2 Synopsis – Including CTR Amendment 1, Dated 28 May 2009

Trial Registration ID-number	**EudraCT number**
NCT00331851	2005-003415-71

Title of Trial

Liraglutide Effect and Action in Diabetes (LEAD-5): Effects on glycaemic control after once daily administration of liraglutide in combination with glimepiride and metformin versus glimepiride and metformin combination therapy, and versus insulin glargine added to glimepiride and metformin combination therapy in subjects with type 2 diabetes. A six-month randomised, double-blind, parallel-group, multi-centre, multi-national trial with an open-label treat-to-target insulin glargine control arm

Investigator(s)

A total of 107 principal investigators in 17 countries. Professor [redacted] from [redacted] in [redacted] was appointed as Signatory Investigator.

Trial Site(s)

A total of 107 centres in 17 countries participated. Argentina (5), Austria (7), Denmark (7), Finland (5), France (9), India (5), Italy (8), The Netherlands (8), Norway (5), Philippines (4), Poland (5), Russia (4), Serbia and Montenegro (4), Slovakia (6), South Africa (4), Spain (9) and United Kingdom (12).

Publications

No publications to date.

Trial Period	**Development Phase**
30 May 2006 to 20 April 2007	Phase 3a

Objectives

Primary Objective:

- To assess and compare the effect on glycaemic control (assessed by change in HbA_{1c}) of once daily administration of liraglutide in combination with glimepiride and metformin versus glimepiride and metformin combination therapy, and versus insulin glargine added to glimepiride and metformin 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 8-point plasma glucose profiles (self-measured)).
- To assess and compare β-cell function (fasting insulin, fasting C-peptide, fasting pro-insulin) and fasting glucagon. The homeostasis model assessment (HOMA) were to 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.

Safety Objectives

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

Other Objectives

- To assess and compare cardiovascular effects (highly sensitive C reactive protein (hsCRP), plasminogen activator inhibitor-1 (PAI-1), N-terminal pro-B-type natriuretic peptide (NT-proBNP)).
- To assess and compare waist and hip circumference and waist-to-hip ratio.

Methodology

This was a 6-month randomised, double-blind, parallel-group, multi-centre, multi-national trial in subjects with type 2 diabetes investigating the safety and efficacy of liraglutide as add-on to a combination treatment of metformin and glimepiride. This treatment was compared to a combination treatment of OADs alone and a combination treatment with OADs and insulin glargine.

Subjects were randomised in 3 groups (2:1:2) to receive 1.8 mg once-daily liraglutide (blinded), once-daily liraglutide placebo (blinded) or once-daily insulin glargine (open-label) – in each group combined with metformin and glimepiride therapy. Subjects receiving 1.8 mg liraglutide are referred to as the liraglutide 1.8 mg+glimepiride+metformin group, subjects receiving liraglutide placebo were referred to as the glimepiride+metformin group and subjects receiving insulin glargine were referred to as the glargine+glimepiride+metformin group. At randomisation, the subjects were stratified with respect to their previous treatment: OAD monotherapy or combination therapy.

Randomisation took place after a run-in period including a 3-week forced metformin and glimepiride titration period followed by a maintenance period of 3 weeks. During the titration period, doses of metformin and glimepiride were to be increased up to 2000 mg/day and 4 mg/day, respectively. Subjects already on metformin and glimepiride combination therapy at enrolment could go through a modified titration period or advance directly to the maintenance period at the discretion of the investigator.

After randomisation, the subjects underwent a 2-week period of titration with liraglutide for reaching a daily dose of 1.8 mg liraglutide in the last week. Daily liraglutide placebo injection volumes were similar to the volumes of active liraglutide. After this 2-week titration period, a 24-week maintenance period commenced, during which doses of liraglutide/liraglutide placebo and metformin were fixed, although glimepiride and insulin glargine doses could be adjusted. These 26 weeks are referred to as the 26-week treatment period. The dose of insulin glargine was to be adjusted by the subject following a titration guideline.

Liraglutide/liraglutide placebo and insulin glargine were to be administered as subcutaneous (s.c.) injections once daily. Metformin was to be taken orally twice daily and glimepiride was to be taken orally once daily.

The 26-week treatment period was followed by a one-week follow-up period and a follow-up visit.

Number of Subjects Planned and Analysed

A total of 1036 subjects with type 2 diabetes were screened in order to include 621 subjects in the run-in period and to be able to randomise 570 subjects. It was anticipated to reach 428 evaluable subjects, based on an estimated drop-out rate of 25%. The actual subject disposition (including analysis sets) was as follows:

	LIRA 1.8 mg + OAD N (%)	OAD N (%)	Glargine + OAD N (%)	All N (%)
Screened				973
Screening failures				392
Randomized	232 (100)	115 (100)	234 (100)	581 (100)
Exposed	230 (99.1)	114 (99.1)	232 (99.1)	576 (99.1)
Withdrawn	25 (10.8)	19 (16.5)	15 (6.4)	59 (10.2)
Adverse Events	11 (4.7)	1 (0.9)	5 (2.1)	17 (2.9)
Ineffective therapy	2 (0.9)	13 (11.3)	1 (0.4)	16 (2.8)
Non-compliance with protocol	1 (0.4)	1 (0.9)	5 (2.1)	7 (1.2)
Other	11 (4.7)	4 (3.5)	4 (1.7)	19 (3.3)
Completers	207 (89.2)	96 (83.5)	219 (93.6)	522 (89.8)
ITT analysis set	230 (99.1)	114 (99.1)	232 (99.1)	576 (99.1)
PP analysis set	195 (84.1)	90 (78.3)	205 (87.6)	490 (84.3)
Safety analysis set	230 (99.1)	114 (99.1)	232 (99.1)	576 (99.1)

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, both inclusive (as allowed according to local guidelines for metformin and glimepiride treatment), BMI ≤ 45.0 kg/m^2 and HbA_{1c} values of 7.5-10.0% (both incl.) in subjects on OAD monotherapy and 7.0-10.0% (both incl.) in subjects on OAD combination therapy.

Test Product, Dose and Mode of Administration, Batch Number

Liraglutide (6.0 mg/mL) in 3 mL FlexPen® (Batch nos. SP51131 and RP52009) to be injected subcutaneously (s.c.)

in the upper arm, abdomen or thigh. Daily liraglutide dose was 1.8 mg.
Metformin tablets (500 mg) (Batch nos. 102602 and 102527) for oral administration. Daily metformin dose was 2000 mg.
Glimepiride tablets (1 mg) (Batch no. E479) for oral administration. Daily glimepiride dose was 2-4 mg.

Duration of Treatment

A metformin and glimepiride run-in period of 3 weeks and a 3-week mandatory maintenance period on metformin and glimepiride followed by a 26-weeks treatment period during which subjects in the liraglutide 1.8 mg+glimepiride+metformin group started with a 2-week titration of liraglutide and the glargine+glimepiride+metformin group were titrated according to a titration guideline.

Reference Therapy, Dose and Mode of Administration, Batch Number

Liraglutide placebo in 3 mL FlexPen® (Batch nos. SP51130 and RP51969) to be injected subcutaneously (s.c.) in the upper arm, abdomen or thigh. Daily liraglutide placebo injection volumes were similar to the volumes of active liraglutide.
Insulin glargine (Lantus 100 IU/mL OptiSet® 3 mL) (Batch nos. 40N012 and 50E145) to be injected s.c. in upper arm, abdomen or thigh. Daily insulin glargine dose was titrated individually according to a titration guideline.

Criteria for Evaluation – Efficacy

HbA_{1c}, body weight, fasting plasma glucose (FPG), self-measured 8-point plasma glucose profiles, β-cell function (fasting insulin, fasting pro-insulin, fasting C-peptide), fasting glucagon, systolic and diastolic blood pressure, fastin lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, FFA and ApoB, cardiovascular risk biomarkers (hsCRP, PAI-1 and NT-proBNP) and waist and hip circumference.

Criteria for Evaluation – Safety

Adverse events, physical examination, pulse, ECG, ophthalmoscopy and hypoglycaemic episodes. 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 all efficacy endpoints and included all subjects who had been randomised and 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:
  - completed the blinded 26-week treatment period.
  - had an evaluable HbA_{1c} observation at Week 0 and Week 26 collected within the allowed window (5 days before the visit until 7 days after the visit).
  - had no protocol deviations with potential impact on the primary efficacy assessment.
  - fulfilled the first 3 inclusion criteria (for HbA_{1c} an extended range of ±0.25% was allowed).
  - fulfilled all randomisation criteria (for FPG an extended range of ±0.5 mmol/L was allowed).
  - did not meet any withdrawal criteria.
- The safety analysis set was used for all safety endpoints and included all subjects who had been exposed to at least one dose of the trial products.

Statistical Methods

Primary Endpoint

The primary endpoint was the change in HbA_{1c} after 26 weeks of treatment. The 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 in combination with metformin and glimepiride was superior to therapy with metformin and glimepiride. If so, it was tested whether liraglutide in combination with metformin and glimepiride was non-inferior to the therapy with insulin glargine, metformin and glimepiride. If non-inferiority could be demonstrated, it was tested whether liraglutide in combination with metformin and glimepiride was superior to the therapy with insulin glargine, metformin and glimepiride. Finally, as assay sensitivity, it was tested whether glargine with metformin and glimepiride was superior to treatment

with metformin and glimepiride. Superiority was always concluded if the upper limit of the 2-sided 95% confidence interval was below 0 and non-inferiority was concluded if the upper limit of the 2-sided 95% confidence interval 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 (main effects were in the original model)
- Treatment by country interaction (main effects were in the original model)
- Main effect of gender
- Main effect of race
- Main effect of age group (< 65 years and ≥ 65 years)
- 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)

The proportion of subjects achieving HbA_{1c} target (ADA target < 7% and AACE target ≤ 6.5%) was compared between treatments using a logistic regression model with treatment as fixed effect and baseline HbA_{1c} as a covariate.

Secondary Endpoints

Change in body weight was analysed using the same model as for the primary endpoint. Superiority of liraglutide to both comparator groups was tested. The following additional analyses related to body weight were performed:

- The impact of baseline BMI on change in body weight was explored 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 and BMI ≥ 35 kg/m^2) as a fixed effect to the ANCOVA model.
- The weight loss responder rate after 26 weeks of treatment was categorised in four groups]-∞;0%[, [0%; 5%[, [5%; 10%[, [10%; ∞[) and summarised.
- The proportion of subjects achieving the weight loss target of ≥ 5% and ≥ 10% of baseline body weight was compared between treatments using a logistic regression model with treatment as fixed effect and baseline BMI as covariate.
- The change in body weight was evaluated for different nausea subgroups.

Fasting plasma glucose (FPG) was analysed using the same model as for the primary endpoint. Moreover, the likelihood 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 8-point plasma glucose profiles.
- β-cell function (fasting insulin, fasting C-peptide, pro-insulin to insulin ratio and HOMA index 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.
- Waist circumference and waist-to-hip ratio.

Summary and change from baseline in the cardiovascular effects hsCRP, PAI-1 and NT-proBNP were presented by week and treatment using descriptive statistics. For hsCRP and NT-proBNP, the changes from baseline were analysed using the standard ANCOVA model, while for PAI-1 the changes from baseline was analysed by nonlinear mixed modelling including subjects as random effects and allowing for left and right censoring.

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

- Distribution of subjects having 0, 1, 2 or 3 post-prandial glucose measurements < 10 mmol/L.
- The proportion of subjects reaching targets for 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 the metabolic syndrome (defined as that 3 of 5 conditions regarding abdominal obesity, triglycerides, HDL-C, blood pressure and fasting glucose had to be met in order to fulfil the criteria for metabolic syndrome).

Safety Endpoints

The following safety endpoints were compared between treatment groups using descriptive statistics:
- Adverse events
- Physical examination
- ECG
- Opthalmoscopy
- Haematology (haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes and differential cell count)
- Biochemistry (creatinine, CPK, urea, albumin, total bilirubin, ALAT, ASAT, ALP, sodium, potassium, free and total calcium and calcitonin)
- Urinalysis (haemoglobin, protein, glucose, ketones, pH, creatinine and albumin)
- Antibodies (against liraglutide, cross-reacting and neutralising)

As a substantial number of the calcitonin measurements were below LLOQ, 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 the calcitonin was the (censored) response. The model included time, treatment, gender and treatment by time interaction as fixed effects with the restriction that at baseline means for treatment groups were assumed equal. Furthermore, subjects were entered as random effects.

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 (and duration of treatment as an offset variable in the model) 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 (56.5%) and female (43.5%) subjects with type 2 diabetes. The majority of subjects were white (75%) and approximately 16% of the subjects were categorized as Asian or Pacific Islanders. The subjects had a mean age of 58 years (range 24 to 80 years), a mean body weight of 85 kg (range 46 to 150 kg), a mean BMI of 31 kg/m^2 (range 17 to 45 kg/m^2), a mean duration of diabetes of 9 years and a mean HbA_{1c} of 8.5% at screening. About 6% of the subjects were previously on OAD monotherapy and the remaining were previously on OAD combination therapy.

Efficacy Results

Primary Endpoint

- **HbA_{1c}**
  - The estimated mean changes in HbA_{1c} from baseline to end of treatment were -1.33% in the liraglutide 1.8 mg+glimepiride+metformin group, -0.24% in glimepiride+metformin group and -1.09% in glargine+glimepiride+metformin group. Mean HbA_{1c} values at end of treatment were 7.0% in the liraglutide 1.8 mg+glimepiride+metformin group, 8.1% in the glimepiride+metformin group and 7.2% in the glargine+glimepiride+metformin group.
  - The estimated mean change in HbA_{1c} at end of treatment was shown to be superior for the liraglutide 1.8 mg+glimepiride+metformin group compared to both the glimepiride+metformin group (estimated difference of -1.09%, 95% CI for treatment difference was [-1.28;-0.90], and p<0.0001) and to the glargine+glimepiride+metformin group (estimated difference of -0.24%, 95% CI for treatment difference was [-0.39;-0.08] and p=0.0015).

- Supplementary analyses of mean change in HbA_{1c} did not reveal a by pre-treatment, country, gender, race, age or BMI interaction.
- The likelihood of subjects reaching ADA and AACE HbA_{1c} targets (< 7% and ≤6.5%, respectively) was higher in the liraglutide 1.8 mg+glimepiride+metformin group (51.7% and 36.1%, respectively) as compared to both the glimepiride+metformin group (14.9% and 10.5%, respectively) and the glargine+glimepiride+metformin group (44.4% and 22.8%, respectively).

Secondary Endpoints

- **Body weight**
  - The estimated mean weight change was -1.81 kg from baseline in the liraglutide 1.8 mg+glimepiride+metformin group, -0.42 kg in the glimepiride+metformin group and +1.62 kg in the glargine+glimepiride+metformin group.
  - The estimated mean weight loss in the liraglutide 1.8 mg+glimepiride+metformin group was statistically significantly greater than the glimepiride+metformin group (estimated difference of -1.39 kg, 95% CI for treatment difference was [-2.10;- 0.69] and p=0.0001) and the glargine+glimepiride+metformin group (estimated difference of -3.43 kg, 95% CI for treatment difference was [-4.00;-2.86] and p<0.0001).
  - Treatment by BMI interaction was not statistically significant (p=0.2892).
  - The distribution of weight loss rates among the 3 treatment groups reflected that more subjects lost weight in the liraglutide 1.8 mg+glimepiride+metformin group and furthermore the mean weight losses were more extensive than in the 2 comparator groups. In the liraglutide 1.8 mg+glimepiride+metformin group 47.8% lost up to 5% of the baseline body weight and 20.9% lost between 5 and 10% of the baseline body weight. In the glargine+glimepiride+metformin group, the majority of subjects (71.6%) experienced a weight increase or unchanged weight.
  - The likelihood of achieving a weight loss of ≥ 5% of the baseline body weight was statistically significantly higher in the liraglutide 1.8 mg+glimepiride+metformin group as compared to the comparator groups (p=0.0031 in comparison to glimepiride+metformin group and p<0.0001 in comparison to the glargine+glimepiride+metformin group) whereas there was no significant difference in the percentage of subjects achieving a weight loss of ≥ 10% of the baseline body weight between any group.
  - A classification of subjects into 'nausea groups' demonstrated that the majority of subjects were classified in the nausea group 'none' (meaning nausea reported for less than or equal to 7 days during the trial). In this group, subjects treated with liraglutide (90.4%) had a mean weight change of -1.7 kg compared to glimepiride+metformin (-0.4 kg) and glargine+glimepiride+metformin (+1.6 kg).
- **Glycaemic control parameters**
  - The estimated mean changes in FPG were -1.55 mmol/L in the liraglutide 1.8 mg+glimepiride+metformin group, +0.53 mmol/L in the glimepiride+metformin group, and -1.79 mmol/L in the glargine+glimepiride+metformin group. The estimated mean change in the liraglutide 1.8 mg+glimepiride+metformin group was statistically significantly greater than the glimepiride+metformin group (p<0.0001) but not different from the glargine+glimepiride+metformin group (p=0.2002).
  - The likelihood of achieving ADA targets (FPG between 5 and 7.2 mmol/L) was significantly higher in the liraglutide 1.8 mg+glimepiride+metformin group as compared to the glimepiride+metformin group (p<0.0001) but not as compared to glargine (p=0.9490).
  - Mean post-prandial plasma glucose (self-measured) at the end of treatment was statistically significantly lower in the liraglutide 1.8 mg+glimepiride+metformin group as compared to the glimepiride+metformin group (estimated mean difference of -1.84 mmol/L and p<0.0001) but not when compared to glargine (p=0.3364).
  - The reduction in mean prandial increment of plasma glucose (self-measured) at the end of treatment in the liraglutide 1.8 mg+glimepiride+metformin group was not statistically significantly different from both comparator groups.
  - The likelihood of achieving ADA targets for post-prandial glucose (≤10 mmol/L) were statistically significant higher for the liraglutide 1.8 mg+glimepiride+metformin group as compared to the glimepiride+metformin group (p<0.0001) but not when compared to the glargine+glimepiride+metformin group (p= 0.4125).
- **β-cell function**
  - Based on estimated mean changes in fasting insulin, pro-insulin to insulin ratio and HOMA index of β-cell

function, a statistically significant improvement in β-cell function was observed in the liraglutide 1.8 mg+glimepiride+metformin group as compared to the glimepiride+metformin group (the glargine+glimepiride+metformin group was not assessed for these parameters). Changes in HOMA index of insulin resistance were not statistically significantly different.
  - There was a reduction in the pro-insulin to C-peptide ratio in the liraglutide 1.8 mg+glimepiride+metformin group which was statistically significantly greater than both comparators.
  - The increase in mean fasting glucagon was not statistically significantly different from the increase seen in both comparator groups.
- **Fasting lipid profile**
  - Statistically significant effects on fasting lipids were limited to reductions in TC and LDL-C for the liraglutide 1.8 mg+glimepiride+metformin group in comparison to the glargine+glimepiride+metformin group. In addition an increase in FFA in the glimepiride+metformin group was statistically significantly different from the very small increase in FFA in the liraglutide 1.8 mg+glimperide+metformin group.
  - The proportion of subjects achieving ADA targets (LDL-C < 2.6 mmol/L, TG < 1.7 mmol/L and HDL-C > 1.0 mmol/L) was not significantly higher for the liraglutide 1.8 mg+glimepiride+metformin group than the comparator groups.
- **Blood pressure (BP)**
  - There was a statistically significant change in estimated mean systolic blood pressure (-3.97 mmHg) from baseline to end of treatment in the liraglutide 1.8 mg+glimepiride+metformin group when compared to the glargine+glimepiride+metformin group (estimated difference of -4.51 mmHg, 95% CI for the difference were [-6.82;-2.20] and p=0.0001). There was no difference when compared to the glimepiride+metformin group (estimated difference of -2.53 mmHg and 95% CI for the difference were [-5.36;0.29] and p=0.0791).
  - Reduction in diastolic blood pressure from baseline to end of treatment was not statistically significantly different from reductions in both comparator groups.
  - The proportion of subjects achieving blood pressure targets (SBP < 130 mmHg and DBP < 80 mmHg) was not statistically significantly different in the liraglutide 1.8 mg+glimepiride+metformin group (24.3%) when compared to the 2 comparator groups (21.6% in the glargine+glimepiride+metformin group and 18.4% in the glimepiride+metformin group).
- **Cardiovascular risk biomarkers including albumin-to-creatinine ratio**
  - Change in cardiovascular risk markers showed no differences between liraglutide treatment and comparators.
- **Waist circumference and waist-to-hip ratio**
  - The estimated mean change in waist circumference was -1.50 cm in the liraglutide 1.8 mg+glimepiride+metformin group, -0.62 cm in the glimepiride+metformin group, and +0.89 cm in the glargine+glimepiride+metformin group. The reduction was statistically significant for the liraglutide 1.8 mg+glimepiride+metformin group as compared to the glargine+glimepiride+metformin group (p<0.0001) but not when compared to the glimepiride+metformin group.
  - No or very slight changes in mean waist-to-hip ratio was seen in all 3 groups and the changes were not statistically significantly different.
- **Metabolic syndrome**
  - The proportion of subjects without metabolic syndrome at the end of treatment in the liraglutide 1.8 mg+glimepiride+metformin group was not statistically significantly different from the glimepiride+metformin and the glargine+glimepiride+metformin group.

Safety Results

- **Adverse events**
  - Adverse events were reported by 65.7% of the subjects in the liraglutide 1.8 mg+glimepiride+metformin group, 56.1% in the glimepiride+metformin group, and 54.7% in the glargine+glimepiride+metformin group. The most frequently reported adverse events in the liraglutide 1.8 mg+glimepiride+metformin group were diarrhoea and nausea, whereas in the glimepiride+metformin and glargine+glimepiride+metformin groups it was nasopharyngitis and headache. The majority of these events were mild in severity.
  - Adverse events considered to have a probable or possible relation to treatment regimen were reported by 36.1% of the subjects in the liraglutide 1.8 mg+glimepiride+metformin group, 11.4% in the glimepiride+metformin

group, and 4.3% in the glargine+glimepiride+metformin group. The most frequently reported adverse events were from the gastrointestinal system in all treatment groups.
  - Serious adverse events (SAEs) were reported by 3.5% of the subjects in the liraglutide 1.8 mg+glimepiride+metformin group (8 subjects), 6.1% in the glimepiride+metformin group (7 subjects), and 7.8% in the glargine+glimepiride+metformin group (18 subjects). In the liraglutide 1.8 mg+glimepiride+metformin group the most frequently reported SAEs were from the cardiac system, infections and infestations and metabolism and nutrition disorders. In the glimepiride+metformin and glargine+glimepiride+metformin groups, the most frequently reported SAEs were of the cardiac system organ class. Four (4) SAEs (renal cell carcinoma, 2 events of hypoglycaemia and 1 event of gastroenteritis) were reported as probable or possible related to the treatment regimen by the investigator and they were all from the liraglutide 1.8 mg+glimepiride+metformin group.
  - Eleven (11) subjects withdrew due to adverse events in the liraglutide 1.8 mg+glimepiride+metformin group, 1 subject in the glimepiride+metformin group and 5 subjects in the glargine+glimepiride+metformin group. In the liraglutide 1.8 mg+glimepiride+metformin group, 4 of the 11 subjects withdrew due to adverse events related to the gastrointestinal system. In total, 8 subjects withdrew due to serious adverse events.
  - Two (2) deaths were reported, 1 from the glimepiride+metformin group and 1 from the glargine+glimepiride+metformin group. Both events were acute myocardial infarctions and were evaluated as being unlikely related to the treatment regimen.
  - Gastrointestinal disorders were reported more frequently in the liraglutide 1.8 mg+glimepiride+metformin group (37.8%) as compared to the glimepiride+metformin group (15.8%), and the glargine+glimepiride+metformin group (7.8%). The adverse events in the liraglutide 1.8 mg+glimepiride+metformin group occurred more frequently in the titration period and both the duration of the gastrointestinal symptoms and percentage of subjects having gastrointestinal symptoms decreased over time.
- **Laboratory analyses**
  - No clinically relevant differences were observed for standard safety laboratory analyses.
- **Calcitonin**
  - For both glargine+glimepiride+metformin and liraglutide 1.8 mg+glimepiride+metformin there was a comparable but significant increase at week 26 in comparison to the glimepiride+metformin group, with mean levels remaining within the normal range.
- **Vital signs, physical findings and other observations related to safety**
  - An increase in pulse was seen in all 3 groups with the largest increase seen in the liraglutide 1.8 mg+glimepiride+metformin group (+2.62 beats/min). The changes were not considered to be clinically relevant. No clinically relevant differences were observed for physical examination, ECG, and ophthalmoscopy.
- **Hypoglycaemic episodes**
  - Major hypoglycaemic episodes were only reported in the liraglutide 1.8 mg+glimepiride+metformin group where 6 events were reported in 5 subjects.
  - No statistically significant difference in rate of minor episodes between the liraglutide 1.8 mg+glimepiride+metformin group (1.156 events/subject year) and both comparator groups (glargine+glimepiride+metformin group: 1.287 minor events/subject year and glimepiride+metformin group: 0.946 minor events/subject year). For 'symptoms only' episodes there were statistically significantly more episodes in the glargine+glimepiride+metformin group (1.814 events/subject year) as compared to the liraglutide 1.8 mg+glimepiride+metformin group (0.998 events/subject year) (p=0.0322) but no statistically significant difference from the glimepiride+metformin group (0.530 events/subject year).
  - Rates of all the different types of nocturnal hypoglycaemic episodes appeared to be lower in the liraglutide 1.8 mg+glimepiride+metformin group as compared to the glargine+glimepiride+metformin group (not tested by statistical analysis).
- **Liraglutide antibodies**
  - Antibodies towards liraglutide were demonstrated in 20 (9.8%) of the subjects from the liraglutide 1.8 mg+glimepiride+metformin group and in 1 subject in each of the glimepiride+metformin and glargine+glimepiride+metformin groups at end of treatment.

Conclusions

- Glycaemic control, as measured by change in HbA1c, was better in the liraglutide 1.8 mg+glimepiride+metformin group as compared to the glimepiride+metformin and the glargine+glimepiride+metformin groups.
- The reduction in body weight in the liraglutide 1.8 mg+glimepiride+metformin group was greater in comparison to the glimepiride+metformin and the glargine+glimepiride+metformin groups.
- The reduction in FPG and post-prandial glucose in the liraglutide 1.8 mg+glimepiride+metformin group were greater when compared to the glimepiride+metformin group but not compared to the glargine+glimepiride+metformin group. The reduction in prandial increments of plasma glucose was not larger than any of both comparator groups.
- The improvement in β-cell function in the liraglutide 1.8 mg+glimepiride+metformin group was greater in comparison to the glimepiride+metformin group (based on fasting insulin, fasting C-peptide, pro-insulin to insulin ratio, pro-insulin to C-peptide ratio, and HOMA index of β-cell function) whereas no difference in the HOMA index of insulin resistance was observed. β-cell function in the glargine+glimepiride+metformin group could only be assessed by C-peptide and pro-insulin to C-peptide ratio where the liraglutide 1.8 mg+glimepiride+metformin group was different from both comparators with no change in C-peptide and a reduction in the pro-insulin to C-peptide ratio.
- The changes in the fasting lipid profile were marginal in all 3 treatment groups and there was no clear treatment effect.
- A larger reduction in systolic blood pressure was observed as compared to the glargine+glimepiride+metformin group whereas there was no change in comparison to the glimepiride+metformin group. No significant difference in the reduction in diastolic blood pressure was observed as compared to both comparators.
- With regard to hypoglycaemic episodes, there was no difference on minor episodes whereas the rate of 'symptoms only' episodes was significantly lower in the liraglutide 1.8 mg+glimepiride+metformin group as compared to the glargine+glimepiride+metformin group but not to the glimepiride+metformin group. Major hypoglycaemic episodes were only reported in the liraglutide 1.8 mg+glimepiride+metformin group with 6 major episodes in 5 subjects.
- The proportion of subjects with adverse events was higher in the liraglutide 1.8 mg+glimepiride+metformin group than in the comparator groups. The majority of adverse events were from the gastrointestinal system, mild or moderate. The gastrointestinal adverse events were transient. Adverse event withdrawal due to these gastrointestinal adverse events was more frequent in the liraglutide 1.8 mg+glimepiride+metformin group.
- The safety profile as reflected by standard laboratory parameters, vital signs, and physical findings was similar between the 3 treatment groups.
- For both glargine+glimepiride+metformin and liraglutide 1.8 mg+glimepiride+metformin there was a comparable but significant increase at week 26 in comparison to the glimepiride+metformin group, with mean levels remaining within the normal range.
- Antibodies towards liraglutide were demonstrated in 20 (9.8%) of the subjects from the liraglutide 1.8 mg+glimepiride+metformin group and in 1 subject in each of the glimepiride+metformin and glargine+glimepiride+metformin groups at end of treatment.
- There was no clear treatment effect on the cardiovascular risk biomarkers in the liraglutide 1.8 mg+glimepiride+metformin group as compared to both comparators.
- The reduction in waist circumference for the liraglutide 1.8 mg+glimepiride+metformin group was greater when compared to the glargine+glimepiride+metformin group but not when compared to the glimepiride+metformin group. The changes in waist-to-hip ratio were not significant in the liraglutide 1.8 mg+glimepiride+metformin group as compared to both comparators.

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