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 initiated: 24 August 2007 LPLV for the 14-week extension: 15 July 2008	**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 the objectives for 14-week extension were regarded as secondary objectives. For the 14-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, beta-cell function and fasting glucagon, lipid profiles, and selected biomarkers of cardiovascular risk • 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 • In a subset of subjects: to explore patient reported outcomes (PRO) assessed by the Diabetes Treatment Satisfaction Questionnaire (DTSQ).	
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 14-week 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. During the 14-week extension, subjects originally randomised to receive with 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 originally in the liraglutide group continued treatment with liraglutide 1.8 mg during the 14-week extension. 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.

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 14-week extension period was as follows:

	Lira→Lira N (%)	Exenatide→Lira 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	3 (1.5)	10 (5.3)	13 (3.3)
Adverse Events	0 (0.0)	6 (3.2)	6 (1.5)
Ineffective therapy	2 (1.0)	0 (0.0)	2 (0.5)
Non-compliance with protocol	1 (0.5)	0 (0.0)	1 (0.3)
Withdrawal criteria	0 (0.0)	1 (0.5)	1 (0.3)
Other	0 (0.0)	3 (1.6)	3 (0.8)
Completers	199 (98.5)	177 (94.7)	376 (96.7)
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.

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 3 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) ≤ 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 number: TP50254 used for all subjects in the 14-week extension) to be injected q.d. in the upper arm or abdomen. Daily dose was 1.8 mg.

Duration of Treatment

At the end of the 26-week randomised period and the non-randomised 14-week extension period, subjects had received 40 weeks of treatment. Subjects originally randomised to the liraglutide group received 40 weeks of liraglutide therapy and subjects originally randomised to the exenatide group received 26 weeks of exenatide therapy and 14 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 14-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), cardiovascular biomarkers (hsCRP, PAI-1 and NT-proBNP, IL-6, adiponectin and TNF〈), waist and hip circumference, patient reported outcomes (in a subset of subjects).

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 had been exposed to at least one dose of the trial products. The safety analysis set included all randomised subjects 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 14-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 40 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 40 were constructed. H_0 was $\mu_{40} - \mu_{26} = 0$ against the alternative H_A: $\mu_{40} - \mu_{26} \neq 0$. A difference between the two means (Week 26, and Week 40) 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 $\mu_{40} - \mu_{26}$ were all negative for the exenatide group, it means subjects switched to liraglutide from exenatide provided a statistically significant higher reduction in HbA_{1c}. The change from baseline (Week 0 at the beginning of the randomisation period) in HbA_{1c} (%) to Week 40 within each treatment group was also analysed.

The effect of the following subgroups on change of HbA_{1c} were explored and summarised separately: current OAD, region, race, ethnicity, age quartile, BMI quartiles. 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 40 and from Week 26 to Week 40 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, 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 was presented. Patient reported outcomes and the change in patient reported outcomes were presented for a subset of subjects.

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 40 period and during the Week 26 to Week 40 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 kg/m^2, a mean duration of diabetes of 8.1 years and a mean HbA_{1c} of 8.3%. The majority of subjects (93.0%) were white with 4.9% of subjects being 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 Endpoints for the 14-week Extension

- HbA_{1c}
  - Mean HbA_{1c} values at Week 40 (LOCF) were 6.9% and 6.9% in the liraglutide→liraglutide and exenatide→liraglutide treatment groups, respectively. From baseline to Week 40 (LOCF), the mean decrease in HbA_{1c} was 1.29% for the liraglutide→liraglutide group and 1.17% for the exenatide→liraglutide group ($p<0.0001$ for both groups). From Week 26 to 40 (LOCF), subjects who switched from exenatide→liraglutide experienced a significant improvement in HbA_{1c} (0.32%, $p<0.0001$), and HbA_{1c} values were sustained for subjects in the liraglutide→liraglutide group (0.06% reduction).
  - Decreases in HbA_{1c} from baseline to Week 40 (LOCF) were significant for all previous/background OAD therapies evaluated (metformin: 1.2% and 1.2%; SU: 1.2% and 1.1%; metformin/SU combination therapy: 1.3% and 1.1%, for liraglutide→liraglutide and exenatide→liraglutide groups respectively, $p<0.0001$ for all). Decreases in HbA_{1c} from Week 26 to Week 40 were significant for liraglutide→liraglutide+metformin (0.2%, $p=0.0200$), exenatide→liraglutide+metformin (0.4%, $p<0.0001$), exenatide→liraglutide+SU (0.4%, $p=0.0209$), and exenatide→liraglutide+metformin/SU combination therapy groups (0.3%, $p<0.0001$).
  - Significant HbA_{1c} reductions were observed for subjects in both treatment groups and did not appear to be dependant on region, gender, ethnicity, age at baseline, or BMI at baseline.
  - At Week 40 (LOCF), the estimated percentages of subjects achieving ADA (< 7%) and AACE (≤ 6.5%) targets for HbA_{1c} were 61.1% and 39.4% in the liraglutide→liraglutide group and 57.9% and 41.0% in the exenatide→liraglutide group.

Secondary Endpoints for the 14-week Extension

- Glycaemic control parameters
  - Decrease in FPG from baseline to Week 40 (LOCF) was 2.2 mmol/L in the liraglutide→liraglutide group and 1.7 mmol/L in the exenatide→liraglutide treatment group ($p<0.0001$ for both groups). The decrease in FPG from Week 26 to Week 40 was significant for the exenatide→liraglutide group (0.9 mmol/L, $p<0.0001$).
  - The percentage of subjects achieving the ADA target of FPG ≤ 7.2 mmol/L at Week 40 was 48.7% in the liraglutide→liraglutide group and 51.4% in the exenatide→liraglutide group.

- The decreases in prandial increment of plasma glucose from baseline to Week 40 were significant for both treatment groups at breakfast ($p<0.0001$ for both groups) and for the exenatide→liraglutide group at lunch ($p=0.0423$) and dinner ($p=0.0004$). The change from Week 26 to Week 40 was significant for the exenatide→liraglutide group at breakfast ($p=0.0001$) and dinner ($p=0.0006$).
- The mean reduction in post-prandial plasma glucose from baseline to Week 40 was significant ($p<0.0001$) for all meals for both treatment groups and the change from Week 26 to Week 40 was significant for the exenatide→liraglutide group at lunch ($p=0.0032$).

- Body weight
  - From Week 26 to Week 40 (LOCF), subjects had significant decreases in body weight of 0.4 kg with continued liraglutide→liraglutide ($p=0.0089$) and 0.9 kg after switching from exenatide→liraglutide ($p<0.0001$). Decrease in body weight from baseline to Week 40 (LOCF) was 3.2 kg in the liraglutide→liraglutide group ($p<0.0001$) and 3.4 kg in the exenatide→liraglutide group ($p<0.0001$).
- Beta-cell function parameters, insulin resistance, and fasting glucagon
  - The increase from baseline to Week 40 (LOCF) in fasting insulin was significant for the liraglutide→liraglutide group (14.06 pmol/L, $p=0.0029$) but not for the exenatide→liraglutide group (3.0 pmol/L). Changes from Week 26 to Week 40 were not significant.
  - The increase from baseline to Week 40 (LOCF) in fasting C-peptide was significant for the liraglutide→liraglutide group (0.09 nmol/L, $p=0.0079$) and the exenatide→liraglutide group (0.10 nmol/L, $p=0.0194$). Changes from Week 26 to Week 40 were not significant.
  - The decrease from baseline to Week 40 (LOCF) in pro-insulin to insulin ratio was significant for the exenatide→liraglutide group (0.09, $p=0.0008$) but not for the liraglutide→liraglutide group (0.04, $p=0.0700$). Changes from Week 26 to Week 40 were not significant.
  - The increase from baseline to Week 40 (LOCF) in the HOMA index of beta-cell function was significant for the liraglutide→liraglutide group (42.5%, $p<0.0001$) and the exenatide→liraglutide group (23.1%, $p = 0.0011$). The change from Week 26 to Week 40 was significant for the exenatide→liraglutide group (14.5%, $p=0.0010$).
  - No significant changes were observed for HOMA-IR.
  - The decrease from baseline to Week 40 (LOCF) for fasting glucagon was significant for the liraglutide→liraglutide group (9.43 ng/L, $p<0.0001$) and the exenatide→liraglutide group (12.96 ng/L, $p<0.0001$). The increase from Week 26 to Week 40 was significant for the liraglutide→liraglutide group (4.82 ng/L, $p=0.0301$).
- Blood pressure
  - The decrease from baseline to Week 40 in SBP was significant for the liraglutide→liraglutide group (4.9 mmHg, $p<0.0001$) and the exenatide→liraglutide group (6.9 mmHg, $p< 0.0001$). The decrease from Week 26 to Week 40 was significant for liraglutide→liraglutide group (2.2 mmHg, $p=0.0128$) and the exenatide→liraglutide group (3.8 mmHg, $p<0.0001$).
  - The decrease from baseline to Week 40 in DBP was significant for the liraglutide→liraglutide group (1.7 mmHg, $p=0.0027$) and the exenatide→liraglutide group (1.9 mmHg, $p=0.0033$). The decreases in DBP from Week 26 to Week 40 were not significant.
- Fasting lipid profile
  - The liraglutide→liraglutide group had significant decreases from baseline to Week 40 in total cholesterol, LDL-C, triglycerides, free fatty acid, and apolipoprotein B and significant increases in VLDL-C. The exenatide→liraglutide group had significant decreases from baseline to Week 40 in LDL-C, free fatty acids, and apolipoprotein B and significant increases in VLDL-C. The changes from Week 26 to Week 40 were significant for the liraglutide→liraglutide group for VLDL-C and HDL-C and for the exenatide→liraglutide group for HDL-C and apolipoprotein B.
  - Similar percentages of subjects in the liraglutide→liraglutide group (26.8%) and the exenatide→liraglutide group (29.1%) 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
  - The liraglutide→liraglutide group had significant decreases from baseline to Week 40 in hsCRP, NT-pro-BNP and significant increases in PAI-1. The exenatide→liraglutide group had significant decreases from baseline to

Week 40 in NT-pro-BNP. A significant decrease in adiponectin from Week 26 to Week 40 was observed in the liraglutide→liraglutide group. There were no significant changes in IL-6 or TNF-alpha for either group.

- Waist circumference and waist-to-hip ratio
  - From baseline to Week 40, mean waist circumference significantly decreased by 3.05 cm ($p<0.0001$) and 3.66 cm ($p<0.0001$) in the liraglutide→liraglutide and exenatide→liraglutide treatment groups, respectively. From Week 26 to Week 40, mean waist circumference significantly decreased by 0.87 cm ($p=0.0002$) in the exenatide→liraglutide treatment group.
  - From baseline to Week 40, mean waist-to-hip ratio significantly decreased by 0.008 ($p=0.0074$) and 0.014 cm ($p<0.0001$) in the liraglutide→liraglutide and exenatide→liraglutide treatment groups, respectively.
- Patient reported outcome
  - DTSQs: Mean overall treatment satisfaction increased from baseline to Week 40 by 5.9 and 4.3 for liraglutide→liraglutide and exenatide→liraglutide, respectively. Mean overall treatment satisfaction changed from Week 26 to Week 40 by -0.2 and 1.3 in the liraglutide→liraglutide and exenatide→liraglutide groups, respectively. Perceived frequency of hyperglycaemia decreased from baseline to Week 40 for both treatment groups.
  - The results from DTSQc supported the conclusions based on DTSQs.

Safety Results

- Adverse events
  - During the Week 26 to Week 40 period, TEAEs were reported by 37.6% and 37.4% of the subjects in the liraglutide→liraglutide and exenatide→liraglutide treatment groups, respectively. The TEAEs with ≥ 3.0% of subjects reporting were diarrhoea (exenatide→liraglutide group), nausea (exenatide→liraglutide group), nasopharyngitis (both groups), and back pain (liraglutide→liraglutide group).
  - During the Week 26 to Week 40 period, 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. TEAEs assessed by the investigator as 'severe' were reported in 3.5% and 1.1% of subjects in the liraglutide→liraglutide and exenatide→liraglutide treatment groups. There was no pattern to the severe TEAEs, as all events were reported by only one subject. The only system organ classes with more than one subject reporting a severe event were cardiac disorders (liraglutide→liraglutide group: 2 subjects, 2 events; exenatide→liraglutide group: 1 subject, 1 event) and gastrointestinal disorders (liraglutide→liraglutide group: 1 subject, 1 event; exenatide→liraglutide group: 1 subject, 1 event).
  - During the Week 26 to Week 40 period, the proportions of subjects with TEAEs assessed by the investigator to be possibly or probably related to trial products were similar between the liraglutide→liraglutide and exenatide→liraglutide treatment groups (10.4% and 13.9%, respectively).
  - During the Week 26 to Week 40 period, TESAEs were reported in 2.5% and 2.1% of the subjects in the liraglutide→liraglutide and exenatide→liraglutide treatment groups, respectively. Five subjects in the liraglutide→liraglutide group reported 8 TESAEs (cerebral infarction, cerebrovascular accident, transient ischaemic attack, acute coronary syndrome, coronary artery occlusion, portal vein thrombosis, rectal cancer, and depression). Four subjects in the exenatide→liraglutide group reported 7 TESAEs (cardiac failure, myocardial infarction, cataract, chest discomfort, chronic obstructive pulmonary disease [2 events], and dyspnoea). All events were judged by the investigators as unlikely to be related to trial product.
  - A total of 6 subjects (3.2%), all in the exenatide→liraglutide group, were withdrawn from the 14-week extension due to TEAEs, primarily gastrointestinal TEAEs.
  - Two deaths occurred as a result of TESAEs reported during the Week 26 to Week 40 period (liraglutide→liraglutide: cerebral infarction [subject completed the study but expired after the treatment period]; exenatide→liraglutide: myocardial infarction)
  - Gastrointestinal TEAEs were reported by 13.4% of subjects (32 events) in the liraglutide→liraglutide group and 15% of subjects (41 events) in the exenatide→liraglutide group during the Week 26 to Week 40 period. The percentage of subjects with at least one GIAE remained higher in the exenatide→liraglutide group than in the liraglutide→liraglutide group during the extension period. The relative presence of gastrointestinal events during the extension maintenance period was 1.24% in the liraglutide→liraglutide group and 8.31% in the

exenatide→liraglutide group.
  - During the Week 26 to Week 40 period, no events of pancreatitis were reported, 1 non-serious event of goitre/struma nodosa was reported (exenatide→liraglutide group), and 1 moderate event of urticaria/hives (exenatide→liraglutide group) was reported.
- Laboratory analyses
  - No clinically relevant changes were observed for standard safety laboratory analyses.
  - The relative difference between treatments (using a repeated measurement analysis of calcitonin with censored observation) was not significant at any timepoint (Weeks 12, 20, 26, 34, and 40). No TEAEs of the preferred term 'blood calcitonin increased' were reported during the Week 26 to Week 40 period.
- Vital signs and physical findings
  - Significant increases in mean pulse from baseline to Week 40 were observed for the liraglutide→liraglutide group (1.9 beats per min, p = 0.0033) and the exenatide→liraglutide group (2.5 beats per min, p = 0.0002). Significant decreases in mean pulse from Week 26 to Week 40 was observed for the liraglutide→liraglutide treatment group (1.4 beats per min, p=0.0244).
- Hypoglycaemic episodes
  - During the Week 26 to Week 40 extension period, the proportion of subjects experiencing minor hypoglycaemic episodes in the liraglutide→liraglutide and exenatide→liraglutide treatment group was 6.4% and 11.8%, respectively and the event rate of minor hypoglycaemia was 0.739 and 1.300 events per subject year, respectively.
  - During the Week 26 to Week 40 extension period, one subject treated with liraglutide→liraglutide+metformin experienced a major hypoglycaemic episode.
  - During the Week 26 to Week 40 extension period, the overall frequency of minor hypoglycaemia when liraglutide or exenatide was combined with metformin was (0.400 events/subject year and 0.149 events/subject year, respectively) and it was higher (0.869 events/subject year and 1.743 events/subject year, respectively) when liraglutide or exenatide was combined with an SU or metformin/SU combination therapy.
- Antibodies
  - At the end of the 14-week extension period (LOCF), for the 17 subjects in the liraglutide→liraglutide group off drug for five or more days, one subject (6%) had positive antibodies to liraglutide and positive cross reactivity to GLP-1. None of the 17 subjects in the liraglutide→liraglutide group had antibodies with neutralising effect.
  - At the end of the 14-week extension period (LOCF), for the 27 subjects in the exenatide→liraglutide group off drug for five or more days, no subjects had positive antibodies to liraglutide and 14 subjects (52%) had positive antibodies to exenatide, six (22%) with neutralising effect.
- Pregnancy: There was no positive pregnancy test reported during the trial.

Conclusions

- Glycaemic control improvements observed during 26 weeks of treatment with once-daily liraglutide + metformin and/or SU therapy were maintained over an additional 14 weeks.
- Additional glycaemic control improvements were obtained when subjects previously treated with twice-daily exenatide for 26 weeks transitioned to receive 14 weeks of therapy with once-daily liraglutide.
- Significant reductions in body weight and improvements in beta-cell function parameters (fasting insulin, fasting C-peptide, HOMA index of beta-cell function, and fasting glucagon) were observed after 40 weeks of treatment with liraglutide.
- Forty weeks of treatment with liraglutide was associated with improvements in systolic blood pressure, diastolic blood pressure, total cholesterol, LDL-C, triglycerides, free fatty acid and apolipoprotein B.
- During the 14-week extension period, 93.6% and 88.2% of subjects reported no episodes of minor hypoglycaemia in the liraglutide→liraglutide and the exenatide→liraglutide treatment groups, respectively. No additional safety concerns were raised from the results of this trial.
- 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.