2 Synopsis

Trial Registration ID-number 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. *This report covers the 26-week randomised part of the trial.*	
Investigators A total of 134 principal investigators from 15 countries participated. Dr. [redacted] was appointed as signatory investigator for the trial.	
Trial Sites A total of 133 centres in 15 countries participated: AT (4), CH (4), DE (14), DK (6), ES (4), IE (4), FI (5), FR (5), MK (1), NO (4), PL (9), RO (3), SI (3), SE (2), and US (65). Of the 133 sites which were approved by an independent ethics committee (IEC), 100 sites actively screened and enrolled subjects.	
Publications None	
Trial Period 24 August 2007 to 9 April 2008	**Development Phase** Phase 3b

Objectives

Primary Objective:

- 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.

Secondary Objectives:

- To assess and compare the effect on other parameters of glycaemic control: FPG (fasting plasma glucose), self-measured 7-point plasma glucose profiles and fraction of subjects reaching target HbA_{1c} of $< 7.0\%$ or $\leq 6.5\%$ at week 26.
- To assess and compare the effect on body weight.
- To assess and compare the incidence of hypoglycaemic episodes.
- To assess the safety and tolerability.
- To assess the formation of liraglutide and exenatide antibodies.

Other Objectives:

- To compare waist and hip circumference and waist to hip ratio, respectively.
- To compare biomarkers of cardiovascular risk (high sensitivity C-reactive protein [hsCRP], plasminogen activator inhibitor 1 [PAI-1], N-terminal-pro-B-type natriuretic peptide [NT-pro-BNP], interleukin 6 [IL-6], adiponectin, TNFα).
- To assess and compare beta-cell function (fasting insulin, fasting pro-insulin and fasting C-peptide) and fasting glucagon. The homeostasis model assessment (HOMA, Matthews et al. Diabetologia. 1985;28:412-9)) will be used.
- To assess and compare lipid profiles (total cholesterol [TC], low density lipoprotein cholesterol [LDL-C], very low density lipoprotein cholesterol [VLDL-C], high density lipoprotein cholesterol [HDL-C], triglyceride [TG], free fatty acid [FFA], apolipoprotein B [ApoB]).
- To assess and compare the effect on systolic blood pressure (SBP) and diastolic blood pressure (DBP).

In a Subset of Subjects:

- Patient reported outcomes assessed by Diabetes Treatment Satisfaction Questionnaire (DTSQ).
- PK profiles of liraglutide and exenatide.

Methodology

This was a 6-month 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 26 week randomised part of the trial.
Subjects were randomised in 2 groups (1:1) to receive open-labelled 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 pre-study dose on the maximally tolerated doses of these therapies at the discretion of the investigator (same drug, dose and frequency for at least 3 months). At randomisation (Visit 2), the subjects were stratified with respect to their previous OAD treatment.

After randomisation followed a titration period (2 weeks with liraglutide, 4 weeks with exenatide). The initial dose of 0.6 mg of liraglutide 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. Dose reductions were not allowed at any time during the trial. For subjects not participating in the extension period, the 26-weeks of treatment were followed by a 1-week follow-up period and a follow-up visit.
A sub-study of PK profiles of liraglutide and exenatide were done in connection with Visit 7 (week 26) in PL. The sub-study population included 8 subjects in the liraglutide+OAD treatment group and 8 subjects in the exenatide+OAD treatment group and at randomisation these were not stratified with respect to their previous OAD.
Patient reported outcome recordings by use of DTSQ were done in AU, DK, FI, DE, IE, PL, RO and US.

Number of Subjects Planned and Analysed

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%. Three (3) subjects were not randomised in the interactive voice response system before they were exposed to treatment. These subjects were therefore only included in the safety analysis set. The actual subject disposition (including analysis sets) was as follow:

	Liraglutide + OAD N (%)	Exenatide + OAD N (%)	All N (%)
Screened			663
Screening failures			196
Randomized	233 (99.1)	231 (99.6)	464 (99.4)
Exposed	235 (100)	232 (100)	467 (100)
Withdrawn	33 (14.0)	45 (19.4)	78 (16.7)
Adverse Events	23 (9.8)	31 (13.4)	54 (11.6)
Ineffective therapy	1 (0.4)	0 (0.0)	1 (0.2)
Non-compliance with protocol	4 (1.7)	3 (1.3)	7 (1.5)
Withdrawal criteria	1 (0.4)	1 (0.4)	2 (0.4)
Other	4 (1.7)	10 (4.3)	14 (3.0)
Completers	202 (86.0)	187 (80.6)	389 (83.3)
ITT analysis set	233 (99.1)	231 (99.6)	464 (99.4)
PP analysis set	193 (82.1)	172 (74.1)	365 (78.2)
Safety analysis set	235 (100)	232 (100)	467 (100)

Percentages are calculated relative to number of exposed 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 pH8.15) in 3 mL Flexpen® pen-injectors (Batch no: TP50254) 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

A 26-weeks treatment period including a forced 3 week dose escalation period with liraglutide (0.6 mg/day and followed by weekly increments of 0.6 mg/day to final dose, 1.8 mg/day) and a exenatide dose of 5 µg b.i.d for 4 weeks before increasing to 10 µg b.i.d. for reaching the intended daily dose.

Reference Therapy, Dose and Mode of Administration, Batch Number

Exenatide, Byetta™, in pre-filled pens (Batch nos: A316294, A316296, A313549, A276435, A301978, A254098) to be injected b.i.d in the upper arm, abdomen or thigh (PK sub-study: in the abdomen). Daily dose was 20 µg. Metformin and SUs were not trial products.

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 TNFα), waist and hip circumference, patient reported outcome (in a subset of subjects) and pharmocokinetic profiles of liraglutide and exenatide (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

Analysis Sets

The intention to treat (ITT) analysis set was used for analyses of all efficacy endpoints and included all randomised subjects who had been exposed to at least one dose of the trial products.

The PP analysis set was used for analysis of the primary endpoint and included all subjects who had at least 24 weeks between first and last dose on randomised treatment, had no protocol deviations with potential impact on the primary efficacy assessment, fulfilled the first three inclusion criteria, fulfilled all randomisation criteria, did not meet any withdrawal criteria, had an evaluable HbA_{1c} observation at baseline Visit 2 (or if missing at screening, Visit 1) and at Visit 7 (end of randomised treatment).

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, country and current anti-diabetic treatment (metformin monotherapy, SU monotherapy or metformin plus SU combination therapy) as explanatory variables and baseline HbA_{1c} as covariate. It was tested whether liraglutide+OAD was as least as good as or better than exenatide+OAD. If the upper limit of the 95% CI was below 0.4% non-inferiority was concluded. If non-inferiority was met, then it was tested if the treatment with liraglutide was better than exenatide, i.e. if superiority could be established. Superiority was concluded if the upper limit of the 2-sided 95% CI for the treatment difference was below 0%.

The following main effects and interactions were explored separately by adding them to the original model: Treatment by current OAD treatment interaction (main effect is in the original model): treatment by country

interaction (main effect is in the original model), gender, race, ethnicity, age quartiles (age<50, 50≤age<58, 58≤age<64, age≥64) and BMI quartiles (BMI<28.60, 28.60≤BMI<32.04, 32.04≤BMI<36.78, BMI≥36.78).
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, country, current OAD treatment as explanatory variables and baseline HbA_{1c} as covariate.

Secondary Endpoints
For the secondary endpoints the objective was to demonstrate that treatment with liraglutide+OAD was different from treatment with exenatide+OAD. 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, country and current anti-diabetic treatment as explanatory variables and baseline value of the endpoint in question as covariate.

The following endpoints were analysed using the described ANCOVA model: FPG, 7-point plasma glucose profiles, 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 TNFα), waist circumference and waist-to-hip ratio, patient reported outcome (in a subset of subjects) and pharmacokinetic profiles of liraglutide and exenatide.

Furthermore, the proportion of subjects reaching the ADA target FPG ≤ 7.2mmol/L was compared between treatment groups using a logistic regression model with treatment as fixed effect and baseline FPG as covariate. The proportion of subjects having the post-prandial measurement below 10 mmol/L for each of the three meals was compared between the liraglutide and exenatide treatments using a chi square test. The proportion of subjects reaching the ADA target for lipids (LDL-Chol<2.6 mmol/L, TG<1.7 mmol/L and HDL-Chol>1.0 mmol/L) was also compared between treatment groups using a chi-square test.

Safety Endpoints
The following safety endpoints were compared between the 2 treatment groups 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.

Treatment emergent hypoglycaemic episodes were analysed using a generalised linear model under the assumption of hypoglycaemic episodes per subject-year followed a negative-binomial distribution. The model included treatment, current OAD treatment and country as fixed effects. Hypoglycaemic events per subject-year by treatment was 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 population consisted of male (51.9%) and female (48.1%) subjects with type 2 diabetes. They had a mean age of 56.7 years, a mean weight of 93.1 kg, a mean BMI of 32.9 kg/m^2, a mean duration of diabetes of 8.2 years and a mean baseline HbA_{1c} of 8.3%. The majority of subjects (91.8%) were white with 5.4% of subjects being Black or African American. Approximately 12% were of Hispanic or Latino ethnicity. Approximately one-third of the subjects had previously received OAD monotherapy (metformin 27.4% and SU 9.7%) while the other two-thirds had previously received OAD combination therapy. Summary of baseline demographics were as follow:

	Liraglutide + OAD	Exenatide + OAD	All Randomised
All randomised patients	233	231	464
Sex, N (%)			
N	233 (100)	231 (100)	464 (100)
Male	114 (48.9)	127 (55.0)	241 (51.9)
Female	119 (51.1)	104 (45.0)	223 (48.1)
Age (years)			
N	233	231	464
Mean (SD)	56.3 (9.8)	57.1 (10.8)	56.7 (10.3)
Median	57.0	58.0	58.0
Min ; Max	28.0 ; 78.0	25.0 ; 78.0	25.0 ; 78.0
Race, N (%)			
N	233 (100)	231 (100)	464 (100)
White	216 (92.7)	210 (90.9)	426 (91.8)
Asian	0 (0.0)	4 (1.7)	4 (0.9)
Black or African American	13 (5.6)	12 (5.2)	25 (5.4)
American Indian or Alaska Native	0 (0.0)	1 (0.4)	1 (0.2)
Hawaiian or other Pacific Island	1 (0.4)	1 (0.4)	2 (0.4)
Other	3 (1.3)	3 (1.3)	6 (1.3)
Ethnicity, N (%)			
N	233 (100)	231 (100)	464 (100)
Hispanic or Latino	32 (13.7)	25 (10.8)	57 (12.3)
Not Hispanic or Latino	201 (86.3)	206 (89.2)	407 (87.7)

Efficacy Results

Primary Endpoint

- HbA_{1c}
  - Mean HbA_{1c} values at end of treatment were 7.0% and 7.3% in the liraglutide+OAD and exenatide+OAD treatment groups. Estimated changes in HbA_{1c} from baseline to end of treatment were -1.12% and -0.79% in the liraglutide+OAD and exenatide+OAD treatment groups. The change in HbA_{1c} for the liraglutide+OAD group was shown to be non-inferior to exenatide+OAD (95% CI for treatment difference was [-0.47; -0.18]). This also showed that liraglutide+OAD treatment group was superior to exenatide+OAD treatment.
  - The differences between treatment groups with respect to change in HbA_{1c} did not appear to depend on OAD therapy at entry into the trial, BMI, country, gender, ethnicity nor age. A treatment by race interaction was found but the finding may be due to random variation.
  - The percentages of subjects achieving ADA (< 7%) and AACE (≤ 6.5%) targets for HbA_{1c} were 54.2% and 43.4% in the liraglutide+OAD group and 35.2% and 20.8% in the exenatide+OAD. The percentages of subjects reaching the targets were significantly higher in the liraglutide+OAD group compared with exenatide+OAD group.

Secondary Endpoints

- Glycaemic control parameters
  - Estimated change in FPG from baseline to end of treatment was -1.61 and -0.60 mmol/L in the liraglutide+OAD and exenatide+OAD treatment groups. The change was statistically significantly different between the treatment groups (95% CI for treatment difference was [-1.37; -0.65]).
  - The percentage of subjects achieving the ADA target of FPG ≤ 7.2 mmol/L was statistically significantly higher in the liraglutide groups (42.2%) compared with the exenatide+OAD group (25.6%).
  - The observed reductions in mean prandial increments of plasma glucose and mean post-prandial plasma glucose at end of treatment were statistically significantly greater in the exenatide+OAD group compared to the liraglutide+OAD group after breakfast and dinner whereas no treatment differences were found in the comparison of changes after lunch.

- Body weight
  - Estimated change in body weight from baseline to end of treatment was -3.24 kg and -2.87 kg in the liraglutide+OAD and exenatide+OAD treatment groups. The change was not significantly different between the treatment groups (95% CI for treatment difference was [-0.99; 0.23]).
- Beta-cell function parameters
  - The HOMA index of beta-cell function was statistically significantly improved from baseline to end of treatment in the liraglutide+OAD treatment group (increased by 40 percentage point) compared with the exenatide+OAD (increased by 8 percentage point) whereas no treatment differences in changes in pro-insulin to insulin ratio and fasting C-peptide was found.
  - The increase in fasting insulin from baseline to end of treatment was statistically significantly greater in the liraglutide+OAD treatment group compared with exenatide+OAD group. No relevant changes were observed in HOMA-IR in the treatment groups.
  - Fasting glucagon slightly decreased from baseline to end of treatment in both treatment groups.
- Blood pressure
  - Reductions of 2.6 and 3.2 mmHg in SBP from baseline to end of treatment were seen in the liraglutide+OAD and exenatide+OAD treatment groups. No significant differences were observed between treatments with respect to SBP.
  - Reductions of 1.1 and 1.7 mmHg in DBP from baseline to end of treatment were seen in the liraglutide+OAD and exenatide+OAD treatment groups. No significant difference between treatments was observed.
- Fasting lipid profile
  - Statistically significant greater reductions in TG and FFA concentrations were seen in the liraglutide+OAD treatment group (-0.41 mmol/L and -0.17 mmol/L) compared to the exenatide+OAD group (-0.23 mmol/L and -0.10 mmol/L). The increase in VLDL-C however, was statistically significantly greater in the exenatide+OAD treatment group (0.27 mmol/L) compared to the liraglutide+OAD group (0.20 mmol/L).
  - No significant differences were observed between the 2 treatment groups with respect to TC, LDL-C, HDL-C, ApoB and the percentage of subjects achieving ADA targets for lipids (LDL-C<2.6 mmol/L, TG<1.7 mmol/L and HDL-C>1.0 mmol/L).
- Biomarkers of cardiovascular risk
  - No statistically significant difference was found between liraglutide and exenatide treatments on hsCRP, PAI-1, NT-proBNP, Il-6, adiponectin and TNFα.
- Waist circumference and waist-to-hip ratio
  - Mean waist circumference decreased by 2.6 cm and 2.4 cm in the liraglutide and exenatide+OAD treatment groups. No significant difference between treatments was observed.
  - No relevant changes in waist-to-hip ratio were observed from baseline to end of treatment in the treatment groups.
- Patient reported outcome
  - DTSQs: A significantly greater increase in overall treatment satisfaction was measured in the liraglutide+OAD treatment group compared with the exenatide+OAD group. Perceived frequency of hyperglycaemia decreased in both treatment groups, however, no significant difference between liraglutide+OAD and exenatide+OAD treatments was observed. Perceived frequency of hypoglycaemia did not change in the treatment groups.
  - The results from DTSQc supported the conclusions based on DTSQs. There was a statistically significant improvement in overall treatment satisfaction in favour of liraglutide+OAD treatment compared to exenatide+OAD treatment. Furthermore, perceived frequency of hypoglycaemia and hyperglycaemia decreased in both treatment groups. The decrease was statistically significantly greater in the liraglutide+OAD group compared with the exenatide group.

- Pharmacokinetic profiles
  - Mean liraglutide C_{max} was 16955 pmol/L, mean liraglutide C_{min} was 6724 pmol/L and mean AUC_{τ} was 282124 pmol x h/mL.
  - Mean exenatide C_{max} was 138 pmol/L following the morning dose and 155 pmol/L following the evening dose, mean exenatide C_{min} was 27 pmol/L following the morning dose and 35 pmol/L following the evening dose and mean exenatide AUC_{τ} was 708 pmol x h/ml following the morning dose and 1126 pmol x h/ml following the evening dose.

Safety Results

- Adverse events
  - AEs were reported in 74.9% and 78.9% of the subjects in the liraglutide+OAD and exenatide+OAD treatment groups. The most frequently reported AEs were gastrointestinal disorders as nausea, diarrhoea, dyspepsia and vomiting.
  - 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 TEAEs were reported in 7.2% and 4.7% of subjects in the liraglutide+OAD and exenatide+OAD treatment groups. The most commonly reported severe TEAEs were gastrointestinal disorders with 3.4% and 2.2% of subjects reporting TEAEs in the liraglutide+OAD and exenatide+OAD treatment groups.
  - The number of AEs assessed by the investigator to be probably or possibly related to trial product was similar for the liraglutide+OAD and exenatide+OAD treatment groups (49%). The most frequently reported AEs being possibly or probably related to trial products were gastrointestinal disorders in both treatment groups.
  - SAEs were reported in 5.1% and 2.6% of the subjects in the liraglutide+OAD and exenatide+OAD treatment arms, respectively. The majority of the reported SAEs were severe and showed no consistent pattern with respect to system organ class of events. One SAE was judged by the investigator as being probably related to the trial product (1 case of hypoglycaemia in the exenatide+OAD treatment group).
  - A total of 54 subjects (11.6%) were withdrawn. The percentage of subjects withdrawn from the trial due to AEs was higher in the exenatide+OAD treatment group compared to the liraglutide+OAD group (13.4% versus 9.8%). In both treatment groups the majority of the AE withdrawals were caused by gastrointestinal disorders (19 and 22 subjects in the liraglutide+OAD and exenatide+OAD treatment groups).
  - Gastrointestinal AEs were common in both treatment groups with comparable numbers of events reported. The percentage of subjects with at least one GIAE increased during the titration periods but decreased over time most markedly for subjects in liraglutide+OAD treatment. During the maintenance part incidences of GIAEs (in particular nausea and vomiting) appeared transient in the liraglutide+OAD treatment group but more persistent in the exenatide+OAD treatment group. The relative presence of gastrointestinal events during the period of maintenance decreased in the liraglutide+OAD treatment group (nausea in particular) whereas the relative presence of GIAE increased in the exenatide+OAD treatment group.
  - Pancreatitis, thyroid and immunogenicity related AEs: one (1) non-serious chronic pancreatitis was reported by a subject in liraglutide+OAD treatment. Eight (8) non-serious thyroid related AEs were reported by 2 and 6 subjects treated with liraglutide+OAD and exenatide+OAD, respectively. One (1) serious event of thyroid neoplasm (unlikely related to trial drug) was reported by a subject in liraglutide+OAD treatment. The subject recovered and continued in the trial. Two events of urticaria (mild and moderate) and a moderate event of circulatory collapse were reported by three subjects in exenatide+OAD treatment.
- Laboratory analyses
  - No clinically relevant differences from baseline to end of treatment or between the liraglutide and exenatide treatment groups were observed for standard safety laboratory analyses.
  - The pattern of individual calcitonin shifts from baseline to end of treatment was comparable between the

treatment groups. The proportion of subjects with abnormal calcitonin values did not change during the trial and did not differ between treatment groups.

- Mean calcitonin at end of treatment was 0.38 ng/L and 0.36 ng/L in the liraglutide+OAD and exenatide+OAD groups. No significant difference in calcitonin levels between the 2 treatment groups was seen at Week 12, 20 or 26.
- One (1) TEAE of the preferred term 'increased blood calcitonin' was reported for Subject [redacted] treated with liraglutide. This mild and non-serious event was assessed by the investigator to be possibly related to liraglutide. A non-TEAE of 'increased blood calcitonin' was reported for Subject [redacted] at Visit 2 before exposure to any trial product.

- Vital signs and physical findings
  - Mean increases in pulse were 3.28 and 0.69 beats per minute in the liraglutide+OAD and exenatide+OAD treatment groups. The increase in pulse seen in the liraglutide+OAD treatment group was statistically significantly greater than the increase seen in the exenatide+OAD treatment group. However, the observed increases in pulse were evaluated as not clinically relevant.
  - No clinically relevant differences from baseline to end of treatment or between the two treatment groups were observed for physical examination.
- Hypoglycaemic episodes
  - The proportion of subjects experiencing minor hypoglycaemic episodes (plasma glucose < 3.1 mmol/L) was 25.5% and 33.6% in the liraglutide and exenatide+OAD treatment groups. The rate of minor hypoglycaemic episodes was 1.932 versus 2.600 events/subject year in the liraglutide and exenatide+OAD treatment groups. The rate of minor hypoglycaemic episodes was statistically significantly lower in the liraglutide arm compared to the exenatide arm.
  - The proportion of subjects experiencing minor hypoglycaemic episodes was lower in the liraglutide/exenatide+metformin groups (6.3% and 11.1%) compared to the liraglutide/exenatide treatment groups with SU/metformin+SU as add-on (32.7% and 42.0%).
  - The overall frequency of hypoglycaemia was low when liraglutide or exenatide was combined with metformin (1.071 versus 0.503 events/subject year, respectively) whereas it was markedly higher when liraglutide or exenatide was combined with an SU (2.262 versus 3.392 events/subject year, respectively).
- Liraglutide and Exenatide Antibodies
  - About 58% (109 of 187 subjects) of the subjects in the exenatide group were positive for exenatide antibodies after termination of exenatide treatment. A few showed partial cross-reactivity to native GLP-1 (5 subjects, 2.7%) and liraglutide (2 subjects, 1.1%) and about 6% (12 subjects) showed *in vitro* neutralising effect of exenatide.
  - When liraglutide and exenatide antibodies were summarised at end of treatment only in those subjects who had not received liraglutide/exenatide for at least 5 days (a total of 34 subjects), none of the subjects was positive for liraglutide antibodies and 6 subjects (27.3%) were positive for exenatide antibodies but did not show cross-reactivity to native GLP-1 and liraglutide. Three (3) of the subjects showed *in vitro* neutralising effect of exenatide.
- Pregnancy
  - There was no positive pregnancy test reported during the trial.

Conclusions

- Glycaemic control (based on change in HbA_{1c}) was improved following 6 months of treatment with liraglutide+OAD and exenatide+OAD therapy. The improvement was greater (superior) after liraglutide treatment compared with exenatide treatment. The percentages of subjects achieving ADA (< 7%) and AACE (≤ 6.5%) targets for HbA_{1c} were significantly higher in the liraglutide+OAD group compared with the exenatide+OAD treatment group. Results on FPG and to a lesser extent post-prandial plasma glucose supported

the HbA_{1c} results.

- A weight loss of 3.2 kg and 2.9 kg was observed after 6 months of treatment with liraglutide+OAD and exenatide+OAD (no statistically significant difference).
- The HOMA index of beta-cell function was statistically significantly improved in the liraglutide+OAD treatment group (increased by 40 percentage points) compared with the exenatide+OAD (increased by 8 percentage point) whereas no treatment differences in changes in pro-insulin to insulin ratio and fasting C-peptide were found.
- Fewer minor hypoglycaemic episodes were reported with liraglutide+OAD compared with exenatide+OAD treatment. The rate of minor hypoglycaemic episodes was statistically significantly lower in the liraglutide arm compared to the exenatide arm.
- Liraglutide+OAD and exenatide+OAD treatment led to blood pressure reductions to the same extent. Liraglutide treatment was better in terms of lowering levels of TG and FFA. No treatment effect was seen in cardiovascular risk markers.
- The overall treatment satisfaction was statistically significantly greater in the liraglutide arm compared to the exenatide arm.
- No safety concerns were raised from the results of this trial. The safety profiles of liraglutide and exenatide were comparable with equally reported frequencies of GIAEs in the 2 treatment groups. GIAEs, in particular nausea and vomiting, appeared transient in the liraglutide+OAD treatment arm, occurring mainly during the first 4 weeks of treatment, whereas the incidences appeared more persistent during the duration of the trial when treated with exenatide+OAD. The serious adverse events seen with liraglutide+OAD and exenatide+OAD treatments showed no consistent pattern with respect to system organ class. No concerns were raised from events related to pancreatitis, thyroid and immunogenicity.

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).