2 Synopsis

Trial Registration ID-NCT00518882	**IND Number –** 61040 **EudraCT number –** 2006-006092-21
Title of Trial Liraglutide Effect and Action in Diabetes (LEAD-6): Effect on Glycaemic Control of Liraglutide or Exenatide Added to Metformin, Sulphonylurea or a Combination of Both in Subjects with Type 2 Diabetes. A 26-Week Randomised, Open-Label, Active Comparator, 2-Armed, Parallel-Group, Multi-Centre, Multi-National Trial with a 14-Week, Non-Randomised Extension Period Followed by an Additional 38-Week Non-Randomised Extension Period.	
Investigator(s) A total of 134 principal investigators from 15 countries participated. Dr. John Buse from the United States was appointed as signatory investigator for the trial.	
Trial Site(s) A total of 133 centres in 15 countries participated: Austria (4), Denmark (6), Finland (5), France (5), Germany (14), Ireland (4), Macedonia (1), Norway (4), Poland (9), Romania (3), Slovenia (3), Spain (4), Sweden (2), Switzerland (4) and United States (65). Of the 133 sites which were approved by an IEC, 99 sites actively screened and enrolled subjects.	
Publications None	
Trial Period Trial (main study) initiated: 24 August 2007 LPLV for the 38-week extension: 14 April 2009	**Development Phase** 3b
Objectives **Primary Objective:** The primary objective of the trial applied to the 26-week randomised period. • To assess and compare the efficacy (as measured by HbA_{1c}) of adding liraglutide versus exenatide in subjects with type 2 diabetes, inadequately controlled on metformin, sulphonylurea (SU) or a combination of both, after 26 weeks. All of the objectives for the 52-week extension period (14-week + 38-week extensions) were regarded as secondary objectives. For the 52-week extension, HbA_{1c} was treated as the primary endpoint of the secondary objectives. **Secondary Objectives:** • To explore the effect of changing therapy from exenatide to liraglutide on glycaemic control, body weight, β-cell function and fasting glucagon, and lipid profiles; selected biomarkers of cardiovascular risk were only assessed through Week 40 • To explore the sustainability of glycaemic control for liraglutide treatment in combination with metformin and/or sulfonylurea • To explore the effect of liraglutide on body weight, β-cell function and fasting glucagon and lipid profiles • To explore hypoglycaemic episodes, AEs, pulse, blood pressure, laboratory tests (haematology and biochemistry), and formation of liraglutide or exenatide antibodies • To explore the waist and hip circumference and waist-to-hip ratio • To assess patient reported outcomes (PRO) in a subset of subjects by the Diabetes Treatment Satisfaction Questionnaire (DTSQ); data was only assessed through Week 40	
Methodology This was a 26-week randomised, open-label, active comparator, 2-armed, parallel-group, multi-centre, multi-national trial with a 14-week non-randomised extension period followed by an additional 38-week non-randomised extension period in subjects with type 2 diabetes. This report covers the 52-week (14-week + 38-week extension periods) non-	

randomised extension part of the trial.

At Visit 2, subjects were randomised (1:1) into 2 groups to receive open-label 1.8 mg q.d. (once-daily) liraglutide or 10 µg b.i.d. (twice-daily) exenatide. Both treatments were added to a background treatment of metformin monotherapy, SU monotherapy, or a combination of both at a stable maximally-tolerated pre-study dose of these therapies at the discretion of the investigator (same drug, dose and frequency for at least 3 months). At randomisation, subjects were stratified with respect to their previous OAD treatment. After randomisation a 2-week liraglutide or 4-week exenatide titration period commenced. The liraglutide dose was escalated to 1.8 mg in weekly increments of 0.6 mg and the exenatide dose was escalated to 10 µg b.i.d. after a 4-week period of 5 µg b.i.d. treatment. The titration period was followed by a 22 to 24-week treatment period with fixed doses of liraglutide and exenatide. At the beginning of the 52-week extension, subjects originally randomised to receive exenatide were switched to liraglutide with weekly titration from 0.6 mg q.d. to 1.2 mg q.d. and then 1.8 mg q.d. for the remainder of the extension. Subjects in the liraglutuide+OAD group continued treatment with liraglutide 1.8 mg during the extension period. Dose reductions were not allowed at any time during the trial. Patient reported outcome recordings by use of DTSQ were performed in Austria, Denmark, Finland, Germany, Ireland, Poland, Romania and the United States, but data was only collected through the initial 14-week extension period.

Number of Subjects Planned and Analysed

Sample size was determined for the primary endpoint of the 26-week, randomised portion of the study. A total of 723 subjects were planned to be screened in order to be able to randomise 434 subjects. It was anticipated to reach 326 evaluable subjects, based on an estimated drop-out rate of 25%.

The actual subject disposition of subjects that continued into the 52-week extension period was as follows:

	Liraglutide→ Liraglutide N (%)	Exenatide→ Liraglutide N (%)	All N (%)
Extension Population	202 (100.0)	187 (100.0)	389 (100.0)
Extension Randomised Population	200 (99.0)	186 (99.5)	386 (99.2)
Withdrawn	23 (11.4)	24 (12.8)	47 (12.1)
Adverse Events	3 (1.5)	9 (4.8)	12 (3.1)
Ineffective therapy	6 (3.0)	5 (2.7)	11 (2.8)
Non-compliance with protocol	3 (1.5)	4 (2.1)	7 (1.8)
Withdrawal criteria	1 (0.5)	2 (1.1)	3 (0.8)
Other	10 (5.0)	4 (2.1)	14 (3.6)
14-Week Ext. Completers#	18 (8.9)	25 (13.4)	43 (11.1)
Completers	161 (79.7)	138 (73.8)	299 (76.9)
Extension ITT analysis set	200 (99.0)	186 (99.5)	386 (99.2)
Extension Safety analysis set	202 (100.0)	187 (100.0)	389 (100.0)

Percentages are calculated relative to number of extension period subjects.
#Subjects that completed the 14-week extension, but did not enter the 38-week extension

Diagnosis and Main Criteria for Inclusion

Male and female subjects diagnosed with type 2 diabetes, treated with metformin, SU or a combination for at least three months on maximally tolerated doses, aged 18-80 years inclusive (as allowed according to local guidelines for metformin, exenatide and SU treatment), body mass index (BMI) $\leq$ 45.0 kg/m^2 and HbA_{1c} 7.0-11.0% (both

inclusive).

Test Product, Dose and Mode of Administration, Batch Number

Liraglutide 6.0 mg/mL, pH 8.15 (Novo Nordisk A/S) in 3 mL Flexpen® pen-injectors (Batch numbers: TP50254, TP51313) to be injected q.d. in the upper arm, abdomen or thigh (PK sub-study: in the abdomen). Daily dose was 1.8 mg.

Duration of Treatment

At the end of the 26-week randomised period and the non-randomised 52-week extension period, subjects had received 78 weeks of treatment. Subjects randomised to the liraglutide+OAD group received 78 weeks of liraglutide therapy and subjects randomised to the exenatide+OAD group received 26 weeks of exenatide therapy and 52 weeks of liraglutide therapy.

Reference Therapy, Dose and Mode of Administration, Batch Number

During the 26-week randomised treatment period: exenatide, Byetta™, in pre-filled pens (Batch nos: A316294, A316296, A313549, A276435, A301978, A254098) was to be injected b.i.d in the upper arm, abdomen or thigh. Daily dose was 20 µg. No subjects received exenatide during the 52-week extension.

Criteria for Evaluation – Efficacy

HbA_{1c}, FPG, self-measured 7-point plasma glucose profiles, body weight, beta-cell function (fasting insulin, fasting C-peptide, pro-insulin to insulin ratio, beta-cell function [HOMA-B], insulin resistance [HOMA-IR]), fasting glucagon, SBP and DBP, fasting lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, FFA and ApoB), waist and hip circumference; cardiovascular biomarkers (hsCRP, PAI-1 and NT-proBNP, IL-6, adiponectin and TNF̃alpha) and patient reported outcomes (in a subset of subjects) were only assessed through Week 40.

Criteria for Evaluation – Safety

Physical examination, pulse, hypoglycaemic episodes, adverse events (AE), laboratory safety parameters (standard analyses of calcitonin, haematology, biochemistry and formation of liraglutide or exenatide antibodies) and pregnancy test.

Statistical Methods

The extension intention to treat (ITT) analysis set was used for analyses of all efficacy endpoints and included all randomised subjects who entered the extension period and who had been exposed to at least one dose of the trial products. The extension safety analysis set included all subjects who entered the extension period and who had been exposed to at least one dose of the trial products. Missing baseline values were imputed with values from the screening visit (i.e. subjects without baseline values were only excluded from the analysis if the screening value was also missing). Post-baseline missing values were replaced using the last observation carried forward (LOCF) approach.

There was no primary objective for the 52-week extension. However, HbA_{1c} (%) was treated as the primary endpoint of the secondary objectives. The change from Week 26 (at the end of randomisation period) in HbA_{1c} (%) to Week 78 within each treatment group was the primary analysis. The analysis was made with a paired t test within each treatment group and 95% confidence intervals for the difference between Week 26 and Week 78 were constructed. H_0 was $\mu_{78} - \mu_{26} = 0$ against the alternative H_A: $\mu_{78} - \mu_{26} \neq 0$. A difference between the two means (Week 26 and Week 78) was concluded when H_0 was rejected at the 5% level. If both of the lower and upper limits for the 95% confidence interval for $\mu_{78} - \mu_{26}$ were negative for the treatment group, it was concluded that subjects experienced a statistically significant reduction in HbA_{1c} from Week 26 to Week 78. The change from baseline (Week 0 at the beginning of the randomisation period) in HbA_{1c} (%) to Week 78 within each treatment group was also analysed.

The effect of the following subgroups on change in HbA_{1c} were explored and summarised separately: current OAD, region, race, ethnicity, age quartile, BMI quartile. The proportion of subjects achieving HbA_{1c} values < 7 % (ADA target for good glycaemic control) were presented. The proportion of subjects achieving HbA_{1c} values ≤ 6.5 % (AACE target for good glycaemic control) were presented.

The changes from baseline to Week 78 and from Week 26 to Week 78 for the following secondary efficacy endpoints were analysed as described above for HbA_{1c}: FPG, 7-point plasma glucose profiles (prandial increment of

plasma glucose by meal, post prandial glucose by meal), body weight, fasting insulin, fasting C-peptide, pro-insulin to insulin ratio, beta-cell function [HOMA-B], insulin resistance [HOMA-IR]), fasting glucagon, SBP and DBP, fasting lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, FFA and ApoB), cardiovascular biomarkers (hsCRP, PAI-1 and NT-proBNP, IL-6, adiponectin and TNF-alpha) (only assessed through Week 40), waist circumference and waist-to-hip ratio. The distribution of post-prandial glucose by meal by treatment and the distribution of subjects reaching lipid targets (LDL-C < 2.6 mmol/L and TG <1.7 mmol/L and HDL-C > 1.0 mmol/L) were presented. Patient reported outcomes and the change in patient reported outcomes were presented for a subset of subjects; data was only assessed through Week 40.

The following additional endpoints were presented using descriptive statistics: change in HbA_{1c} (%) by current OAD treatment, change in body weight (kg) by current OAD treatment, change in HbA_{1c} (%) by region and treatment, change in body weight (kg) by region and treatment, change in beta-cell function parameters (unit) by current OAD treatment.

The following safety endpoints were presented for the two groups during the Week 0 to Week 78 period and during the Week 26 to Week 78 period using descriptive statistics: physical examination, pulse, hypoglycaemic episodes, adverse events (AE), laboratory safety parameters (haematology, biochemistry), formation of liraglutide or exenatide antibodies and pregnancy test. Calcitonin was evaluated 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. Hypoglycaemic events per subject-year by treatment were calculated as the number of hypoglycaemic events 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 extension population consisted of male (55.4%) and female (44.6%) subjects with type 2 diabetes. They had a mean age of 56.7 years, a mean BMI of 33.0 kg/m^2, a mean duration of diabetes of 8.0 years and a mean HbA_{1c} of 8.3% (at screening). The majority of subjects (93.0%) were white; 4.9% of subjects were Black or African American, and 11.1% were of Hispanic or Latino ethnicity. Approximately one-third of the subjects had previously received OAD monotherapy (metformin 27.7% and SU 10.4%) while the other two-thirds (61.9%) had previously received OAD combination therapy. Baseline characteristics and demographics appeared similar across treatment groups.

Efficacy Results

Primary Endpoint of the Secondary Objectives for the 52-week Extension

- HbA_{1c}
  - Mean HbA_{1c} values at Week 78 (LOCF) were 7.21% and 7.19% in the liraglutide→liraglutide and exenatide→liraglutide treatment groups, respectively. From Week 0 to Week 78 (LOCF), the mean decrease in HbA_{1c} was 0.98% for the liraglutide→liraglutide group and 0.85% for the exenatide→liraglutide group ($p < 0.0001$ for both treatment groups). At Week 26 (LOCF), mean HbA_{1c} was 6.95% for liraglutide→liraglutide group and 7.21% for the exenatide→liraglutide group. Subjects previously treated with exenatide were switched to liraglutide at Week 26, which resulted in HbA_{1c} values approximately equal to the liraglutide→liraglutide group at Week 34. From Week 34 through Week 52, mean HbA1c remained relatively stable in both groups; a slight increase in HbA1c was observed in both groups from Week 52 to Week 78. Overall, from Week 26 to 78 (LOCF), subjects who switched from exenatide→liraglutide experienced no change in HbA_{1c} (-0.00%, p=0.9872), while those in the liraglutide→liraglutide group experienced an increase in HbA_{1c} (0.25%, p<0.0001).
  - Decreases in HbA_{1c} from Week 0 to Week 78 (LOCF) were significant for both treatment groups among subjects previously treated with metformin, SU and metformin/SU combination therapy (metformin: 0.89% and 1.02%, p<0.0001 for both; SU: 1.09% and 0.69%, p=0.0009 and p=0.0322; metformin/SU combination therapy: 1.01% and 0.80%; p< 0.0001 for both, respectively). Changes in HbA_{1c} from Week 26 to Week 78 were only significant for the liraglutide→liraglutide+metformin (0.21%, p = 0.0068) and the liraglutide→liraglutide+metformin/SU combination therapy groups (0.29%, p=0.0002).

- Significant HbA_{1c} reductions were observed for subjects in both treatment groups and did not appear to be dependent on region, gender, ethnicity, age at baseline, or BMI at baseline.
- At Week 78 (LOCF), the estimated percentages of subjects achieving ADA (<7%) and AACE (≤6.5%) targets for HbA_{1c} were 46.5% and 31.0% in the liraglutide→liraglutide group and 47.8% and 34.9% in the exenatide→liraglutide group, respectively.

Secondary Endpoints

- Glycaemic control parameters
  - Decrease in FPG from Week 0 to Week 78 (LOCF) was 1.3 mmol/L in the liraglutide→liraglutide group and 0.8 mmol/L in the exenatide→liraglutide treatment group (p <0.0001 for both groups). The increase in FPG from Week 26 to Week 78 was significant for the liraglutide→liraglutide group (0.7 mmol/L, p <0.0001).
  - The percentage of subjects achieving the ADA target of FPG ≤ 7.2 mmol/L at Week 78 was 36.7% in the liraglutide→liraglutide group and 35.5% in the exenatide→liraglutide group.
  - The decreases in prandial increment from Week 0 to Week 78 (LOCF) were significant for both treatment groups after breakfast and for the exenatide→liraglutide group after dinner. The increase from Week 26 to Week 78 was significant for the exenatide→liraglutide group after breakfast and dinner.
  - The mean reduction in post-prandial plasma glucose from Week 0 to Week 78 (LOCF) was significant for all meals for both treatment groups. The increase in post-prandial plasma glucose from Week 26 to Week 78 was significant for the exenatide→liraglutide group after breakfast and after dinner, as well as for the liraglutide→liraglutide group after lunch.
- Body weight
  - Decrease in body weight from Week 0 to Week 78 (LOCF) was 3.3 kg and 3.2 kg in the liraglutide→liraglutide and exenatide→liraglutide groups, respectively (p<0.0001 for both). From Week 26 to Week 78 (LOCF), subjects had a decrease of body weight of 0.4 kg (p=0.0793) with continued liraglutide→liraglutide and 0.7 kg (p=0.0075) after switching from exenatide→liraglutide.
- Beta-cell function parameters
  - The change from Week 0 to Week 78 (LOCF) in fasting insulin was significant for the liraglutide→liraglutide group (16.65 pmol/L, p = 0.0009) but not for the exenatide→liraglutide group (2.16 pmol/L, p=0.7121). Changes from Week 26 to Week 78 were not significant.
  - The changes from Week 0 to Week 78 (LOCF) and from Week 26 to Week 78 in fasting C-peptide were not significant for both treatment groups.
  - The decreases from Week 0 to Week 78 (LOCF) and from Week 26 to Week 78 in pro-insulin to insulin ratio were significant for both treatment groups.
  - The increase from Week 0 to Week 78 (LOCF) in the HOMA index of beta-cell function was significant for the liraglutide→liraglutide group (24.86, p<0.0001), but not the exenatide→liraglutide group (11.13, p=0.0920). From Week 26 to Week 78 a significant decrease in HOMA-B was observed in the liraglutide→liraglutide group (-18.18, p<0.0001), while no significant change was observed in the exenatide→liraglutide group.
  - The changes from Week 0 to Week 78 (LOCF) and from Week 26 to Week 78 in HOMA-IR were not significant for both treatment groups.
  - The decreases from Week 0 to Week 78 (LOCF) in fasting glucagon were significant for both treatment groups. The increase from Week 26 to Week 78 was significant for the liraglutide→liraglutide group (7.81 ng/L, p =0.0029), but not for the exenatide→liraglutide group (0.14, p=0.9686).
- Blood pressure
  - The decreases from Week 0 to Week 78 (LOCF) in SBP were significant for both treatment groups (liraglutide→liraglutide: 1.9 mmHg, p=0.0364; exenatide→liraglutide: 4.4 mmHg, p<0.0001). The changes from Week 26 to Week 78 were not significant for both treatment groups.
  - The decrease from Week 0 to Week 78 in DBP was significant for the exenatide→liraglutide group (1.3 mmHg, p=0.0445), but not for the liraglutide→liraglutide group (0.8 mmHg, p=0.1943). The changes from Week 26 to Week 78 were not significant for both treatment groups.
- Fasting lipid profile
  - The liraglutide→liraglutide group had significant decreases from Week 0 to Week 78 in LDL-C, HDL-C, triglycerides, free fatty acids, and apolipoprotein B and significant increases in VLDL-C. The

exenatide→liraglutide group had significant decreases from Week 0 to Week 78 in LDL-C, free fatty acids, and apolipoprotein B and significant increases in VLDL-C. The changes from Week 26 to Week 78 were significant for the liraglutide→liraglutide group for VLDL-C and free fatty acids, and for the exenatide→liraglutide group for apolipoprotein B.
  - At Week 78, a somewhat greater percentage of subjects in the exenatide→liraglutide group (26.9%) compared to the liraglutide→liraglutide group (21.0%) reached all three ADA lipid targets (LDL-C < 2.6 mmol/L, TG < 1.7 mmol/L, HDL-C > 1.0 mmol/L).
- Cardiovascular biomarkers
  - Data was not collected after Week 40. Results are presented in the 14-week extension clinical trial report.
- Waist circumference and waist-to-hip ratio
  - From Week 0 to Week 78, mean waist circumference significantly decreased by 3.46 cm ($p< 0.0001$) and 3.09 cm ($p < 0.0001$) in the liraglutide→liraglutide and exenatide→liraglutide treatment groups, respectively. From Week 26 to Week 78, decreases in mean waist circumference were not significant for both treatment groups.
  - From Week 0 to Week 78, mean waist-to-hip ratio significantly decreased by 0.008 ($p = 0.0140$) in the liraglutide→liraglutide group, but no change was observed in the exenatide→liraglutide group (-0.007, p=0.1824). From Week 26 to Week 78, no change was observed in mean waist-to-hip ratio in both treatment groups.
- Patient reported outcome
  - Data was not collected after Week 40. Results are presented in the 14-week extension clinical trial report.

Safety Results

Adverse Events

- During the extension period, TEAE's were reported in 66.8% (135 subjects) and 64.7% (121 subjects) in the liraglutide→liraglutide and exenatide→liraglutide groups, respectively.
- During the extension period, the TEAE's reported by > 5% of patients in both groups were nasopharyngitis (both groups), upper respiratory tract infection (both groups), diarrhoea and nausea (exenatide→liraglutide), back pain (liraglutide→liraglutide), and nervous system disorders, notably headache (both groups). Greater than 5% of patients in both groups also reported TEAEs under Respiratory, thoracic and mediastinal disorders, Injury, poisoning and procedural complications, Investigations, and under General disorders and administrative site conditions.
- During the extension period, severe TEAEs were reported by 5.9% and 5.3% of subjects in the liraglutide→liraglutide and exenatide→liraglutide group, respectively. The majority of TEAEs were of mild severity (52.0% and 51.9%) and moderate severity (33.7% and 29.9%) in the liraglutide→liraglutide and exenatide→liraglutide groups, respectively.
- During the extension period, the system organ classes with more than one subject reporting a severe event were cardiac disorders (liraglutide→liraglutide group: 4 subjects, 6 events; exenatide→liraglutide group: 3 subjects, 3 events), infections and infestations (liraglutide→liraglutide: 2 subjects, 2 events; exenatide→liraglutide: 3 subjects, 5 events), and gastrointestinal disorders (liraglutide→liraglutide group: 1 subject, 1 event; exenatide→liraglutide group: 2 subject, 2 events). Neoplasms were exhibited by 2 patients in the liraglutide→liraglutide group (1 brain neoplasm; 1 rectal cancer) and by 2 patients in the exenatide→liraglutide group (1 multiple myeloma; 1 prostate cancer). All were considered unlikely to be related to trial product.
- During the extension period, the proportions of subjects with TEAEs assessed by the investigator to be possibly or probably related to treatment were similar between the liraglutide→liraglutide and exenatide→liraglutide treatment groups (15.3% and 18.2%, respectively). The most frequently reported TEAEs being possibly or probably related to trial product were gastrointestinal disorders (9.4% and 12.3%, respectively). The most common gastrointestinal disorders assessed to be possibly or probably related to trial products were nausea (1.5% and 4.3%), diarrhoea (1.0% and 3.2%), gastroesophageal reflux (1.5% and 1.1%), vomiting (1.5% and 1.1%) and constipation (1.0% and 1.6%), for the liraglutide→liraglutide and exenatide→liraglutide treatment groups, respectively.
- During the 52-week extension period, TESAEs were reported by 6.4% of subjects (20 events in 13 subjects) and 8% of subjects (27 events in 15 subjects) in the liraglutide→liraglutide and exenatide→liraglutide treatment groups, respectively. There was one report of acute pancreatitis considered to be of moderate severity in the

liraglutide→liraglutide group, from which the subject recovered, but which was considered as possibly related to trial product. All other TESAEs reported for the liraglutide→liraglutide group and for the exenatide→liraglutide group were considered unlikely to be related to trial product.

- Three subjects in each treatment arm withdrew during the final 38 weeks of the extension period (Week 40 to Week 78). Six subjects in the exenatide→liraglutide group withdrew during the first 14 weeks of the extension period (Week 26 to Week 40).
- There were no deaths during the final 38 weeks of the extension period (Week 40 to Week 78). Two deaths occurred as a result of TESAEs reported during Week 26 to Week 40 (liraglutide→liraglutide: cerebral infarction [subject completed the Week 14 to Week 40 study but expired after the treatment period]; exenatide→liraglutide: myocardial infarction).
- During the 52-week extension period, gastrointestinal TEAEs were reported by 23.3% of subjects (69 events) in the liraglutide→liraglutide group and 26.2% of subjects (78 events) in the exenatide→liraglutide group. Dyspepsia, diarrhoea, gastritis and nausea occurred in ≥ 3% of subjects in both treatment groups.
- During the 52-week extension period, thyroid disorders were exhibited by 6 subjects in the liraglutide→liraglutide group and 9 in the exenatide→liraglutide group. Three disorders in the liraglutide→liraglutide group and 7 in the exenatide→liraglutide group were considered to be unlikely related to trial product. Thyroid disorders in 2 subjects in the liraglutide→liraglutide group and in one subject in the exenatide→liraglutide group were considered possibly to be related to trial product. Increased blood calcitonin in 1 subject in the exenatide→liraglutide group was considered to possibly be related to trial product. Thyroid neoplasia in one patient in the liraglutide→liraglutide group was considered to possibly be related to trial product. Three other reports of thyroid neoplasia (2 in the liraglutide→liraglutide and 2 in the exenatide→liraglutide group) were considered unlikely to be related to trial product.
- During the 52-week extension period, urticaria and hives were exhibited by 1 subject (mild severity) in the liraglutide→liraglutide group and by 1 subject (moderate severity) in the exenatide→liraglutide group. These events were considered to be unlikely to be related to trial product.

Laboratory analyses

- During Weeks 26 to Week 78, no clinically relevant effects on clinical chemistry parameters were observed.
- During Weeks 26 to Week 78, there were no shifts to abnormal clinical laboratory readings in the liraglutide→liraglutide group, and one case of decreased hematocrit and once case of decreased RBC readings in the exenatide→liraglutide group.

Calcitonin

- During the 52-week extension period, calcitonin levels shifted from UNR-2*UNR to > 2*UNR for one male subject in the liraglutide→liraglutide group (not considered to be a TEAE and unlikely to be related to trial product) and for one male and one female subject in the exenatide→liraglutide group, with only the latter considered to be possibly or probably related to trial product.
- During the 52-week extension period the majority of subjects exhibited calcitonin levels < LLOQ or between LLOQ and UNR.

Vital Signs and Physical Exam Findings

- During the 52-week extension period, fewer than 1% of subjects in either treatment group exhibited switches from normal physical examination values to clinically significant, abnormal ones.
- Statistically significant changes in mean pulse (beats/minute) from Week 26 to Week 78 were measured for subjects in the liraglutide→liraglutide group of -1.2 beats/minute ($p = 0.0387$) and in the exenatide→liraglutide group +1.6 beats/minute ($p = 0.0200$).

Hypoglycaemia

- During the 52-week extension period, 19.3% and 19.8% of subjects in the liraglutide→liraglutide and exenatide→liraglutide group, respectively, experienced minor hypoglycaemic episodes, with an event rate of 0.786 and 1.125 per subject-year, respectively.
- One subject in the liraglutide→liraglutide group experienced a major hypoglycaemic episode between Week 26 and Week 40. No major hypoglycemia was reported during the 38-week extension period.

Antibodies

- For the safety analysis LOCF set, 5 subjects (2.8%) of the liraglutide→liraglutide group were positive for

liraglutide antibodies, 5 samples were cross reactive to native GLP-1, and 1 sample was neutralizing. Of the exenatide→liraglutide group, 4 samples (2.4%) were positive for liraglutide antibodies, 3 were cross reactive with native GLP-1 and 3 samples were neutralizing. In this same group, 23.6% of samples were positive for exenatide antibodies, 6 of which cross reacted with liraglutide, 5 cross reacted with native GLP-1 and 10 were neutralizing.

- Exenatide antibodies persisted in subjects who had switched to liraglutide at Week 26, and were still detected in 18.7 % of patients 52 weeks later at Week 78.

Pregnancy

- There were no pregnancies reported during the 52-week extension period.

Conclusions

- Glycaemic control improvements observed during 26-weeks of treatment with once-daily liraglutide+OAD were generally maintained over an additional 52 weeks of therapy; small increases in HbA_{1c} and FPG were observed after Week 52.
- Additional glycaemic control improvements were obtained when subjects previously treated with twice-daily exenatide+OAD for 26 weeks transitioned to receive 52 weeks of therapy with once-daily liraglutide+OAD; these improvements were maintained through Week 52, after which slight increases in HbA_{1c} and FPG were observed.
- Sustained weight loss and improvements in beta-cell function parameters (fasting insulin, pro-insulin to insulin ratio, and HOMA index of beta-cell function) were observed after 78 weeks of treatment with liraglutide+OAD.
- Seventy-eight weeks of treatment with liraglutide+OAD were associated with improvements in LDL-C, triglycerides, free fatty acid and apolipoprotein B.
- During the extension period, the majority of TEAEs were of mild or moderate severity for each treatment group.
- Subjects in both treatment groups demonstrated similar frequency of hypoglycaemic events during the 52-week extension period: 19.3% for liraglutide→liraglutide subjects and 19.8% for exenatide→liraglutide subjects. No other safety concerns were raised from the results of this trial.
- During the 52-week extension period the majority of subjects exhibited calcitonin levels < LLOQ or between LLOQ and UNR.
- The switch from exenatide to liraglutide therapy using a standard dose escalation schedule was well-tolerated.

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice (refer to applicable edition).

The results presented reflect data available in the clinical database as of 26-May-2009.