2 Synopsis – Including CTR Amendment 1, Dated 10 February 2010

Trial Registration ID-number NCT00700817	**IND Number** 61040 **EudraCT number** 2007-003937-17
Title of Trial 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. *Clinical trial report covering the 26-week (main) part of the trial.*	
Investigator(s) A total of 158 principal investigators in 13 countries. Dr. [redacted] was appointed as signatory investigator.	
Trial Site(s) 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). Of the 158 sites, which were approved by an IEC, 151 actively screened and enrolled subjects. Sites in France were also planned to be included but did not receive approval from the Health Authorities before screening closure.	
Publications None	
Trial Period 16 June 2008 to 11 June 2009 (main part)	**Development Phase** Phase 3b

Objectives

Primary Objective:

- 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.

Secondary Objectives:

- To assess and compare the effect on:
  - other parameters of glycaemic control
  - beta-cell function (incl. using homeostasis model assessment (HOMA) using the method of Matthews *et al*. Diabetologia, 1985;28:412-19)
  - fasting lipid profile
  - cardiovascular biomarkers
  - body weight
  - waist circumference and waist to hip ratio
  - blood pressure

In a subset of subjects: PRO assessed by 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 covers the first 26-week randomised part of the trial.

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. Dose changes were not allowed at any time during the trial.

During the trial, the subjects had to attend a total of 7 visits (screening, randomisation and 4, 8, 12, 20 and 26 weeks after randomisation).

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 excluding Serbia, Slovakia and Slovenia).

Number of Subjects Planned and Analysed

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) was as follows:

	Lira 1.2 + Met N (%)	Lira 1.8 + Met N (%)	Sitagliptin + Met N (%)	All N (%)
Screened				1302
Screening failures				637
Randomised	225 (100)	221 (100)	219 (100)	665 (100)
Exposed	221 (98.2)	218 (98.6)	219 (100)	658 (98.9)
Withdrawn	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)
Ineffective therapy	4 (1.8)	0 (0.0)	4 (1.8)	8 (1.2)
Non-compliance with protocol	14 (6.2)	4 (1.8)	4 (1.8)	22 (3.3)
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)
Completers	169 (75.1)	191 (86.4)	194 (88.6)	554 (83.3)
Full analysis set	221 (98.2)	218 (98.6)	219 (100)	658 (98.9)
PP analysis set	158 (70.2)	177 (80.1)	182 (83.1)	517 (77.7)
Safety analysis set	221 (98.2)	218 (98.6)	219 (100)	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 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 157.5 days for the liraglutide 1.2 mg+metformin group and 167.3 days for the liraglutide 1.8 mg+metformin group.

For subjects randomised to treatment with sitagliptin, the planned treatment was 26 weeks with the same dose of 100 mg sitagliptin. The actual mean duration of treatment was 172.3 days.

Reference Therapy, Dose and Mode of Administration, Batch Number

Sitagliptin, Januvia®, tablets (Batch no.: S6004) 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), cardiovascular biomarkers (hsCRP, PAI-1, NT-proBNP, IL-6, adiponectin, TNF-alpha and vWf), 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 HbA_{1c} efficacy data.

The PP 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 in the FAS, who completed the 26 week treatment period with an evaluable HbA_{1c} observation at that week and who did not significantly violate the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the primary endpoint HbA_{1c}. Furthermore, subjects with Visit 7 HbA_{1c} values taken more than 14 days before or after the Visit 7 window were excluded from the PP population.

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

Primary Endpoint

The primary 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. Hypothesis was done in a hierarchical manner. First 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. If so, 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 sequence applied for the liraglutide 1.2 mg dose if the liraglutide 1.8 mg dose was superior.

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), cardiovascular biomarkers (hsCRP, PAI-1, NT-proBNP, IL-6, adiponectin, TNF-alpha and vWf), 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 two composite endpoints combining percentages of subjects reaching the two 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 26.

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 as fixed effect and baseline HbA_{1c} as covariate.

PAI-1 was evaluated as a censored response. The analysis was conducted as an ANCOVA for normal censored data where PAI-1 was the censored response, treatment was included as fixed effect and the baseline value was a covariate.

Safety Endpoints

The following safety endpoints were compared between the treatment groups using descriptive statistics: adverse events (AE), 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 55.2 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 patients	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 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

- HbA_{1c}
  - With metformin as background treatment, both treatment with liraglutide 1.2 mg and liraglutide 1.8 mg were superior to sitagliptin (95% CIs for treatment differences [liraglutide+metformin versus sitagliptin+metformin] were [-0.51;-0.16] and [-0.77;-0.43], respectively, with P<0.0001 for both comparisons). At Week 26, mean HbA_{1c} had decreased by 1.24% and 1.50% for the two liraglutide+metformin groups as compared to a reduction of 0.90% for the sitagliptin+metformin group.

Secondary Endpoints

- Target HbA_{1c}
  - At Week 26 the proportion of subjects achieving the ADA (< 7%) targets for HbA_{1c} were significantly higher for subjects treated with liraglutide+metformin 1.2 mg (43.4%) and liraglutide+metformine 1.8 mg (54.6%) as compared to sitagliptin+metformin (22.4%). Correspondingly, significant higher percentages for subjects reached AACE (≤ 6.5%) targets when liraglutide-metformin treated (22.6%, 35.8%) versus sitagliptin+metformin treated (11.9%).
- Body weight
  - With metformin as background treatment, both treatment with liraglutide 1.2 mg and liraglutide 1.8 mg were significantly better than sitagliptin (95% CIs for treatment differences [liraglutide+metformin versus sitagliptin+metformin] were [-2.61;-1.18] and [-3.14;-1.70]). At Week 26, mean body weight had decreased by 2.86 kg and 3.38 kg for the two liraglutide+metformin groups as compared to a reduction of 0.96 kg for the sitagliptin+metformin group.
- Glycaemic control parameters
  - Both liraglutide+metformin groups demonstrated significantly greater reductions in FPG than sitagliptin+metformin (95% CI for treatment differences were [-1.43; -0.64] and [-1.70; -0.91]). At Week 26, mean FPG had decreased by 1.87 mmol/L and 2.14 mmol/L for the two liraglutide+metformin groups as compared to a reduction of 0.83 mmol/L for the sitagliptin+metformin group.

  - The 3-hour postprandial plasma glucose profile (based on AUC) decreased significantly with liraglutide 1.2 mg+metformin as compared to sitagliptin+metformin (95% CI for treatment differences was [-6.55; -1.19]) whereas there was no difference between the sitagliptin+metformin group compared to liraglutide 1.8 mg+metformin. At Week 26, mean AUC had decreased by 10.33 mmol*h/L and 7.44 mmol*h/L for the two liraglutide+metformin groups as compared to a reduction of 6.46 mmol*h/L for the sitagliptin+metformin group.
- Beta-cell function parameters
  - HOMA-B, fasting C-peptide and the pro-insulin to insulin ratio improved significantly in both liraglutide+metformin groups as compared to sitagliptin+metformin. At Week 26, mean HOMA-B increased by 27.2% and 28.7% in the two liraglutide+metformin groups compared with 4.2% in sitagliptin+metformin. Fasting C-peptide increased by 0.09 nmol/L in both liraglutide+metformin groups as compared to a reduction of 0.04 nmol/L in the sitagliptin+metformin group. Pro-insulin to insulin ratio decreased by 0.08 and 0.10 in both liraglutide+metformin groups as compared to a reduction of 0.03 in the sitagliptin+metformin group.
  - There were no differences between treatment groups for fasting insulin and HOMA-IR.
- Fasting lipid profile
  - No major differences between treatment groups were found on the lipid profile, apart from a slightly greater reduction in total cholesterol seen in the liraglutide 1.8 mg+metformin group (0.17 mmol/L) versus the reduction in the sitagliptin+metformin group (0.02 mmol/L).
  - No statistically significant differences were found between treatment groups on the remaining lipid parameters (HDL-C, LDL-C, VLDL-C, TG, FFA and ApoB).
- Cardiovascular biomarkers
  - No statistically significant differences were found between treatment groups on cardiovascular biomarkers (hsCRP, PAI-1, NT-proBNP, IL-6, adiponectin, TNF-alpha and von Willebrand factor).
- Waist circumference and waist-to-hip ratio
  - The changes in waist circumference in both liraglutide+metformin treatment groups were statistically significantly greater than in the sitagliptin+metformin treatment group. At Week 26, the mean waist circumferences had decreased by 2.69 cm and 2.63 cm in the two liraglutide+metformin treatment groups as compared to a decrease of 1.12 cm in the sitagliptin+metformin group.
  - No relevant differences in waist-to-hip ratio were observed between the treatment groups.
- Blood pressure and pulse
  - There was a small decrease in diastolic BP in the sitagliptin+metformin group (1.78 mmHg), which was significantly different from the increase with liraglutide 1.8 mg+metformin (0.07 mmHg), but not significantly different from the reduction with liraglutide 1.2 mg+metformin (0.71 mmHg).
  - No differences in systolic 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 small decrease 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 significantly with liraglutide 1.8 mg+metformin as compared to sitagliptin+metformin. 'Perceived frequency of hyperglycaemia' improved 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.
- Composite endpoint
  - The percentages of subjects reaching the two pre-specified 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 26 were significantly higher for both liraglutide+metformin groups as compared to the sitagliptin+metformin group.

Safety Results

- Adverse events (AE)
  - AEs were reported by 66.1% and 72.9% of the subjects in the liraglutide+metformin groups (1.2 mg and 1.8 mg) and by 58.0% of subjects in the sitagliptin+metformin group. The most frequently reported AEs in the liraglutide+metformin groups were gastrointestinal disorders (nausea, diarrhoea and vomiting) and the frequency appeared to increase with increasing dose. Nausea was transient.
  - The majority of AEs were mild in severity or to a lesser extent moderate and assessed by the investigator to be unlikely related to trial products. Severe AEs were reported by 3.2% of the subjects in both liraglutide+metformin groups (1.2 mg and 1.8 mg) and 3.7% of subjects in the sitagliptin+metformin group. The most commonly reported severe TEAEs were gastrointestinal disorders in all groups, reported by 1.4% of subjects in both liraglutide+metformin groups and 1.8% of subjects in the sitagliptin+metformin group.
  - AEs assessed by the investigator to be probably or possibly related to trial products were reported by 31.2% and 44.0% of subjects in the liraglutide+metformin groups (1.2 mg and 1.8 mg) and by 18.7% of subjects in the sitagliptin+metformin group. The most frequently reported AEs being possibly or probably related to trial products were gastrointestinal disorders in all three treatment groups.
  - Two (2) deaths were reported and occurred after 8 days of treatment with liraglutide 1.8 mg+metformin and 48 days of treatment with sitagliptin+metformin, respectively. Both were evaluated as unlikely related to trial product.
  - Serious adverse events (SAEs) were reported by 2.7% and 2.8% of subjects in the liraglutide+metformin groups (1.2 mg and 1.8 mg) and by 1.8% of the subjects in the sitagliptin+metformin group. The majority of the reported SAEs were severe and showed no consistent pattern with respect to system organ class of events. Only one (1) SAE was judged by the investigator as being probably related to the trial product (liraglutide 1.2 mg+metformin, thyroid disorder, for details, see 'Thyroid related AEs' below).
  - A total of 33 subjects (5.0%) were withdrawn due to AEs. The percentage of subjects withdrawn from the trial due to AEs was generally higher in the two liraglutide+metformin groups (6.3% and 6.9%) than in the sitagliptin+metformin group (1.8%). In the liraglutide+metformin groups, the majority of the AE withdrawals were caused by gastrointestinal disorders leading to withdrawal within the first months of randomised treatment.
  - No cases of pancreatitis were reported.
  - Thyroid related AEs: A total of 33 thyroid related AEs were reported by 8, 11 and 8 subjects in the liraglutide 1.2 mg+metformin (3.6%), liraglutide 1.8 mg+metformin (5.0%) and sitagliptin+metformin (3.7%) groups. These included 11 clinical events, which were evenly distributed across the three groups (4, 3, and 4, respectively), while the remaining 22 events were reports of increased calcitonin.
  - One (1) AE of thyroid disorder was reported to be serious and possibly related to trial drug (liraglutide 1.2 mg). The subject was withdrawn. There were no signs of malignancy.
- Laboratory analyses
  - No clinically relevant changes from baseline to Week 26 or differences between the three treatment groups were observed for standard safety laboratory analyses.
  - The pattern of individual calcitonin shifts from baseline to Week 26 was comparable between the 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 Week 26 was 1.05 ng/L and 1.11 ng/L in the two liraglutide+metformin (1.2 mg and 1.8 mg) groups and 1.04 ng/L in the sitagliptin+metformin group. There were no significant differences in the change in calcitonin levels at Week 12 or Week 26.
- Physical findings
  - No clinically relevant shifts from baseline to Week 26 or differences between the treatment groups were observed for physical examination.
- Hypoglycaemic episodes
  - One (1) major hypoglycaemic episode was reported in a subject treated for 40 days with liraglutide 1.2 mg+metformin. Blood glucose was [redacted] mmol/L [redacted]. This episode was evaluated as a non-serious AE.

- The proportion of subjects experiencing minor hypoglycaemic episodes (confirmed plasma glucose < 3.1 mmol/L) was similar across groups (5.4% and 5.0% in subjects treated with liraglutide+metformin, respectively, and 4.6% in the sitagliptin+metformin group). The corresponding rates of minor episodes were 0.178, 0.370 and 0.106 episodes per subject year.
- The rate of minor hypoglycaemic episodes was statistically significantly higher in the liraglutide 1.8 mg+metformin group compared with the sitagliptin+metformin group (P=0.0206). When excluding Subject [redacted] (post-hoc analysis), there was no statistically significant difference in the rates of minor hypoglycaemic episodes.
- The proportion of subjects experiencing symptoms only episodes was low in all three groups.

• Pregnancy
- There was no positive pregnancy test reported during the trial.

Conclusions

• Liraglutide, 1.2 or 1.8 mg once daily, in combination with metformin provided superior glycaemic control (as measured by change in HbA_{1c} from baseline) than sitagliptin in combination with metformin. Both liraglutide doses were statistically significantly better regarding other glycaemic parameters such as FPG and proportions reaching ADA and AACE targets as well. Although there was a higher incidence of gastrointestinal adverse events, especially nausea, with liraglutide treatment, these adverse events were generally transient and mild or moderate in severity. Less than 6% of subjects treated with liraglutide+metformin reported minor hypoglycaemic events. In this clinical trial, both doses of liraglutide+metformin were confirmed to be an effective and safe treatment 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 17 September 2009 and 2 February 2010.