±0.5 mmol/L was allowed)
  - did not meet any withdrawal criteria
  - had an evaluable $HbA_{1c}$ observation at Visits 3 and 10 collected within the allowed window (5 days before the visit until 7 days after the visit) and
- The safety analysis set included all randomised subjects who had been exposed to at least one dose of the trial products.

**Statistical Methods (Continued)**

**Primary Endpoint**

Change in $HbA_{1c}$ from baseline to end of treatment was analysed using an analysis of covariance (ANCOVA) model with treatment, country and previous anti-diabetic treatment as fixed effects and baseline $HbA_{1c}$ as covariate. Hypothesis testing was done in a hierarchical manner. First, it was tested whether liraglutide 1.8 mg+metformin was superior to metformin. If so, it was tested whether liraglutide 1.8 mg+metformin was non-inferior to glimepiride+metformin. If so, it was tested whether liraglutide 1.8 mg+metformin was superior to glimepiride+metformin. The same testing sequence applied for the 2 lower liraglutide dose levels. Furthermore, a given liraglutide dose level was only tested for superiority to metformin if the upper liraglutide dose level had shown non-inferiority to glimepiride+metformin. A test for superiority of glimepiride+metformin to metformin was also performed to verify assay sensitivity. Superiority was always concluded if the upper limit of the 2-sided 95% CI for the treatment difference was below 0%. Non-inferiority was concluded if the upper limit of the 2-sided 95% CI for the treatment difference was below 0.4%.

The following main effects and interactions were explored separately by adding them to the original model:

- Treatment by pre-treatment interaction (the main effect was in the original model)
- Treatment by country interaction (the main effect was in the original model)
- Main effect of gender as well as treatment by gender interaction
- Main effect of race as well as treatment by race interaction
- Main effect of age group (< 65 years and ≥ 65 years) as well as treatment by age group interaction
- Main effect of BMI group (BMI < 25 kg/m$^2$, 25 kg/m$^2$ ≤ BMI < 30 kg/m$^2$, 30 kg/m$^2$ ≤ BMI < 35 kg/m$^2$ and BMI ≥ 35 kg/m$^2$) as well as treatment by BMI group interaction

The proportion of subjects achieving $HbA_{1c}$ target (American Diabetes Association [ADA] target: < 7%; American Association of Clinical Endocrinologists [AACE] target ≤ 6.5%) was compared between treatments using a logistic regression model with treatment and baseline $HbA_{1c}$.

**Secondary Endpoints**

The key secondary endpoint, change in body weight, was analysed using the same model as for the primary endpoint. For each liraglutide dose level it was tested whether liraglutide plus metformin was different from glimepiride+metformin and metformin respectively. The following additional analyses related to body weight were performed:

- The impact of baseline BMI on change in body weight was analysed by including BMI group (BMI<25 kg/m$^2$; 25 kg/m$^2$≤BMI<30 kg/m$^2$;30 kg/m$^2$≤BMI<35 kg/m$^2$;BMI≥35 kg/m$^2$) as a fixed effect in the ANCOVA model.
- The weight loss responder rate after 26 weeks of treatment was categorised in 4 groups (]-∞;0%[, [0%; 5%[, [5%;10%[, [10%; ∞[) and summarised.
- The proportion of subjects achieving weight loss targets of weight loss ≥ 5% and weight loss ≥ 10% was compared between treatments using a logistic regression model with treatment as fixed effect and baseline BMI as covariate.
- The change in body weight was evaluated for different nausea subgroups.

FPG was analysed using the same approach as for body weight. Moreover, the proportion of subjects reaching the ADA target for FPG (5.0 ≤ FPG ≤ 7.2 mmol/L) was analysed using a logistic regression model with treatment as fixed effect and baseline FPG as covariate.

The following secondary endpoints were analysed using the same approach as for FPG:

- Prandial increments of plasma glucose and post-prandial plasma glucose based on self-measured 7-point plasma glucose profiles
- β-cell function (fasting insulin, fasting C-peptide, pro-insulin to insulin ratio and HOMA indices of β-cell function and insulin resistance)
- Fasting glucagon
- Systolic and diastolic blood pressure
- Fasting lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, FFA and ApoB)

**Statistical Methods (Continued)**

- Albumin to creatinine ratio in urine
- Waist circumference and waist-to-hip ratio
- Patient reported outcome (overall treatment satisfaction, perceived frequency of hyperglycaemia and perceived frequency of hypoglycaemia based on DTSQ status version and DTSQ change version and total score, physical function, self-esteem, sexual life, public distress and work based on IWQOL-Lite)
- DEXA scan (total body fat mass, lean mass and fat percentage and trunk fat mass, lean mass and fat percentage)
- CT scan (visceral adipose tissue area, subcutaneous adipose tissue area, visceral to subcutaneous adipose tissue ratio and liver to spleen attenuation ratio)

Summary and change from baseline in the cardiovascular effects hsCRP, PAI-1 and NT-proBNP were presented by week and treatment using descriptive statistics. For hsCRP and NT-proBNP, the changes from baseline were analysed using the standard ANCOVA model, while for PAI-1 the changes from baseline was analysed by nonlinear mixed modelling including subjects as random effects and allowing for left and right censoring.

The following endpoints were calculated at end of treatment and analysed using a chi square test:

- The proportion of subjects having 0, 1, 2 or 3 post-prandial glucose measurements < 10 mmol/L
- The proportion of subjects with diastolic blood pressure < 80 mmHg and systolic blood pressure < 130 mmHg
- The proportion of subjects reaching the ADA target for lipids (LDL-C < 2.6 mmol/L, TG < 1.7 mmol/L and HDL-C > 1.0 mmol/L)
- The proportion of subjects having metabolic syndrome

**Safety Endpoints**

The following safety endpoints were compared between treatment groups using descriptive statistics:

- Adverse events
- Physical examination
- ECG
- Ophthalmoscopy
- Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes and differential cell count)
- Biochemistry (creatinine, creatine phosphokinase, urea, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, sodium, potassium and free and total calcium)
- Urinalysis (haemoglobin, protein, glucose, ketones, pH)
- Antibodies (against liraglutide, cross-reacting with native GLP-1 and neutralising effect on liraglutide)

As a substantial number of the calcitonin measurements were below the lower limit of quantification, it was decided to evaluate calcitonin as a censored response. The analysis of calcitonin was conducted as a repeated measures model for normal censored data, where the logarithm of calcitonin was the (censored) response. The model included time, treatment, gender and treatment by time interaction as fixed effects and subject as random effect. Baseline means were assumed equal between treatment groups.

Treatment emergent hypoglycaemic episodes per subject-year was calculated as the number of hypoglycaemic episodes divided by total exposure in years where total exposure in years was estimated as total days of exposure divided by 365.25. Hypoglycaemic episodes were analysed using a generalised linear model including treatment and country as fixed effects under the assumption that the number of hypoglycaemic episodes per subject followed a negative-binomial distribution.

**Demography of Trial Population**

The population consisted of male (58.2%) and female (41.8%) subjects with type 2 diabetes. The majority of subjects were white (87%) and 9% of the subjects were categorised as Asian/Pacific Islanders. Subjects had a mean age of 56.8 (range 25-79) yrs, a mean body weight of 88.6 (42-151) kg, a mean BMI of 31.0 (17.0-41.4) kg/m$^2$, a mean duration of diabetes of 7.4 (0.3-40.6) yrs and a mean $HbA_{1c}$ of 8.4 (7.0-12.9)% at screening. One third of the subjects

had received previous OAD monotherapy and the other two thirds had received OAD combination therapy.

**Efficacy Results**

**Primary Endpoint**

- $HbA_{1c}$
  - Mean $HbA_{1c}$ values at end of treatment were 7.8%, 7.5%, 7.5%, 8.6% and 7.5% in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. Estimated changes in $HbA_{1c}$ from baseline to end of treatment were -0.69%, -0.97%, -1.00%, +0.09% and -0.98% in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. The changes in $HbA_{1c}$ for all 3 liraglutide groups were shown to be superior to metformin (95% CIs for treatment differences [liraglutide+metformin versus metformin] were [-0.99;-0.57], [-1.27;-0.85] and [-1.30;-0.88] for liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin respectively). Liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin were shown to be non-inferior to glimepiride+metformin (95% CIs for treatment differences [liraglutide+metformin versus glimepiride+metformin] were [-0.16;0.18] and [-0.19;0.15] respectively).
  - The observed decrease in $HbA_{1c}$ from baseline to end of treatment was dose dependent across all 3 liraglutide dose levels in subjects having received OAD combination therapy at entry into the trial (-0.5%, -0.6% and -0.7% in liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin respectively). The observed decrease in $HbA_{1c}$ was greater in the liraglutide 1.8 mg+metformin group (-1.1%) than in the liraglutide 1.2 mg+metformin (-0.9%) and glimepiride+metformin (-0.6%) groups in subjects with baseline BMI ≥ 35 kg/m$^2$. The differences between treatment groups with respect to change in $HbA_{1c}$ did not appear to depend on country, gender, race nor age.
  - The percentages of subjects achieving ADA (< 7%) and AACE (≤ 6.5%) targets for $HbA_{1c}$ increased dose dependently across all 3 liraglutide dose levels and were 28.1% and 11.2% in the liraglutide 0.6 mg+metformin group, 35.0% and 20.0% in the liraglutide 1.2 mg+metformin group, and 41.7% and 24.0% in the liraglutide 1.8 mg+metformin group. In liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin, these percentages were comparable to the level seen in the glimepiride+metformin group (36.0% and 21.9%), whereas in the liraglutide 0.6 mg+metformin group they were significantly lower. The percentages were all significantly higher than the level seen in the metformin group (10.7% and 4.1%).

**Secondary Endpoints**

- Body weight
  - Estimated change in body weight from baseline to end of treatment was dose dependent across all 3 liraglutide dose levels and was -1.78, -2.58, -2.79, -1.51 and +0.95 kg in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. The changes in body weight for all 3 liraglutide groups were shown to be superior to glimepiride+metformin (95% CIs for treatment differences were [-3.47;-2.00], [-4.27;-2.79] and [-4.48;-3.01] for liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin respectively). liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin were shown to be superior to metformin (95% CIs for treatment differences were [-1.94;-0.19] and [-2.16;-0.41] respectively).
  - The observed decrease in body weight from baseline to end of treatment was greater in the liraglutide 1.8 mg+metformin group (-4.4 kg) than in the liraglutide 1.2 mg+metformin group (-3.2 kg) in subjects with baseline BMI ≥ 35 kg/m$^2$.
  - The percentages of subjects achieving weight loss ≥ 5% were dose dependent across all 3 liraglutide dose levels and significantly higher in the 3 liraglutide groups (19.8%, 22.5% and 33.2% in liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin respectively) than the glimepiride+metformin group (7.2%). The percentage of subjects achieving weight loss ≥ 5% was also significantly higher in the liraglutide 1.8 mg+metformin group than the metformin group (16.7%).

– There was no consistent pattern with respect to the relation between nausea and change in body weight. However, very few subjects had nausea for a sustained period of time.

**Efficacy Results (Continued)**

- Glycaemic control parameters
  - Estimated change in FPG from baseline to end of treatment was -1.13, -1.63, -1.68, +0.40 and -1.31 mmol/L in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. Changes in FPG in the 3 liraglutide groups were significantly different from the metformin group and comparable to the glimepiride+metformin group.
  - The percentages of subjects achieving the ADA target of FPG between 5.0 and 7.2 mmol/L were significantly higher in the 3 liraglutide groups (21.8%, 34.2% and 28.9% in liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin respectively) compared with the metformin group (11.2%). The percentage was significantly higher in the liraglutide 1.2 mg+metformin group than the glimepiride+metformin group (26.1%).
  - Change in mean post-prandial plasma glucose from baseline to end of treatment was dose dependent across all 3 liraglutide dose levels and was -1.68, -2.33, -2.57, -0.62 and -2.46 mmol/L in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. Decreases in mean post-prandial plasma glucose in the 3 liraglutide groups were significantly greater than the metformin group. The decrease in the liraglutide 0.6 mg+metformin group was significantly smaller than the glimepiride+metformin group.
  - Significantly more subjects in the 3 liraglutide groups and the glimepiride+metformin group had 2 or 3 post-prandial plasma glucose measurements below the ADA target of 10 mmol/L compared with the metformin group.
  - Observed reductions in mean prandial increments of plasma glucose at end of treatment were liraglutide dose dependent in favor of liraglutide 1.8 mg+metformin. None of the comparisons between the liraglutide groups and the metformin and glimepiride+metformin groups were significant.
- β-cell function
  - β-cell function (as assessed by HOMA-B, pro-insulin to insulin ratio and fasting C-peptide) was significantly improved from baseline to end of treatment in all 3 liraglutide groups in comparison with the metformin group with no difference compared with the glimepiride+metformin group.
  - The increase in fasting insulin from baseline to end of treatment was similar in all 5 treatment groups. No relevant changes were observed in HOMA-IR in any of the groups.
  - Fasting glucagon did not change from baseline to end of treatment in the 3 liraglutide groups and the metformin group, but an increase was observed in the glimepiride+metformin group (significantly different from the 3 liraglutide groups).
- Blood pressure
  - A 2-3 mmHg decrease in SBP seen in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups was significantly different from the 0.4 mmHg increase seen in the glimepiride+metformin group. SBP decreased by 1.8 mmHg in the metformin group and by 0.6 mmHg in the liraglutide 0.6 mg+metformin group.
  - No significant differences were observed between the 5 treatment groups with respect to DBP and the proportion of subjects achieving blood pressure targets of SBP < 130 mmHg and DBP < 80 mmHg.
- Fasting lipid profile
  - Decreases from baseline to end of treatment were observed in VLDL-C (0.09-0.15 mmol/L) and TG (0.16-0.29 mmol/L) in all 3 liraglutide groups and the glimepiride+metformin group. The decrease from baseline in the 3 liraglutide groups was significantly different from the metformin group where no change was observed for VLDL-C and an increase was seen for TG (0.18 mmol/L).
  - No significant differences were observed between the 5 treatment groups with respect to TC, LDL-C, HDL-C, FFA, ApoB and the percentage of subjects achieving ADA targets for lipids (LDL-C < 2.6 mmol/L, TG < 1.7 mmol/L and HDL-C > 1.0 mmol/L).

**Efficacy Results (Continued)**

- Cardiovascular biomarkers including urine albumin-to-creatinine ratio
  - No change in hsCRP was observed from baseline to end of treatment in the 3 liraglutide groups and the glimepiride+metformin group, but there was an increase in the metformin group. None of the differences between treatment groups were significant.
  - Decreases in PAI-1 from baseline to end of treatment were observed in all 5 treatment groups. The decreases were significantly greater in the liraglutide 0.6 mg+metformin, 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups than in the glimepiride+metformin group and in the liraglutide 1.8 mg+metformin than in the metformin group.
  - No relevant changes in NT-proBNP or urine albumin-to-creatinine ratio were observed from baseline to end of treatment in any of the treatment groups.
- Waist circumference and waist-to-hip ratio
  - Mean waist circumference decreased dose dependently (by 1.4-2.4 cm) in the 3 liraglutide groups. A 1.4 cm reduction was seen in the metformin group and no change was seen in the glimepiride+metformin group. The change in the 3 liraglutide groups (decrease from baseline) was significantly different from the glimepiride+metformin group (no change from baseline).
  - No relevant changes in waist-to-hip ratio were observed from baseline to end of treatment in any of the treatment groups.
- Metabolic syndrome
  - The observed percentage of subjects without metabolic syndrome at end of trial was dose dependent in the 3 liraglutide groups in favor of liraglutide 1.8 mg+metformin (31.8, 32.5 and 34.7% in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups respectively). The percentage of subjects without metabolic syndrome was significantly higher in the 3 liraglutide groups than the metformin group (20.7%). The difference between the liraglutide 1.8 mg+metformin group and the glimepiride+metformin group (26.0%) was also significant.
- DEXA scan
  - Estimated decreases in total body fat tissue, lean tissue and fat percentage from baseline to end of treatment were dose dependent across the 3 liraglutide dose levels (the decreases were greater with increasing liraglutide dose level). The weight loss seen in the 3 liraglutide groups, for fat as well as lean tissue, was significantly different from the glimepiride+metformin group but not from the metformin group. The decrease in total body fat percentage was significantly greater in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups compared with the glimepiride+metformin group. Results for the trunk supported the conclusions for the total body.
- CT scan
  - Visceral adipose tissue area was reduced by approximately 20-31 $cm^2$ in the 3 liraglutide groups with reductions of 5-11 $cm^2$ in the metformin and glimepiride+metformin groups. Reductions in visceral adipose tissue area in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups were significantly greater than in the glimepiride+metformin group.
  - Subcutaneous adipose tissue area was reduced from baseline to end of treatment by 17-26 $cm^2$ in all 3 liraglutide groups (dose dependently in favor of liraglutide 1.8 mg+metformin) and the metformin group with a slight increase (7 $cm^2$) in the glimepiride+metformin group. Changes in subcutaneous adipose tissue area differed significantly between the 3 liraglutide groups (decrease from baseline) and the glimepiride+metformin group (increase from baseline).
  - No relevant changes in visceral to subcutaneous adipose tissue ratio were observed from baseline to end of treatment in any of the treatment groups.
  - Liver to spleen attenuation ratio increased from baseline to end of treatment in the

liraglutide 1.8 mg+metformin group (indicating a relief of hepatic steatosis) with no changes in any other group. The increase in the liraglutide 1.8 mg+metformin group was significantly different from the glimepiride+metformin group.

**Efficacy Results (Continued)**

- Patient reported outcome
  - DTSQs: Comparable increases in overall treatment satisfaction were measured in all 5 treatment groups. Perceived frequency of hyperglycaemia decreased in all 5 treatment groups. The decrease was significantly greater in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups than the metformin group and significantly greater in the liraglutide 1.8 mg+metformin group than the glimepiride+metformin group. Perceived frequency of hypoglycaemia did not change in the 3 liraglutide groups, but increased in the metformin and glimepiride+metformin groups. The increase measured in the glimepiride+metformin group was significantly different from all 3 liraglutide groups.
  - The results from DTSQc supported the conclusions based on DTSQs.
  - IWQOL-Lite: Improvements were reported in total IWQOL-Lite score and for each sub-section (physical function, self-esteem, sexual life, public distress and work) in all 5 treatment groups. There were no significant differences between treatment groups except for public distress, which improved significantly more in the 3 liraglutide groups than the glimepiride+metformin group.

**Safety Results**

- Adverse events
  - AEs were reported in 69.4%, 70.4%, 73.6%, 61.2% and 66.1% of subjects in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. The most frequently reported AEs in the liraglutide groups were gastrointestinal disorders such as nausea and diarrhoea. The frequency of these AEs appeared to increase with increasing liraglutide dose level. Nasopharyngitis and headache were common in all 5 treatment groups.
  - The majority of AEs were mild or, to a lesser extent, moderate. Severe AEs were reported in 5.0%, 7.9%, 7.9%, 0.8% and 3.3% of subjects in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. The higher frequency of severe AEs in the 3 liraglutide groups was primarily due to higher frequency of severe gastrointestinal disorders (1.7%, 2.9% and 5.4% of subjects in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups respectively).
  - AEs assessed by the investigator to be probably or possibly related to trial products were reported in 34.7%, 40.0%, 41.3%, 16.5% and 18.2% of subjects in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. The most frequently reported AEs being possibly or probably related to trial products were gastrointestinal disorders in all 5 treatment groups.
  - One (1) death was reported occurring during the run-in period 6 days after initiation of metformin therapy, which was before randomisation.
  - SAEs were reported in 3.3%, 5.8%, 3.7%, 3.3% and 4.1% of subjects in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. The SAEs reported showed no consistent pattern with respect to system organ class of events. Four (4) SAEs were assessed by the investigator to be possibly or probably related to trial products [1 case of gastritis in the liraglutide 0.6 mg+metformin group, 1 case of pancreatitis in the liraglutide 1.2 mg+metformin group and 2 cases (1 case of lung carcinoma cell type unspecified recurrent and 1 case of goitre) in the liraglutide 1.8 mg+metformin group].
  - A total of 73 subjects were withdrawn due to AEs. The percentage of subjects withdrawn from the trial due to AEs was generally higher in the 3 liraglutide groups (4.5-12.0%) than in the metformin (1.6%) and glimepiride+metformin (3.3%) groups. In the liraglutide groups, the majority of the AE withdrawals were caused by gastrointestinal disorders leading to withdrawal within the first month of randomised treatment.

- Gastrointestinal disorders (mainly nausea and diarrhoea) were more common in the 3 liraglutide groups than in the metformin and glimepiride+metformin groups. These events appeared, however, to be transient since the incidences of overall gastrointestinal disorders, as well as nausea and diarrhoea in particular, decreased over time in all 3 liraglutide groups.

**Safety Results (Continued)**

- Laboratory analyses
  - No clinically relevant differences from baseline to end of treatment or between the 5 treatment groups were observed for standard safety laboratory analyses.
  - The pattern of individual calcitonin shifts from baseline to end of treatment was comparable between the 5 treatment groups. The proportion of subjects with abnormal calcitonin values did not change during the trial and did not differ between treatment groups.
  - Mean calcitonin at end of treatment was 0.92, 0.96, 0.94, 0.86 and 0.87 ng/L in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. None of the 3 liraglutide groups differed significantly from the metformin and glimepiride+metformin groups in the calcitonin change from baseline to end of treatment.
- Vital signs and physical findings
  - Mean increases in pulse were 2.9, 2.7, 2.2, 1.3 and 1.0 beats per minute in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. The increases in pulse observed in the liraglutide 0.6 mg+metformin and liraglutide 1.2 mg+metformin groups were significantly greater than in the glimepiride+metformin group.
  - No clinically relevant differences from baseline to end of treatment or between the 5 treatment groups were observed for physical examination, ECG and ophthalmoscopy.
- Hypoglycaemic episodes
  - The proportion of subjects experiencing minor hypoglycaemic episodes (confirmed plasma glucose < 3.1 mmol/L) was 3.3%, 0.8%, 2.5%, 2.5% and 16.9% in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. The rate of minor hypoglycaemic episodes was 0.14, 0.03, 0.09, 0.13 and 1.23 events/subject year in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively.
  - The rate of minor hypoglycaemic episodes was significantly lower for all 3 liraglutide groups compared with the glimepiride+metformin group ($p<0.001$). There were few nocturnal hypoglycaemic episodes during the trial and the distribution of these between treatment arms followed the same pattern as for hypoglycaemic episodes in general.
- Liraglutide antibodies
  - When liraglutide antibodies were summarised at end of treatment only in those subjects who had not received liraglutide for at least 5 days before sampling (a total of 131 subjects; could be withdrawals during the 26 week period or completers who did not participate in the extension part), 1 subject (in the liraglutide 1.2 mg+metformin group) was positive for liraglutide antibodies but showed no cross-reactivity to native GLP-1 and no neutralising effect on liraglutide.
- Pregnancy
  - One (1) pregnancy was reported during the trial in a [redacted]

**Conclusions**

- Glycaemic control (based on change in $HbA_{1c}$) was improved following 6 months of liraglutide treatment at each of three dose levels (0.6, 1.2 or 1.8 mg/day) as add-on to metformin therapy. The improvement in glycaemic control was greater (superior) for all 3 liraglutide dose levels compared with metformin monotherapy. The two highest liraglutide dose levels (plus metformin) showed similar glycaemic control (non-inferiority) as compared with glimepiride in combination with metformin. The percentages of subjects achieving ADA (< 7%) and AACE (≤ 6.5%) targets for $HbA_{1c}$ were dose dependent across all 3 liraglutide dose levels in favor of liraglutide 1.8 mg/day. Percentages of subjects reaching $HbA_{1c}$ targets were greater with the two highest liraglutide dose levels than observed with glimepiride. The percentages for all 3 liraglutide dose levels were significantly higher than the level observed with metformin monotherapy. Results on FPG and post-prandial plasma glucose supported the $HbA_{1c}$ results.
- Subjects lost weight (liraglutide dose dependently) in the order of 2.0-3.0 kg following treatment with liraglutide plus metformin, while a small weight gain was seen following glimepiride plus metformin treatment. Metformin monotherapy resulted in a weight loss of 1.8 kg. The two highest dose levels of liraglutide (plus metformin) were superior to both glimepiride plus metformin and metformin monotherapy. A major part of the weight loss seen with liraglutide was fat tissue as illustrated by the liraglutide dose dependent decreases seen in total body fat tissue and fat percentage, visceral adipose tissue area, subcutaneous adipose tissue area and waist circumference. In addition, hepatic steatosis (as reflected by the liver to spleen attenuation ratio) was reduced following treatment with liraglutide 1.8 mg/day.
- β-cell function was improved to the same extent with liraglutide (at each dose level) plus metformin treatment and with glimepiride plus metformin treatment (as assessed by the HOMA-B index and the pro-insulin to insulin ratio). All 3 liraglutide dose levels as add-on to metformin were superior to metformin monotherapy with respect to β-cell function.
- Fewer minor hypoglycaemic episodes were reported with liraglutide (irrespective of dose level) plus metformin treatment compared with glimepiride plus metformin treatment. Addition of liraglutide to metformin had no effect on the number of minor hypoglycaemic episodes compared with metformin treatment alone.
- Liraglutide treatment in combination with metformin was better than glimepiride and metformin combination therapy in terms of systolic blood pressure reduction and effect on the cardiovascular risk biomarker, PAI-1. Likewise, addition of liraglutide to metformin led to lower levels of VLDL-C and TG than with metformin treatment alone.
- No safety concerns were raised from the results of this trial. Apart from a transiently higher incidence of gastrointestinal adverse events (particularly nausea and diarrhoea) when receiving liraglutide, the safety profile of liraglutide in combination with metformin was comparable to the two comparator arms. The gastrointestinal adverse events were liraglutide dose dependent and occurred mainly during the first 4 weeks of treatment. The serious adverse events seen with liraglutide showed no consistent pattern with respect to system organ class.

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