# 2 Synopsis

| **Trial Registration ID-number**<br>NCT00700817 | **IND Number**<br>61040<br>**EudraCT number**<br>2007-003937-17 |
|---|---|
| **Title of Trial**<br>The effect of liraglutide compared to sitagliptin, both in combination with metformin in subjects with type 2 diabetes. A 26-week, randomised, open-label, active comparator, three-armed, parallel-group, multi-centre, multi-national trial with a 52-week extension.<br>*This Clinical Trial Report Covers the First 26 Weeks of the Extension Period Corresponding to 52 Weeks of Treatment* | |
| **Investigator(s)**<br>A total of 158 principal investigators in 13 countries. Dr. [redacted] was appointed as signatory investigator. | |
| **Trial Site(s)**<br>A total of 158 centres in 13 countries participated: Canada (11), Croatia (3), Germany (12), Ireland (5), Italy (8), Netherlands (8), Romania (4), Serbia (3), Slovakia (6), Slovenia (3), Spain (9), United Kingdom (20) and United States (66). Sites in France were also planned to be included but the current protocol was not approved. Of the 158 sites, which were approved by an IEC, 151 sites actively screened and enrolled subjects for the main trial. Of these 151 sites, a total of 123 sites enrolled subjects into the extension. | |
| **Publications**<br>None | |
| **Trial Period**<br>16 June 2008 to 10 December 2009 (for the first 26-week period of the extension) | **Development Phase**<br>Phase 3b |

**Objectives**

**Primary Objective:**

The primary objective of the trial applied to the first 26-week (main) part of the trial.

- To assess and compare the efficacy (as assessed by change from baseline in $HbA_{1c}$) after 26 weeks of adding liraglutide versus sitagliptin to the pre-trial metformin treatment in subjects with type 2 diabetes inadequately controlled on metformin.

All the objectives for the extensions were regarded as secondary objectives. For the first 26-week part of the extension, $HbA_{1c}$ was treated as the primary endpoint of the secondary objectives.

**Secondary Objectives:**

- To assess and compare the effect of two dose levels of open label liraglutide versus open label sitagliptin after 52 weeks of treatment on $HbA_{1c}$ and on other parameters of glycaemic control (FPG, 7-point meal-related PG profile and percentage of subjects reaching target $HbA_{1c}$), beta-cell function, lipid profiles, body weight, blood pressure, waist circumference and waist to hip ratio.
- In a subset of subjects: Patient Reported Outcomes (PRO) assessed by Diabetes Treatment Satisfaction Questionnaire (DTSQ).

**Safety objectives**

- To assess and compare:
  - incidence of hypoglycaemic episodes
  - clinical and laboratory safety parameters

**Methodology**

This was a 26-week, randomised, open-label, active comparator, three-armed, parallel-group, multi-centre, multi-national trial with a 52-week extension period (two 26-week extension periods) in subjects with type 2 diabetes. This report describes the results after the 26 week main trial and the first 26 week period of the extension (52 weeks of treatment from randomisation).

Subjects inadequately controlled with metformin monotherapy were randomised 2 weeks after screening in 3 groups (1:1:1) to receive open-labelled 1.2 mg or 1.8 mg q.d. (once-daily) liraglutide (s.c. administration) or 100 mg q.d. sitagliptin (oral administration). Both treatments were added to a background treatment of metformin monotherapy at a stable pre-study dose (≥ 1500 mg, stable for at least 3 months).

After randomisation followed a titration period for subjects treated with liraglutide (2 or 3 weeks for liraglutide 1.2 mg and 1.8 mg, respectively). The dose of 100 mg sitagliptin was not titrated. The initial dose of 0.6 mg of liraglutide was escalated to 1.2 mg and 1.8 mg in weekly increments of 0.6 mg. The titration period was followed by a 23/24-week treatment period with fixed doses of liraglutide. The treatment period of sitagliptin was 26 weeks with the same dose. Subjects who decided to participate in the extension signed an informed consent for the entire extension period. For this part of the extension, those subjects were treated for a 49/50-week period with a fixed dose of liraglutide and for 52-week period with a fixed dose of sitaglitptin, respectively. Dose changes were not allowed at any time during the trial.

During the main part of the trial, the subjects had to attend a total of 7 visits (screening, randomisation and 4, 8, 12, 20 and 26 weeks after randomisation) and during the first 26-week part of the extension, the subjects had to attend 2 visits (39 and 52 weeks after randomisation). In United Kingdom, there were two additional visits, 1 and 3 weeks after randomisation, to check FPG levels.

Patient reported outcome recordings by use of DTSQs were done in Canada, Croatia, Germany, Ireland, Italy, Netherlands, Romania, Spain, United Kingdom and United States (all countries except for Serbia, Slovakia and Slovenia).

**Number of Subjects Planned and Analysed**

The sample size was determined for the primary endpoint of the 26-week, randomised portion of the study. A total of 1085 subjects with type 2 diabetes were planned to be screened in order to be able to randomise 651 subjects. It was anticipated to reach 488 evaluable subjects after 6 months of treatment based on an estimated drop-out rate of 25%.

The actual subject disposition (including analysis sets) showing both the main part of the trial and the first 26-week period of the extension was as follows:

| Subjects | Lira 1.2 + Met N (%) | Lira 1.8 + Met N (%) | Sitagliptin + Met N (%) | All N (%) |
|---|---|---|---|---|
| Screened | | | | 1302 |
| Screen failures | | | | 637 |
| Randomised in the 26 week trial | 225 (100.0) | 221 (100.0) | 219 (100.0) | 665 (100.0) |
| Exposed in the 26 week trial | 221 ( 98.2) | 218 ( 98.6) | 219 (100.0) | 658 ( 98.9) |
| Completed the 26 week trial | 169 ( 75.1) | 191 ( 86.4) | 194 ( 88.6) | 554 ( 83.3) |
| Enrolled in the extension period | 155 ( 68.9) | 176 ( 79.6) | 166 ( 75.8) | 497 ( 74.7) |
| Exposed in the extension period | 155 ( 68.9) | 176 ( 79.6) | 166 ( 75.8) | 497 ( 74.7) |
| Completed 52 weeks | 135 ( 60.0) | 150 ( 67.9) | 151 ( 68.9) | 436 ( 65.6) |
| Withdrawals until 26 weeks | 56 ( 24.9) | 30 ( 13.6) | 25 ( 11.4) | 111 ( 16.7) |
| Adverse Events | 14 ( 6.2) | 15 ( 6.8) | 4 ( 1.8) | 33 ( 5.0) |
| Non-compliance with protocol | 14 ( 6.2) | 4 ( 1.8) | 4 ( 1.8) | 22 ( 3.3) |
| Ineffective therapy | 4 ( 1.8) | 0 ( 0.0) | 4 ( 1.8) | 8 ( 1.2) |
| Withdrawal criteria | 10 ( 4.4) | 7 ( 3.2) | 5 ( 2.3) | 22 ( 3.3) |
| Other | 14 ( 6.2) | 4 ( 1.8) | 8 ( 3.7) | 26 ( 3.9) |
| Withdrawals until 52 weeks | 76 ( 33.8) | 56 ( 25.3) | 40 ( 18.3) | 172 ( 25.9) |
| Adverse Events | 19 ( 8.4) | 25 ( 11.3) | 7 ( 3.2) | 51 ( 7.7) |
| Non-compliance with protocol | 17 ( 7.6) | 6 ( 2.7) | 6 ( 2.7) | 29 ( 4.4) |
| Ineffective therapy | 6 ( 2.7) | 3 ( 1.4) | 11 ( 5.0) | 20 ( 3.0) |
| Withdrawal criteria | 16 ( 7.1) | 15 ( 6.8) | 7 ( 3.2) | 38 ( 5.7) |
| Other | 18 ( 8.0) | 7 ( 3.2) | 9 ( 4.1) | 34 ( 5.1) |
| Withdrawn in Extension period | 20 ( 8.9) | 26 ( 11.8) | 15 ( 6.8) | 61 ( 9.2) |
| Adverse Events | 5 ( 2.2) | 10 ( 4.5) | 3 ( 1.4) | 18 ( 2.7) |
| Non-compliance with protocol | 3 ( 1.3) | 2 ( 0.9) | 2 ( 0.9) | 7 ( 1.1) |
| Ineffective therapy | 2 ( 0.9) | 3 ( 1.4) | 7 ( 3.2) | 12 ( 1.8) |

| | | | | |
|---|---|---|---|---|
| Withdrawal criteria | 6 ( 2.7) | 8 ( 3.6) | 2 ( 0.9) | 16 ( 2.4) |
| Other | 4 ( 1.8) | 3 ( 1.4) | 1 ( 0.5) | 8 ( 1.2) |
| Full analysis set | 221 ( 98.2) | 218 ( 98.6) | 219 (100.0) | 658 ( 98.9) |
| Safety analysis set | 221 ( 98.2) | 218 ( 98.6) | 219 (100.0) | 658 ( 98.9) |

The Full analysis set is based on the treatment the subjects were randomised to.
The Safety analysis set is based on the actual treatment the subjects received.

**Diagnosis and Main Criteria for Inclusion**

Male and female subjects diagnosed with type 2 diabetes, stable treatment with metformin for at least 3 months at doses of ≥ 1500 mg, aged 18-80 years inclusive, body mass index (BMI) ≤ 45.0 kg/$m^2$ and $HbA_{1c}$ 7.5–10.0% (both inclusive).

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

Liraglutide (6.0 mg/mL) in 3 mL pen-injector (Batch no.: VP50196 and VP51426) to be injected once-daily s.c. in the abdomen, thigh or upper arm. Daily dose of liraglutide was 1.2 mg or 1.8 mg, respectively.

**Duration of Treatment**

For subjects randomised to treatment with liraglutide, the planned treatment was 26 or 52 weeks and included a forced week dose escalation period with liraglutide (weekly increments of 0.6 mg/day to final dose, 1.2 mg/day or 1.8 mg/day), respectively. The actual mean duration of treatment was 277.9 days for the liraglutide 1.2 mg+metformin group and 304.3 days for the liraglutide 1.8 mg+metformin group.

For subjects randomised to treatment with sitagliptin, the planned treatment was 26 or 52 weeks with the same dose of 100 mg sitagliptin. The actual mean duration of treatment with sitagliptin was 304.2 days.

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

Sitagliptin, Januvia®, tablets (Batch no.: S6004 and T5964) for once-daily oral administration. Daily dose of sitagliptin was 100 mg.

Metformin was not a trial product.

**Criteria for Evaluation – Efficacy**

- $HbA_{1c}$, FPG, self-measured 7-point meal-related plasma glucose profiles, body weight, beta-cell function (fasting insulin, fasting C-peptide, fasting pro-insulin), fasting lipid profile (TC, HDL-C, LDL-C, VLDL-C, TG, FFA and ApoB), vital signs (systolic and diastolic blood pressure and pulse), waist circumference and waist to hip ratio, and patient reported outcome (in a subset of subjects).

**Criteria for Evaluation – Safety**

- Adverse events, physical examination, hypoglycaemic episodes, laboratory safety parameters (standard analyses of haematology, biochemistry and calcitonin) and pregnancy test.

**Statistical Methods**

**Analysis Sets**

The full analysis set (FAS) 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 and who provided post-baseline efficacy data.

The completer analysis set was used for analysis of the primary endpoint as well as selected secondary endpoints (target $HbA_{1c}$ and body weight) and included subjects who completed the 52-week treatment period.

The PRO analysis set was defined for the statistical analyses of the PRO endpoints and included subjects from all countries except for Serbia, Slovakia and Slovenia.

The safety analysis set included all randomised subjects who had been exposed to at least one dose of the trial products.

**Primary Endpoint of the Secondary Objectives**

There was no primary objective for the 52-week extension. However, $HbA_{1c}$ (%) was treated as the primary endpoint of the secondary objectives. The endpoint was analysed using an analysis of covariance (ANCOVA) model with treatment and country as fixed effect and baseline $HbA_{1c}$ value as covariate. It was tested whether each dose of liraglutide+metformin was at least as good as or better than sitagliptin+metformin. It was tested whether treatment with liraglutide 1.8 mg+metformin was non-inferior to sitagliptin+metformin. If the upper limit of the 95% CI was below 0.4%, non-inferiority was concluded. It was also tested whether liraglutide 1.8 mg+metformin was superior to sitagliptin+metformin. Superiority was concluded if the upper limit of the 2-sided 95% CI for the treatment differences were below 0%. The same testing applied for the liraglutide 1.2 mg dose. The same ANCOVA model was used to analyse the difference between the two liraglutide doses.

**Other Secondary Endpoints**

For the secondary endpoints the objective was to demonstrate that treatment with both liraglutide doses (1.2 mg and 1.8 mg) in combination with liraglutide+metformin was different from treatment with sitagliptin+metformin. The endpoints were analysed using an ANCOVA model similar to the one described for the primary endpoint. Thus, the change from baseline to end of treatment was fitted using an ANCOVA with treatment and country as fixed effects and baseline value of the endpoint in question as covariate.

The following endpoints were analysed using the described ANCOVA model: Body weight, FPG, 7-point post-

prandial plasma glucose profiles, fasting insulin, fasting C-peptide, pro-insulin to insulin ratio, beta-cell function (HOMA-B), insulin resistance (HOMA-IR), fasting lipid profile (TC, HDL-C, LDL-C, VLDL-C, TG, FFA and ApoB), vital signs (systolic and diastolic blood pressure and pulse), waist circumference and waist to hip ratio, patient reported outcome (in a subset of subjects) and a composite endpoint including percentages of subjects reaching target $HbA_{1c} < 7\%$ and change in body weight ≤ 0 kg as well as two composite endpoints combining percentages of subjects reaching the composite endpoint including target $HbA_{1c} < 7\%$ and change in body weight ≤ 0 kg as well as either systolic BP < 130 mmHg or no major or minor hypoglycaemia at Week 52.

Furthermore, 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 country as fixed effects and baseline $HbA_{1c}$ as covariate.

**Safety Endpoints**

The following safety endpoints were compared between the treatment groups using descriptive statistics: Adverse events (AEs), physical examination, hypoglycaemic episodes and laboratory safety parameters (haematology, biochemistry).

Calcitonin was evaluated as a censored response. The analysis of calcitonin was conducted as a RMA (repeated measures analysis) 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. The ratio between treatments was calculated after exponential back transformation.

Treatment emergent hypoglycaemic episodes were analysed using a generalised linear model under the assumption that hypoglycaemic episodes per subject-year followed a negative-binomial distribution. The model included treatment as fixed effects. Hypoglycaemic episodes per subject-year by treatment 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.

**Demography of Trial Population**

The population consisted of male (52.9%) and female (47.1%) subjects with type 2 diabetes. They had a mean age of 55.3 years, a mean weight of 93.8 kg, a mean BMI of 32.8 kg/m$^2$, a mean duration of diabetes of 6.2 years and a mean baseline $HbA_{1c}$ of 8.4%. The majority of subjects (86.6%) were white with 7.2% of subjects being Black or African American. Approximately 16% were of Hispanic or Latino ethnicity. Summary of baseline demographics were as follows:

| | Lira 1.2 + Met | Lira 1.8 + Met | Sitagliptin + Met | All Randomised |
|---|---|---|---|---|
| All randomised subjects | 225 | 221 | 219 | 665 |
| Age (years) | | | | |
| N | 225 | 221 | 219 | 665 |
| Mean (SD) | 55.9 ( 9.6) | 55.0 ( 9.1) | 55.0 ( 9.0) | 55.3 ( 9.2) |
| Median | 55.0 | 55.0 | 56.0 | 55.0 |
| Min ; Max | 26.0 ; 79.0 | 23.0 ; 79.0 | 29.0 ; 76.0 | 23.0 ; 79.0 |
| Sex, N (%) | | | | |
| N | 225 ( 100) | 221 ( 100) | 219 ( 100) | 665 ( 100) |
| Male | 116 (51.6) | 116 (52.5) | 120 (54.8) | 352 (52.9) |
| Female | 109 (48.4) | 105 (47.5) | 99 (45.2) | 313 (47.1) |
| Race, N (%) | | | | |
| N | 225 ( 100) | 221 ( 100) | 219 ( 100) | 665 ( 100) |
| White | 184 (81.8) | 193 (87.3) | 199 (90.9) | 576 (86.6) |
| Black or African American | 22 ( 9.8) | 16 ( 7.2) | 10 ( 4.6) | 48 ( 7.2) |
| Asian | 6 ( 2.7) | 4 ( 1.8) | 1 ( 0.5) | 11 ( 1.7) |
| American Indian or Alaska Native | 3 ( 1.3) | 0 ( 0.0) | 0 ( 0.0) | 3 ( 0.5) |
| Native Hawaiian or Other Pacific Islander | 1 ( 0.4) | 0 ( 0.0) | 1 ( 0.5) | 2 ( 0.3) |
| Other | 9 ( 4.0) | 8 ( 3.6) | 8 ( 3.7) | 25 ( 3.8) |
| Ethnicity, N (%) | | | | |
| N | 225 ( 100) | 221 ( 100) | 219 ( 100) | 665 ( 100) |
| Hispanic or Latino | 39 (17.3) | 34 (15.4) | 35 (16.0) | 108 (16.2) |

| | | | | |
|---|---|---|---|---|
| Not Hispanic or Latino | 186 (82.7) | 187 (84.6) | 184 (84.0) | 557 (83.8) |
| **Height (m)** | | | | |
| N | 225 | 221 | 219 | 665 |
| Mean (SD) | 1.69 (0.11) | 1.69 (0.09) | 1.69 (0.10) | 1.69 (0.10) |
| Median | 1.70 | 1.69 | 1.69 | 1.69 |
| Min ; Max | 1.46 ; 2.06 | 1.50 ; 1.92 | 1.46 ; 1.96 | 1.46 ; 2.06 |
| **Weight (kg)** | | | | |
| N | 225 | 221 | 219 | 665 |
| Mean (SD) | 93.7 (18.4) | 94.6 (18.1) | 93.1 (18.9) | 93.8 (18.4) |
| Median | 91.3 | 93.3 | 90.0 | 91.7 |
| Min ; Max | 41.7 ; 146 | 57.0 ; 152 | 54.0 ; 150 | 41.7 ; 152 |
| **BMI (kg/m^2)** | | | | |
| N | 225 | 221 | 219 | 665 |
| Mean (SD) | 32.6 ( 5.2) | 33.1 ( 5.1) | 32.6 ( 5.4) | 32.8 ( 5.2) |
| Median | 32.0 | 33.1 | 31.9 | 32.3 |
| Min ; Max | 18.8 ; 45.0 | 20.9 ; 44.9 | 21.3 ; 44.9 | 18.8 ; 45.0 |
| **HbA1c at baseline (%)** | | | | |
| N | 224 | 220 | 219 | 663 |
| Mean (SD) | 8.4 ( 0.8) | 8.4 ( 0.7) | 8.5 ( 0.7) | 8.4 ( 0.8) |
| Median | 8.2 | 8.3 | 8.4 | 8.3 |
| Min ; Max | 6.3 ; 12.4 | 6.8 ; 10.5 | 6.4 ; 10.6 | 6.3 ; 12.4 |
| **HbA1c at screening (%)** | | | | |
| N | 225 | 221 | 219 | 665 |
| Mean (SD) | 8.5 ( 0.7) | 8.5 ( 0.7) | 8.5 ( 0.7) | 8.5 ( 0.7) |
| Median | 8.3 | 8.4 | 8.4 | 8.4 |
| Min ; Max | 7.5 ; 10.0 | 7.5 ; 10.0 | 7.5 ; 10.3 | 7.5 ; 10.3 |
| **Duration of diabetes (years)** | | | | |
| N | 225 | 221 | 219 | 665 |
| Mean (SD) | 6.0 ( 4.5) | 6.4 ( 5.4) | 6.3 ( 5.4) | 6.2 ( 5.1) |
| Median | 5.5 | 4.9 | 5.2 | 5.2 |
| Min ; Max | 0.3 ; 24.8 | 0.2 ; 30.7 | 0.3 ; 32.7 | 0.2 ; 32.7 |

BMI: body mass index, SD: standard deviation
All the values used in this table are from screening visit

**Efficacy Results**

**Primary Endpoint of the Secondary Objectives**

- $HbA_{1c}$
  - With metformin as background treatment, both treatment with liraglutide 1.2 mg and liraglutide 1.8 mg were superior to sitagliptin (estimated treatment differences were -0.40% and -0.63% and the 95% CIs for treatment differences were [-0.59;-0.22] and [-0.81;-0.44], with p<0.0001 for both comparisons). At Week 52, estimated mean reductions in $HbA_{1c}$ were 1.29% and 1.51% for the two liraglutide+metformin groups as compared to 0.88% for the sitagliptin+metformin group.
  - The superior decreases in $HbA_{1c}$ seen after 26 weeks of treatment with both liraglutide doses were sustained at 52 weeks of the randomised treatment.
  - Reduction in $HbA_{1c}$ was statistically significantly greater with liraglutide 1.8 mg+metformin as compared to liraglutide 1.2 mg+metformin (treatment difference was -0.23% and the 95% CIs for treatment difference was [-0.41;-0.04]).

**Other Secondary Endpoints**

- Target $HbA_{1c}$
  - At Week 52 the estimated proportion of subjects achieving the ADA (< 7%) targets for $HbA_{1c}$ were statistically significantly higher for subjects treated with liraglutide+metformin 1.2 mg (50.3%) and liraglutide+metformin 1.8 mg (63.3%) as compared to sitagliptin+metformin (27.1%).
  - The estimated proportion of subjects achieving the AACE (≤ 6.5%) targets were statistically significantly higher for subjects treated with liraglutide 1.8 mg+metformin (40.4%) as compared to sitagliptin+metformin (16.8%) but not for the liraglutide 1.2 mg+metformin group (24.3%).
  - The estimated proportion of subjects reaching the ADA and AACE targets were statistically significantly higher with liraglutide 1.8 mg+metformin as compared to liraglutide 1.2 mg+metformin.
- Body weight
  - With metformin as background treatment, both liraglutide 1.2 mg and 1.8 mg caused statistically significantly greater body weight loss than sitagliptin (estimated treatment differences were -1.62 kg and -2.53 kg and the 95% CIs for treatment differences were [-2.43;-0.82] and [-3.33;-1.72]). At Week 52, estimated mean body

weight had decreased by 2.78 kg and 3.68 kg for the two liraglutide+metformin groups as compared to 1.16 kg in the sitagliptin+metformin group.
  - Reduction in body weight was statistically significantly greater with liraglutide 1.8 mg+metformin as compared to liraglutide 1.2 mg+metformin (treatment difference was -0.90 kg and the 95% CIs for treatment difference was [-1.71;-0.10]).
- Glycaemic control parameters
  - Both liraglutide+metformin groups demonstrated statistically significantly greater reductions in FPG than sitagliptin+metformin (95% CI for treatment differences were [-1.57; -0.68] and [-1.89; -1.01]). At Week 52, estimated mean FPG had decreased by 1.71 mmol/L and 2.04 mmol/L for the two liraglutide+metformin groups compared to 0.59 mmol/L for the sitagliptin+metformin group.
  - The 3-hour postprandial plasma glucose profile (based on AUC) decreased statistically significantly with liraglutide 1.2 mg+metformin as compared to sitagliptin+metformin (95% CI for treatment differences was [-5.56; -0.61]), while there was no difference between the liraglutide 1.8 mg+metformin and sitagliptin+metformin groups. At Week 52, estimated mean AUC had decreased by 9.24 mmol*h/L and 6.60 mmol*h/L in the two liraglutide+metformin groups versus 6.16 mmol*h/L in the sitagliptin+metformin group.
  - Reduction in AUC was statistically significantly greater with liraglutide 1.2 mg+metformin as compared to liraglutide 1.8 mg+metformin.
- Beta-cell function parameters
  - HOMA-B and the pro-insulin to insulin ratio improved statistically significantly more in both liraglutide+metformin groups as compared to sitagliptin+metformin. At Week 52, estimated mean HOMA-B increased by 22.58% and 25.76% in the two liraglutide+metformin groups compared with 3.98% in the sitagliptin+metformin group. Pro-insulin to insulin ratio decreased by 0.07 and 0.09 in the two liraglutide+metformin groups as compared almost no change (-0.01) in the sitagliptin+metformin group.
  - HOMA-IR improved statistically significantly in the liraglutide 1.8 mg+metformin group as compared to sitagliptin+metformin. At Week 52, estimated mean HOMA-IR decreased by 1.36 in the liraglutide 1.8 mg+metformin group as compared to a reduction of 0.41 in the sitagliptin+metformin group.
  - There were no differences between treatment groups for fasting insulin and fasting C-peptide.
- Fasting lipid profile
  - No statistically significant differences were found between treatment groups on the lipid parameters (total cholesterol, HDL-C, LDL-C, VLDL-C, TG, FFA and ApoB).
- Waist circumference and waist-to-hip ratio
  - The reductions in waist circumference in both liraglutide+metformin treatment groups were statistically significantly greater than in the sitagliptin+metformin treatment group. At Week 52, the estimated mean waist circumferences had decreased by 2.36 cm and 3.02 cm in the two liraglutide+metformin treatment groups as compared to a decrease of 1.23 cm in the sitagliptin+metformin group.
  - No differences in waist-to-hip ratio were observed between the treatment groups.
- Blood pressure and pulse
  - No statistically significant differences in systolic or diastolic BP reductions were observed between the treatment groups.
  - There was an increase in pulse in the two liraglutide+metformin treatment groups, both statistically significantly higher than the smaller increase in the sitagliptin+metformin treatment group.
- Patient reported outcome
  - 'Overall treatment satisfaction', 'satisfaction with current treatment', 'recommendation of present treatment' and 'satisfaction of continuation of present treatment' improved statistically significantly with liraglutide 1.8 mg+metformin as compared to sitagliptin+metformin. 'Perceived frequency of hyperglycaemia' improved statistically significantly in both liraglutide+metformin groups as compared to sitagliptin+metformin.
  - The DTSQs results demonstrated that the subjects did not find treatment with liraglutide (an injectable drug) to be less convenient than treatment with sitagliptin (an orally administered drug) and that the overall treatment satisfaction was greatest with liraglutide 1.8 mg+metformin.
  - Improvement in perceived convenience of treatment was statistically significantly better with liraglutide

1.8 mg+metformin as compared to liraglutide 1.2 mg+metformin.

- Composite endpoint
  - The estimated proportion of subjects reaching the three pre-specified composite endpoint including target $HbA_{1c} < 7\%$ and change in body weight ≤ 0 kg alone, as well as this target including either systolic BP < 130 mmHg or no major or minor hypoglycaemia at Week 52, were statistically significantly higher for both liraglutide+metformin groups as compared to the sitagliptin+metformin group.
  - Liraglutide 1.8 mg+metformin was statistically significantly better than liraglutide 1.2 mg+metformin for two of the composite endpoints (estimated proportion of subjects reaching target $HbA_{1c} < 7\%$ with change in body weight ≤ 0 kg at Week 52 and estimated proportion of subjects reaching target $HbA_{1c} < 7\%$, change in body weight ≤ 0 kg and no major or minor hypoglycaemia at Week 52).

**Safety Results**

- Adverse events (AE)
  - Treatment emergent AEs (TEAEs) were reported by 71.5% and 76.6% of the subjects in the liraglutide+metformin groups (1.2 mg and 1.8 mg) and by 63.5% of subjects in the sitagliptin+metformin group. The most frequently reported TEAEs in the liraglutide+metformin groups were gastrointestinal disorders (nausea, diarrhoea and vomiting) and the frequency appeared to increase with increasing dose. Nausea was mostly mild and transient.
  - The majority of TEAEs were mild in severity or to a lesser extent moderate and assessed by the investigator to be unlikely related to trial products. Severe TEAEs were reported by 5.4% and 6.9% of the subjects in the liraglutide+metformin groups (1.2 mg and 1.8 mg) and by 5.9% of subjects in the sitagliptin+metformin group. The most commonly reported severe TEAEs were gastrointestinal disorders in all groups, reported by 1.8% and 2.3% of the subjects in the liraglutide+metformin groups (1.2 mg and 1.8 mg) and 1.8% of subjects in the sitagliptin+metformin group.
  - TEAEs assessed by the investigator to be probably or possibly related to trial products were reported by 33.9% and 46.3% of subjects in the liraglutide+metformin groups (1.2 mg and 1.8 mg) and by 20.5% of subjects in the sitagliptin+metformin group. The most frequently reported TEAEs being possibly or probably related to trial products were gastrointestinal disorders in all three treatment groups.
  - Three (3) deaths were reported in this trial. The onset of the events with fatal outcomes were [redacted] days after initiation of treatment with liraglutide 1.8 mg+metformin and after [redacted] and [redacted] days of treatment with sitagliptin+metformin, respectively. All three cases were evaluated as unlikely related to trial product.
  - The proportion of subjects reporting serious AEs (SAEs) was comparable in the three treatment groups (4.5% and 6.0% in the liraglutide+metformin groups (1.2 mg and 1.8 mg) and 5.5% of the subjects in the sitagliptin+metformin group). The majority of the reported SAEs were moderate and severe and showed no consistent pattern with respect to system organ class of events. Two (2) SAEs were judged by the investigator as being probably related to the trial product (liraglutide 1.2 mg+metformin, thyroid disorder, for details, see 'Thyroid related TEAEs' below and sitagliptin+metformin, worsening of sleep apnoea syndrome).
  - A total of 51 subjects (7.7%) were withdrawn due to AEs. The percentage of subjects withdrawn from the trial due to TEAEs was slightly higher in the liraglutide 1.8 mg+metformin group (11.5%) as compared to liraglutide 1.2 mg+metformin (8.6%) and higher than in the sitagliptin+metformin group (3.2%). In the liraglutide+metformin groups, the majority of the TEAE withdrawals were caused by gastrointestinal disorders leading to withdrawal within the first months of randomised treatment.
  - There was no pattern in the TEAEs leading to withdrawal during the first 26-week period of the extension, except for 4 subjects withdrawn from the liraglutide 1.8 mg+metformin group due to investigator assessed blood calcitonin increases. It should be noticed that the trial was open-label and coincided with discussions in the medical community/FDA regarding the potential risk of C-cell hyperplasia/carcinoma with liraglutide/GLP-1 agonists in rodents.
  - One (1) non-serious case of mild non-acute pancreatitis was reported (liraglutide 1.8 mg+metformin). The event was considered to be possibly related by the investigator. The subject did not fulfil the Novo Nordisk pre-defined criteria for acute pancreatitis.
  - Thyroid related TEAEs: A total of 42 thyroid related TEAEs were reported by 11, 12 and 10 subjects in the liraglutide 1.2 mg+metformin (5.0%), liraglutide 1.8 mg+metformin (5.5%) and sitagliptin+metformin (4.6%) groups. These included 13 clinical events, which were evenly distributed across the three groups. None of these clinical events were malignant. The remaining 29 events were reports of increased calcitonin.
  - In one subject with increased calcitonin at baseline, 1 TEAE of thyroid disorder was reported to be serious and possibly related to trial drug (liraglutide 1.2 mg+metformin) by the investigator. [redacted]. There were no signs of malignancy.
- Laboratory analyses
  - No differences between the three treatment groups were observed for standard safety laboratory analyses.
  - The pattern of individual calcitonin shifts from baseline to Week 52 was comparable between the treatment groups.
  - Repeated measurement analysis of log-transformed calcitonin values showed that the estimated mean calcitonin

at Week 52 was 1.16 ng/L and 1.19 ng/L in the two liraglutide+metformin (1.2 mg and 1.8 mg) groups and 1.14 ng/L in the sitagliptin+metformin group. There were no statistically significant relative differences in the estimated mean calcitonin levels at Weeks 12, 26, 39 or 52.

- Physical examination
  - No differences between the treatment groups were observed for changes in physical examination from baseline.
- Hypoglycaemic episodes
  - One (1) major hypoglycaemic episode was reported in a subject treated for [redacted] days with liraglutide 1.2 mg+metformin. Blood glucose was [redacted] mmol/L but the subject required third-party assistance (food and drink). This episode was evaluated as a non-serious TEAE.
  - The proportion of subjects experiencing minor hypoglycaemic episodes (confirmed plasma glucose < 3.1 mmol/L) appeared to be comparable across groups (8.1% and 8.7% in subjects treated with liraglutide+metformin, respectively, and 6.4% in the sitagliptin+metformin group). The corresponding rates of minor episodes were 0.143, 0.281 and 0.137 episodes per subject year. The proportion of subjects experiencing symptoms only episodes was low in all three groups (5.9%, 6.9% and 4.1%), respectively.
  - The rate of minor and symptoms only hypoglycaemic episodes was statistically significantly higher in the liraglutide 1.8 mg+metformin group compared with the sitagliptin+metformin group (p=0.0353 and p=0.0456). When excluding an extreme outlier (Subject [redacted]), there was no statistically significant difference in the rate of minor hypoglycaemic episodes.
- Pregnancy
  - There were no positive pregnancy tests reported during the trial.

**Conclusions**

- Liraglutide, 1.2 or 1.8 mg once daily, provided sustained and superior glycaemic control (as measured by change in $HbA_{1c}$ from baseline) compared to sitagliptin both in combination with metformin at 52 weeks of treatment. Both liraglutide doses provided statistically significantly better reductions in other glycaemic parameters such as FPG and proportions reaching ADA and AACE targets. The reduction in body weight was also sustained from the 26 weeks of treatment and was still superior compared to sitagliptin after 52 weeks of treatment. Although there was a higher incidence of gastrointestinal adverse events, especially nausea, with liraglutide treatment, these gastrointestinal adverse events were generally transient and mild or moderate in severity. The rates of minor hypoglycaemic episodes were similar with liraglutide and sitagliptin, after exclusion of an extreme outlier in the liraglutide 1.8 mg+metformin group. This clinical trial confirmed that both doses of liraglutide combined with metformin were effective and safe treatment options for patients with type 2 diabetes.

The trial was conducted in accordance with the Declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Last amended with Note of Clarification on Paragraph 30 by the WMA General Assembly, Tokyo 2004) and ICH Good Clinical Practice (1 May 1996).

The results presented reflect data available in the clinical database as of 21 January 2010.