2 Synopsis

Trial Registration ID-number	**EudraCT number**
NCT00318461	2005-003417-32

Title of Trial

Liraglutide Effect and Action in Diabetes (LEAD-2): Effect on glycaemic control after once daily administration of liraglutide in combination with metformin versus metformin monotherapy versus metformin and glimepiride combination therapy in subjects with type 2 diabetes. A six-month double-blind, double-dummy, randomised, active control, parallel-group, multi-centre, multi-national trial with an 18 months extension period. 2-year clinical trial report.

Investigators

A total of 171 principal investigators in 21 countries. Prof. Dr. Michael A. Nauck from Germany was appointed as Signatory Investigator.

Trial Sites

A total of 170 centres in 21 countries participated: AR (4), AU (19), BE (6), BG (1), DE (33), DK (9), ES (14), GB (11), HR (2), HU (5), IE (4), IN (5), IT (10), NL (5), NZ (3), NO (8), RO (3), RU (6), SE (8), SK (7), ZA (7).

Publications

Nauck, et al. Diabetes Care. 2009 Jan; 32(1):84-90. Epub 2008 Oct 17.

Trial Period	**Development Phase**
30 May 2006 to 11 Nov 2008	Phase 3a

Objectives

Primary Objective:

- To assess and compare the effect on glycaemic control (as measured by HbA_{1c}) of once daily administration of three doses of liraglutide in combination with metformin versus metformin monotherapy versus metformin and glimepiride combination therapy in subjects with type 2 diabetes.

Secondary Objectives:

- To assess and compare the effect on body weight.
- To assess and compare the effect on glycaemic control (fasting plasma glucose [FPG] and 7-point plasma glucose profiles [self-measured]).
- To assess and compare β-cell function (fasting insulin, fasting pro-insulin, 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 blood pressure (BP).

Safety Objectives:

- To assess and compare incidences of hypoglycaemic episodes.
- To assess the safety and tolerability of liraglutide in combination with metformin.
- To assess the formation of liraglutide antibodies.

Other Objectives:

- To assess and compare cardiovascular effects (highly sensitive C reactive protein [hsCRP], plasminogen activator inhibitor-1 [PAI-1] and N-terminal B-type natriuretic peptide [NT-proBNP]).
- To assess and compare waist and hip circumference and waist-to-hip ratio.
- Additionally, for the subjects entering the extension treatment period the β-cell sparing effect will be assessed as the slope of increase in HbA1c per year after nadir and compared.

Objectives (Continued)

In a Subset of Subjects:

- Patient reported outcomes assessed by Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Impact of Weight on Quality of Life Questionnaire – Lite Version (IWQOL-Lite).
- To assess and compare body composition (including fat distribution assessed by DEXA and abdominal CT scan slices).

Methodology

This was a 6-month double-blind, double-dummy, randomised, active control, parallel-group, multi-centre, multi-national trial with an 18 months extension period investigating the safety and efficacy of liraglutide as add-on to metformin. This clinical trial report covers results for the entire 2-year period.

Subjects were randomised in 5 groups (2:2:2:1:2) to receive 0.6 mg once-daily liraglutide plus metformin (liraglutide 0.6 mg+metformin), 1.2 mg once-daily liraglutide plus metformin (liraglutide 1.2 mg+metformin), 1.8 mg once-daily liraglutide plus metformin (liraglutide 1.8 mg+metformin), metformin monotherapy (metformin) or glimepiride plus metformin combination therapy (glimepiride+metformin). At randomisation, subjects were stratified with respect to their previous treatment (oral antidiabetic drug [OAD] monotherapy or combination therapy). Randomisation took place after a metformin run-in period of 3 weeks followed by a metformin maintenance period of 3 weeks. During the run-in period, the dose level of metformin was increased up to 2000 mg/day. Subjects already on metformin therapy at enrolment could go through a modified titration period or advance directly to the metformin maintenance period at the discretion of the investigator.

After randomisation, subjects in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups underwent a 1-2 week period of forced titration with liraglutide (active or placebo) for reaching the intended daily dose level. All subjects underwent a 3 week period of forced titration with glimepiride (active or placebo). After the titration period, a 23 week maintenance treatment period commenced, during which dose levels of liraglutide and glimepiride were fixed while the metformin dose level could be adjusted to between 1500 and 2000 mg/day at the discretion of the investigator in case of unacceptable hypoglycaemia or other adverse events. Liraglutide was administered as subcutaneous (s.c.) injections once daily (active or placebo). Glimepiride was to be taken orally once daily (active or placebo). Metformin was to be taken orally twice daily (open-label). Once all subjects had completed the six-month double-blind part of the trial, the primary database release and statistical analyses were performed on the six-month data. At 26 weeks after randomisation, all subjects were asked to confirm their continued participation in an 18-month open-label treatment extension period. Subjects who continued into the extension period were unblinded to treatment assignment at their first visit at the site after database release and continued the treatment regimen they had been randomised to in the blinded part of 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.

Number of Subjects Planned and Analysed

A total of 1865 subjects with type 2 diabetes were planned to be screened in order to include 1118 subjects in the run-in period and to be able to randomise 1026 subjects. It was anticipated to reach 770 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:

Type 2 Diabetic Subjects (%)	LIRA 0.6 + Met N (%)	LIRA 1.2 + Met N (%)	LIRA 1.8 + Met N (%)	Met N (%)	Met + Glim N (%)	Total N (%)
Screened						1662
Screening failure						571
Randomized	242 (100)	241 (100)	242 (100)	122 (100)	244 (100)	1091 (100)
Exposed	242 (100)	240 (99.6)	242 (100)	121 (99.2)	242 (99.2)	1087 (99.6)
Withdrawals 6 months	34 (14.0)	44 (18.3)	51 (21.1)	48 (39.3)	34 (13.9)	211 (19.3)
Adverse Events	11 (4.5)	23 (9.5)	29 (12.0)	2 (1.6)	8 (3.3)	73 (6.7)
Ineffective therapy	19 (7.9)	8 (3.3)	13 (5.4)	29 (23.8)	9 (3.7)	78 (7.1)
Non-compliance	2 (0.8)	4 (1.7)	4 (1.7)	4 (3.3)	5 (2.0)	19 (1.7)
Other	2 (0.8)	9 (3.7)	5 (2.1)	13 (10.7)	12 (4.9)	41 (3.8)
N/A						
Withdrawals 24 months	78 (32.2)	60 (24.9)	73 (30.2)	43 (35.2)	97 (39.8)	351 (32.2)
Adverse Events	11 (4.5)	8 (3.3)	6 (2.5)	1 (0.8)	6 (2.5)	32 (2.9)
Ineffective therapy	41 (16.9)	33 (13.7)	37 (15.3)	27 (22.1)	63 (25.8)	201 (18.4)
Non-compliance	7 (2.9)	5 (2.1)	3 (1.2)	4 (3.3)	6 (2.5)	25 (2.3)
Other	19 (7.9)	14 (5.8)	27 (11.2)	11 (9.0)	22 (9.0)	93 (8.5)
N/A						
Completers at 6 months	208 (86.0)	197 (81.7)	191 (78.9)	74 (60.7)	210 (86.1)	880 (80.7)
Completers at 24 months	130 (53.7)	137 (56.8)	118 (48.8)	31 (25.4)	113 (46.3)	529 (48.5)
ITT analysis set	242 (100)	240 (99.6)	242 (100)	121 (99.2)	242 (99.2)	1087 (99.6)
EITT analysis set	184 (76.0)	178 (73.9)	174 (71.9)	61 (50.0)	183 (75.0)	780 (71.5)
Safety analysis set	242 (100)	240 (99.6)	242 (100)	121 (99.2)	242 (99.2)	1087 (99.6)
Open-label extension completers analysis set	130 (53.7)	137 (56.8)	118 (48.8)	31 (25.4)	113 (46.3)	529 (48.5)
Sub-study analysis set - CT	34 (14.0)	31 (12.9)	36 (14.9)	19 (15.6)	34 (13.9)	154 (14.1)
Sub-study analysis set - DEXA	35 (14.5)	31 (12.9)	37 (15.3)	20 (16.4)	37 (15.2)	160 (14.7)
Sub-study analysis set - QOL	176 (72.7)	183 (75.9)	184 (76.0)	88 (72.1)	181 (74.2)	812 (74.4)

Diagnosis and Main Criteria for Inclusion

Male and female subjects diagnosed with type 2 diabetes, treated with OAD(s) for at least 3 months, aged 18-80 years inclusive (as allowed according to local guidelines for metformin and glimepiride treatment), body mass index (BMI) ≤ 40.0 kg/m^2 and HbA_{1c} values of 7.0-10.0% (incl.) in subjects on OAD combination therapy and 7.0-11.0% (incl.) in subjects on OAD monotherapy.

Test Product, Dose and Mode of Administration, Batch Number

Liraglutide (6.0 mg/mL) in 3 mL FlexPen® (Batch nos. RP52008, SP51132, SP52281, TP50642 and TP51560) to be injected s.c. in the upper arm, abdomen or thigh. Daily liraglutide doses were 0.6 mg, 1.2 mg and 1.8 mg in the 3 liraglutide groups.

Glimepiride placebo capsules (Batch nos. PBBK034, PBBK035, PBBK036, PBBK037, PBBK038, PBBK041, PBBK042, PBBK071 and SBBK048) for once-daily oral administration.

Metformin tablets (500 mg) (Batch nos. 102525, 102526, 102602, 102803, 102804 and 102974) for oral administration. Daily metformin dose was 1500-2000 mg.

Duration of Treatment

A metformin run-in period of 3 weeks and a metformin maintenance period of 3 weeks followed by a 104-weeks treatment period during which all subjects underwent a 3 week period of forced titration with glimepiride and subjects in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups started with a 1-2 week period of forced titration with liraglutide for reaching the intended daily dose.

Reference Therapy, Dose and Mode of Administration, Batch Number

Liraglutide placebo in 3 mL FlexPen® (Batch nos. RP51969, SP51129, SP51130, TP50221 and SP51130) to be injected s.c. in the upper arm, abdomen or thigh. Daily liraglutide placebo injection volumes were similar to the

volumes of active liraglutide.
Glimepiride tablets (1 and 2 mg) in blinded capsules (Batch nos. E479, E407, 40E524 and B436) for oral administration. Daily glimepiride dose was 1-4 mg during the 3-week titration period and 4 mg during the rest of the trial.
Metformin tablets (500 mg) (Batch nos. 102525, 102526, 102602, 102803, 102804 and 102974) for oral administration. Daily metformin dose was 1500-2000 mg.

Criteria for Evaluation – Efficacy

HbA_{1c}, body weight, FPG, self-measured 7-point plasma glucose profiles, β-cell function (fasting insulin and fasting pro-insulin), fasting glucagon, systolic and diastolic blood pressure, fasting lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, FFA and ApoB), cardiovascular biomarkers (hsCRP, PAI-1 and NT-proBNP), waist and hip circumference, patient reported outcome (in a subset of subjects), dual-energy X-ray absorptiometry (DEXA) scan (in a subset of subjects) and computerised tomography (CT) scan (in a subset of subjects).

Criteria for Evaluation – Safety

Adverse events, physical examination, pulse, electrocardiogram (ECG), opthalmoscopy, hypoglycaemic episodes and CT scan. Laboratory analyses of standard haematology, biochemistry and urine parameters, calcitonin, liraglutide antibody levels 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.
- Extension ITT (EITT) analysis set included all subjects in the ITT who entered the extension period and who were exposed to at least one dose of trial product in the extension period. This analysis set was applied for the efficacy endpoints pertaining to HbA_{1c}, body weight, FPG, HOMA and blood pressure.
- Open-Label Extension Completers (Completers) analysis set included all subjects who completed the 18-month open-label extension. This analysis set was applied for the efficacy endpoints pertaining to HbA_{1c}, body weight, FPG, HOMA and blood pressure.
- The safety analysis set included all randomised subjects who had been exposed to at least one dose of the trial products.

Primary Endpoint

Change in HbA_{1c} from baseline to end of treatment was analysed using an analysis of covariance (ANCOVA) model with treatment, country and previous anti-diabetic treatment as fixed effects and baseline HbA_{1c} as covariate. Hypothesis testing was done in a hierarchical manner. First, it was tested whether liraglutide 1.8 mg+metformin was superior to metformin. If so, it was tested whether liraglutide 1.8 mg+metformin was non-inferior to glimepiride+metformin. If so, it was tested whether liraglutide 1.8 mg+metformin was superior to glimepiride+metformin. The same testing sequence applied for the 2 lower liraglutide dose levels. Furthermore, a given liraglutide dose level was only tested for superiority to metformin if the upper liraglutide dose level had shown non-inferiority to glimepiride+metformin. A test for superiority of glimepiride+metformin to metformin was also performed to verify assay sensitivity. Superiority was always concluded if the upper limit of the 2-sided 95% CI for the treatment difference was below 0%. Non-inferiority was concluded if the upper limit of the 2-sided 95% CI for the treatment difference was below 0.4%.

The following main effects and interactions were explored separately by adding them to the original model:

- Treatment by pre-treatment interaction (the main effect was in the original model)
- Treatment by country interaction (the main effect was in the original model)
- Main effect of gender as well as treatment by gender interaction
- Main effect of race as well as treatment by race interaction
- Main effect of age group (< 65 years and ≥ 65 years) as well as treatment by age group interaction
- Main effect of BMI group (BMI < 25 kg/m^2, 25 kg/m^2 ≤ BMI < 30 kg/m^2, 30 kg/m^2 ≤ BMI < 35 kg/m^2 and BMI ≥ 35 kg/m^2) as well as treatment by BMI group interaction

The proportion of subjects achieving HbA_{1c} target (American Diabetes Association [ADA] target: < 7%; American

Association of Clinical Endocrinologists [AACE] target ≤ 6.5%) was compared between treatments using a logistic regression model with treatment and baseline HbA_{1c}.

Secondary Endpoints

The key secondary endpoint, change in body weight, was analysed using the same model as for the primary endpoint. For each liraglutide dose level it was tested whether liraglutide plus metformin was different from glimepiride+metformin and metformin respectively. The following additional analyses related to body weight were performed:

- The impact of baseline BMI on change in body weight was analysed by including BMI group (BMI<25 kg/m^2; 25 kg/m^2≤BMI<30 kg/m^2;30 kg/m^2≤BMI<35 kg/m^2;BMI≥35 kg/m^2) as a fixed effect in the ANCOVA model.
- The weight loss responder rate after 26 weeks of treatment was categorised in 4 groups (]-∞;0%[, [0%; 5%[, [5%;10%[, [10%; ∞[) and summarised.
- The proportion of subjects achieving weight loss targets of weight loss ≥ 5% and weight loss ≥ 10% was compared between treatments using a logistic regression model with treatment as fixed effect and baseline BMI as covariate.

FPG was analysed using the same approach as for body weight. Moreover, the proportion of subjects reaching the ADA target for FPG (5.0 ≤ FPG ≤ 7.2 mmol/L) was analysed using a logistic regression model with treatment as fixed effect and baseline FPG as covariate.

The following secondary endpoints were analysed using the same approach as for FPG:

- Prandial increments of plasma glucose and post-prandial plasma glucose based on self-measured 7-point plasma glucose profiles
- β-cell function (fasting insulin, pro-insulin to insulin ratio and HOMA indices of β-cell function and insulin resistance)
- Fasting glucagon
- Systolic and diastolic blood pressure
- Fasting lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, FFA and ApoB)
- Albumin to creatinine ratio in urine
- Cardiovascular biomarkers (hsCRP, PAI-1 and NT-proBNP)
- Waist circumference and waist-to-hip ratio
- Patient reported outcome (overall treatment satisfaction, perceived frequency of hyperglycaemia and perceived frequency of hypoglycaemia based on DTSQ status version and DTSQ change version and total score, physical function, self-esteem, sexual life, public distress and work based on IWQOL-Lite)
- DEXA scan (total body fat mass, lean mass and fat percentage and trunk fat mass, lean mass and fat percentage)
- CT scan (visceral adipose tissue area, subcutaneous adipose tissue area, visceral to subcutaneous adipose tissue ratio and liver to spleen attenuation ratio)

The following endpoints were calculated at end of treatment and analysed using a chi square test:

- The proportion of subjects having 0, 1, 2 or 3 post-prandial glucose measurements < 10 mmol/L
- The proportion of subjects with diastolic blood pressure < 80 mmHg and systolic blood pressure < 130 mmHg
- The proportion of subjects reaching the ADA target for lipids (LDL-C < 2.6 mmol/L, TG < 1.7 mmol/L and HDL-C > 1.0 mmol/L)
- The proportion of subjects having metabolic syndrome

Safety Endpoints

The following safety endpoints were compared between treatment groups using descriptive statistics:

- Adverse events
- Physical examination
- ECG
- Ophthalmoscopy

- Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes and differential cell count)
- Biochemistry (creatinine, creatine phosphokinase, urea, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, sodium, potassium and free and total calcium)
- Urinalysis (haemoglobin, protein, glucose, ketones, pH)
- Antibodies (against liraglutide, cross-reacting with native GLP-1 and neutralising effect on liraglutide)

As a substantial number of the calcitonin measurements were below the lower limit of quantification, it was decided to evaluate calcitonin 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 per subject-year 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. Hypoglycaemic episodes were analysed using a generalised linear model including treatment and country as fixed effects under the assumption that the number of hypoglycaemic episodes per subject followed a negative-binomial distribution.

Demography of Trial Population

The population consisted of male (58.2%) and female (41.8%) subjects with type 2 diabetes. The majority of subjects were white (87%) and 9% of the subjects were categorised as Asian/Pacific Islanders. Subjects had a mean age of 56.8 (range 25-79) yrs, a mean body weight of 88.6 (42-151) kg, a mean BMI of 31.0 (17.0-41.4) kg/m^2, a mean duration of diabetes of 7.4 (0.3-40.6) yrs and a mean HbA_{1c} of 8.4 (7.0-12.9)% at screening. One third of the subjects had received previous OAD monotherapy and the other two thirds had received OAD combination therapy.

Efficacy Results

Primary Endpoint

- HbA_{1c}
  - For the ITT population (using LOCF for all subjects in the trial), 24 months of treatment resulted in estimated mean changes in HbA_{1c} from baseline of -0.36%, -0.56%, -0.58%, +0.25% and -0.50% in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. The estimated mean changes in HbA_{1c} for all 3 liraglutide groups were shown to be superior to metformin (95% CIs for treatment differences [liraglutide+metformin versus metformin] were [-0.85;-0.37], [-1.05;-0.57] and [-1.07;-0.59] for liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin respectively). Non-inferiority was demonstrated in estimated mean changes in HbA_{1c} for all liraglutide treatment groups compared with glimepiride+metformin (95% CIs for treatment differences [liraglutide+metformin versus glimepiride+metformin] of [-0.06;0.34], [-0.27; 0.13] and [-0.28;0.12] for liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin, respectively.
  - For the EITT population (using LOCF for subjects entering the extension period), 24 months of treatment resulted in estimated mean changes in HbA_{1c} from baseline of -0.41%, -0.54%, -0.52%, 0.02% and -0.44% in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups, respectively. The estimated mean changes in HbA_{1c} for all 3 liraglutide groups were shown to be superior to metformin (95% CIs for treatment differences [liraglutide+metformin versus metformin] were [-0.76;-0.11], [-0.89;-0.24] and [-0.87;-0.21] for liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin respectively). Non-inferiority was demonstrated in estimated mean changes in HbA_{1c} for all liraglutide treatment groups compared with glimepiride+metformin (95% CIs for treatment differences [liraglutide+metformin versus glimepiride+metformin] were [-0.20;0.26], [-0.33; 0.14] and [-0.31;0.16] respectively).
  - For the open label extension completers, 24 months of treatment resulted in estimated mean changes in HbA_{1c} from baseline to end of treatment of -0.78%, -0.75%, -0.82%, -0.52% and -0.73% in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and

glimepiride+metformin groups, respectively. Superiority could not be demonstrated for the changes in HbA_{1c} for the three liraglutide groups compared to metformin (95% CIs for treatment differences [liraglutide+metformin versus metformin] were [-0.65;0.14], [-0.62;0.16] and [-0.69;0.09] for liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin respectively). Non-inferiority was demonstrated in estimated mean changes in HbA_{1c} for all liraglutide treatment groups compared with glimepiride+metformin (95% CIs for treatment differences [liraglutide+metformin versus glimepiride+metformin] were [-0.30;0.21], [-0.28; 0.23] and [-0.35;0.16] respectively).

- Mean HbA_{1c} values at end of treatment were 7.5%, 7.4%, 7.4%, 7.6% and 7.4% in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively.
- For the ITT population, the observed reduction in HbA_{1c} from baseline to end of treatment increased with increasing liraglutide dose levels (-0.3%, -0.5% and -0.6% in liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin respectively). The differences between treatment groups with respect to change in HbA_{1c} from baseline to end of trial did not appear to depend on country, gender, race, age, length of diabetes or BMI.
- For the ITT population, the observed decrease in HbA_{1c} in the three liraglutide treatment groups were greater in subjects who were treated with OAD monotherapy at trial entry than subjects who received OAD combination therapy at trial entry (-0.5 versus -0.2, -0.9 versus -0.3 and -0.9 versus -0.4 for liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin, respectively).
- The proportion of subjects achieving ADA (< 7%) and AACE (≤ 6.5%) targets for HbA_{1c} increased with increasing liraglutide dose levels (19.7% and 9.2% in the liraglutide 0.6 mg+metformin group, 29.9% and 17.3% in the liraglutide 1.2 mg+metformin group, and 31.1% and 17.9% in the liraglutide 1.8 mg+metformin group). For the ADA target, the estimated proportion of subjects reaching the target was statistical significantly higher in the three liraglutide+metformin treatments groups compared with metformin. In comparison with glimepiride+metformin, a statistical significant higher propotion reached the target in the liraglutide 1.8 mg group. For the AACE target, the estimated proportion of subjects reaching the target was higher in all three liraglutide+metformin treatments groups compared with metformin, with a statistical significant difference for the liraglutide 1.2 mg+metformin and liraglutide 1.8+metformin groups.

Secondary Endpoints

- Body weight
  - For the ITT population, an estimated mean reduction in body weight from baseline to end of treatment was observed with all 3 liraglutide groups (-2.07 kg, -3.03 kg, -2.91 kg in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, respectively) and metformin (-1.80 kg) wheras an increase in estimated mean body weight was observed with glimepiride+metformin (+0.70 kg). The mean reduction in body weight for all 3 liraglutide groups were shown to be statistical significant different from glimepiride+metformin (95% CIs for treatment differences were [-3.67;-1.87], [-4.64;-2.83] and [-4.51;-2.72] for liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin respectively). Estimated mean change in body weight with liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin were shown to be statistical significant different from metformin (95% CIs for treatment differences were [-2.30;-0.16] and [-2.18;-0.05], respectively).
  - The observed reduction in body weight from baseline to end of treatment appeared greater in the liraglutide 1.8 mg+metformin group and the liraglutide 1.2 mg+metformin group in subjects with higher BMI, however no statistical treatment by BMI group interaction was observed, p=0.1421.
  - For the ITT population, the proportion of subjects achieving weight loss ≥ 5% was higher with increasing liraglutide dose levels and significantly higher in the 3 liraglutide groups (23.1%, 29.2% and 34% in liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin respectively) compared with the glimepiride+metformin group (7.6%). The proportion of subjects achieving weight loss ≥ 5% was also significantly higher in the liraglutide 1.8 mg+metformin group than the metformin group (20.8%). The proportion of subjects achieving weight loss ≥ 10% was higher with increasing liraglutide dose levels (4.5%, 7.6% and 9.1% in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8

mg+metformin groups, respectively) and significantly higher in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups than the glimepiride+metformin group (2.1%).

- Glycaemic control parameters
  - For the ITT, estimated mean change in FPG from baseline to end of treatment was -0.80, -1.20, -1.18, +0.75 and -0.64 mmol/L in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. Mean changes in FPG in the 3 liraglutide groups were significantly higher with the 3 liraglutide treatment groups compared with metformin treatment. The change in FPG in the liraglutide 1.2 mg+metformin was significantly different from the glimepiride+metformin groups, while the liraglutide 0.6 mg+metformin and liraglutide 1.8 mg+metformin groups were comparable with glimepiride+metformin group.
  - The proportion of subjects achieving the ADA target of FPG between 5.0 and 7.2 mmol/L were 19.7%, 27.5%, 24.4%, 12.1% and 19.7% in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups, respectively. The proprotion was significantly higher in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups compared with the with the metformin group and between the liraglutide 1.2 mg+metformin and the glimepiride+metformin group.
  - No significant treatment differences with respect to estimated mean change in prandial increments of plasma glucose at end of treatment was observed between the three liraglutide groups, metformin or glimepiride+metformin.
  - Estimated mean change in post-prandial plasma glucose from baseline to end of treatment was significantly greater in the three liraglutide+metformin treatment groups compared to metformin monotherapy (-1.59, -2.22, -2.10 and -0.43 for liraglutide 0.6mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin and metformin, respectively), wheras no significant differences between the three liraglutide+metformin groups and the glimepiride+metformin (-1.80) group were observed.
  - A significant difference in the distribution of subjects with 0, 1, 2 and 3 post-prandial plasma glucose measurements below the ADA target of 10 mmol/L was observed for liraglutide+metformin treatment in comparison with metformin in favour of liraglutide ($p<0.05$).
- β-cell function
  - Increase in estimated mean fasting insulin from baseline to end of treatment was comparable in all 5 treatment groups. No relevant changes were observed in HOMA-IR in any of the groups.
  - For the ITT, β-cell function as assessed by pro-insulin to insulin ratio was significantly improved from baseline to end of treatment in the liraglutide 0.6 mg+metformin and liraglutide 1.2 mg+metformin groups in comparison with the metformin group, while no difference was observed for liraglutide 1.8 mg+metformin (95% CIs for treatment differences were [-0.19; -0.03], [-0.17; -0.01] and [-0.14 ;0.02], respectively). No difference with liraglutide compared with glimepiride+metformin treatment was observed. An increase in estimated mean Homa-B from baseline to end of treatment was observed in all three liraglutide+metformin groups (17.81-64.48%), and the glimepiride+metformin (11.25%) group while a decrease in HOMA-B was observed with metformin (-7.89%). No statistical significant treatment differences were observed.
  - For EITT, the estimated slope of increase in HbA_{1c} per year after nadir was smaller for all three liraglutide+metformin treatment groups compared to the glimepiride+metformin group, this difference was statistical significant for the liraglutide 0.6 mg+metformin group. Analyses based on the ITT were different from the calculations made on the EITT population, as all liraglutide+metformin slopes using ITT were statistical significantly higher than in the metformin group and similar to the glimepiride group.
- Estimated mean fasting glucagon was significantly reduced from baseline to end of treatment in the 3 liraglutide groups compared with the glimepiride+metformin group, where a slight increase was observed. No statistical difference was observed in comparison with metformin.
- Blood pressure
  - For ITT, estimated mean changes in SBP and DBP from baseline to end of treatment were comparable between all five treatment groups as was the proportion of subjects achieving blood pressure targets of SBP < 130 mmHg and DBP < 80 mmHg.
- Fasting lipid profile

- For ITT, estimated mean TG from baseline to end of treatment was statistical significantly reduced from baseline to end of treatment in all three liraglutide treatment groups compared with metformin where estimated mean TG increased. No statistical significant treatment effect was demonstrated for the 3 liraglutide groups compared to the glimepiride+metformin group.
- Estimated mean reduction in HDL-C from baseline to end of treatment was statistical significantly smaller for liraglutide 0.6 mg+metformin compared with metformin and glimepiride+metformin, whereas the reduction in ApoB was statistical significantly greater with liraglutide 0.6 mg+metformin compared with metformin and glimepiride+metformin.
- No statistical significant differences were observed between the five treatment groups with respect to change in TC, VLDL-C, LDL-C, FFA from baseline to end of treatment.
- The proportion 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) was statistical significantly higher in the three liraglutide groups compared with metformin (p=0.0210), but comparable with the glimepiride+ metformin group.

• Cardiovascular biomarkers including urine albumin-to-creatinine ratio
  - For ITT, no change in estimated mean hsCRP was observed from baseline to end of treatment in the 3 liraglutide groups or the glimepiride+metformin group, while an increase was observed with metformin. None of the differences between treatment groups were statistically significant.
  - Estimated mean reductions in PAI-1 from baseline to end of treatment were observed with liraglutide treatment while increases were observed with metformin and glimepiride+metformin. The changes were statistical significantly different with liraglutide 1.8 mg+metformin compared with both metformin and glimepiride+metformin (95% CIs for treatment differences were [-6041;-539] and [-5339;-854], respectively).
  - The estimated change in NT-proBNP from baseline to end of treatment was statistical significantly different between the liraglutide 1.2 mg+metformin group and the glimepiride+metformin group with an estimated mean treatment difference of 4.17 pmol/L in favour of liraglutide 1.2 mg+metformin. No other differences between treatments were observed.
  - No relevant changes in urine albumin-to-creatinine ratio were observed from baseline to end of treatment in any of the treatment groups.

• Waist circumference and waist-to-hip ratio
  - For ITT, estimated mean waist circumference was reduced significantly from baseline to end of treatment (by 1.79-2.80 cm) in the 3 liraglutide groups compared with the glimepiride+metformin group (estimated increase of 0.22 cm), while no difference was observed in comparison with metformin (estimated mean reduction of 1.57 cm).
  - No relevant changes in waist-to-hip ratio were observed from baseline to end of treatment in any of the treatment groups.

• Metabolic syndrome
  - For ITT, the proportion of subjects without metabolic syndrome at end of treatment was statistical significantly higher in liraglutide 0.6 mg+meformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups compared with the metformin group (32.2%, 28.3% and 36.0% versus 18.2%, respectively). Moreover, the liraglutide 0.6 mg+metformin and liraglutide 1.8 mg+metformin groups were statistical significantly higher than the glimepiride+metformin group (23.6%).

• DEXA scan
  - Estimated changes in total body fat tissue, lean tissue, fat percentage, trunk lean and trunk fat tissue from baseline to end of treatment were greater with increasing liraglutide doses (all parameters decreased with liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin). However, the estimated decreases were only significantly greater for the liraglutide 1.8 mg+metformin group compared with the glimepiride+metformin group with respect to trunk lean tissue.

• CT scan
  - Visceral adipose tissue area was reduced by approximately 13 and 18 cm^2 in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups, respectively and increased by approximately 2 cm^2, 9 cm^2 and 5 cm^2 in the liraglutide 0.6 mg+liraglutide, metformin and glimepiride+metformin groups respectively. Changes in visceral adipose tissue area with the three liraglutide dose groups were not significantly different compared

with either the metformin or the glimepiride+metformin group.
- Subcutaneous adipose tissue area was reduced from baseline to end of treatment by all five treatment groups. Increasing reductions were obtained with increasing liraglutide doses (6-56 cm^2). The reductions in subcutaneous adipose tissue area were not significantly different beween the three liraglutide+metformin groups compared with the metformin or the glimepiride+metformin group.
- No relevant changes in visceral to subcutaneous adipose tissue ratio were observed from baseline to end of treatment in any of the treatment groups.
- Liver to spleen attenuation ratio increased slightly from baseline to end of treatment in the liraglutide 1.8 mg+metformin group (indicating a slight relief of hepatic steatosis) with no changes in any other group. The change in liver to spleen attenuation ratio was not significantly different between the 3 liraglutide groups compared with metformin or glimepiride+metformin.

- Patient reported outcome
  - DTSQs: Comparable increases (improvements) in overall treatment satisfaction were measured in all five treatment groups except for the metformin group which decreased slightly. Perceived frequency of hyperglycaemia decreased (improved) in all five treatment groups. The decrease in perceived frequency increased with increasing dose of liraglutide. The decrease was significantly greater in all three liraglutide+metformin groups compared to the metformin group, whereas there were no differences between the liraglutide groups and the glimepiride group. Perceived frequency of hypoglycaemia increased (worsened) slightly in the three liraglutide groups and a little more in the metformin and glimepiride+metformin groups. The increase measured in the glimepiride+metformin group was significantly different from the liraglutide 0.6 mg+metformin and liraglutide 1.8 mg+metformin groups.
  - The results from DTSQc supported the conclusions for overall treatment satisfaction and perceived frequency of hyperglycaemia, based on DTSQs with small differences in response to metformin monotherapy. However, the preceived frequency of hypoglycaemia in DTSQc decreased for all 5 treatment groups. The decrease in the 3 liraglutide groups was significantly different from the smaller decrease in the glimepiride+metformin group.
  - IWQOL-Lite: Improvements were reported in total IWQOL-Lite score for each sub-section (physical function, self-esteem, sexual life, public distress and work) in all 5 treatment groups. There were no significant differences between treatment groups except for public distress, which improved significantly more in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups than the glimepiride+metformin group.

Safety Results

- Adverse events
  - AEs were reported in 81.4%, 81.7%, 83.1%, 72.7% and 77.7% of subjects in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups, respectively. The majority of TEAEs were mild in severity and assessed by the investigator to be unlikely related to trial products. Adverse events reported within the system organ class of infections and infestations were the most frequently reported TEAEs in all treatment groups. Gastrointestinal disorders were more frequently reported within 24 months in the liraglutide+metformin treatment groups compared with the metformin and glimepiride+metformin groups. The higher frequencies of gastrointestinal disorders in the liraglutide+metformin groups were in particular among the preferred terms nausea, diarrhoea, vomiting and dyspepsia.
  - The proportion of subjects with TEAEs assessed by the investigator to be possibly or probably related to trial products was higher in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups (39.7%, 44.6% and 44.2%, respectively) compared with the metformin and glimepiride+metformin groups (17.4% and 22.3%, respectively). The most frequently reported TEAEs within 24 months that were evaluated to be possibly or probably related to trial product were gastrointestinal disorders in all five treatment groups, and the overall greater incidence of possibly or probably related events in the liraglutide+metformin groups was to a large extent attributable to the fact that the incidence of possibly or probably related events of gastrointestinal disorders was higher in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups (26.4%, 32.5% and 36.4%, respectively) compared with the metformin and glimepiride+metformin groups (7.4% and 12.0%, respectively). The most common gastrointestinal disorders assessed to be possibly or probably related to trial products were nausea, diarrhoea, vomiting and dyspepsia, for which the incidence was higher in the three liraglutide+metformin groups compared with the metformin and glimepiride+metformin groups.
  - Serious AEs were reported for 14.9%, 10.4%, 6.2%, 7.4% and 9.9% of subjects in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups, respectively. The treatment emergent SAEs showed no consistent pattern with respect to system organ class of events.
  - Two SAEs including the term pancreatitis were reported during the 6-month double blind trial period. Idiopathic pancreatitis was diagnosed in a subject treated with liraglutide 1.2 mg+metformin for approximately 1½ month and acute pancreatitis was reported in a subject treated with glimepiride+metformin for approximately 3 months.
  - A total of four subjects died during the trial. Two subjects in the liraglutide 0.6 mg+metformin group suffered fatal events of tuberculosis and acute renal failure/pyelonephritis, respectively. One subject in the liraglutide 1.2 mg+metformin group suffered fatal events of hepatic cirrhosis and hepatic malignant neoplasm. In addition, one death occurred during the run in period 6 days after initiation of metformin therapy. All fatal adverse events were deemed unlikely related to trial product by the investigator.
- Laboratory analyses
  - No clinically relevant differences from baseline to end of treatment or between the 5 treatment groups were observed for standard safety laboratory analyses.
  - For calcitonin, a few comparisons of the liraglutide+metformin treatment groups with the comparators resulted in a p-value below 0.05 (Week 65 and 78) indicating higher calcitonin levels in groups treated with liraglutide+metformin, but no consistent or clinically relevant trends were observed across dose groups or with time.
- Vital signs and physical findings
  - Mean increases in pulse from baseline to end of treatment (LOCF) were 1.6, 0.8, 1.9, -0.2 and 0.4 beats per minute in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups, respectively. ANCOVA analysis indicated a trend towards a minor increase in pulse with liraglutide+metformin treatment relative to comparators, which was statistically significant for the comparison of liraglutide 1.8 mg + metformin versus metformin monotherapy. However, the observed increases in pulse were not evaluated to be clinically relevant.

- No clinically relevant differences from baseline to end of treatment or between the 5 treatment groups were observed for physical examination, ECG and ophthalmoscopy.

- Hypoglycaemic episodes
  - The proportion of subjects experiencing minor hypoglycaemic episodes (confirmed plasma glucose < 3.1 mmol/L) during the 104-week treatment period was lower in the 3 liraglutide groups (5.0, 4.2 and 4.1%) and in the metformin group (2.5%) compared to the glimepiride+metformin group (24.0%). The rate of minor hypoglycaemic episodes was 0.067, 0.077, 0.068, 0.055 and 0.864 events/subject year in the liraglutide 0.6 mg+metformin, liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin, metformin and glimepiride+metformin groups respectively. The same pattern was evident for hypoglycaemic episodes in the subclass 'Symptoms only' as well as for nocturnal hypoglycaemic episodes.
  - One major hypoglycaemic episode (a nocturnal episode that occurred in a patient receiving liraglutide 1.2mg+metformin) was reported.
- Liraglutide antibodies
  - When liraglutide antibodies were summarised at end of treatment only in those subjects who had not received liraglutide for at least 5 days before sampling, approximately 5% of subjects evaluated for antibodies in the liraglutide+metformin treatment groups were positive for liraglutide antibodies, with more than half of these showing neutralising and/or cross-reacting effect. None of the subjects in comparator treatment groups were tested positive for liraglutide antibodies.
- Pregnancy
  - One (1) pregnancy was reported during the trial in a 41-year old woman randomised to the metformin group. One month after confirmation of the pregnancy by a β-HCG test, no symptoms of pregnancy had been reported and ultrasound confirmed that the woman was no longer pregnant. No evidence or documentation of a miscarriage has been reported, and the woman cannot recall that she has had a miscarriage.

Overall Conclusions

Two years of once-daily treatment with liraglutide in combination with metformin (0.6, 1.2 and 1.8 mg) provided better glycaemic control (as measured by HbA_{1c} as well as other glycaemic parameters) than metformin monotherapy and comparable to combination therapy with metformin and glimepiride. In addition, subjects treated with liraglutide experienced a weight loss in the initial treatment period that was sustainable throughout the period. The improvement in glycaemic control with liraglutide was obtained with a lower risk of hypoglycaemia compared with the standard treatment of metformin in combination with glimepiride. Although there is an increase in gastrointestinal side effects, mainly nausea and diarrhoea, with liraglutide, these side effects were generally transient and primarily during the early treatment.

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice.