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

Trial Registration ID-number	**EudraCT number**
NCT00318422	2005-003414-15

Title of Trial

Liraglutide Effect and Action in Diabetes (LEAD-1): Effect on glycaemic control after once daily administration of liraglutide in combination with glimepiride versus glimepiride monotherapy versus glimepiride and rosiglitazone 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.

Investigators

A total of 116 principal investigators from 21 countries participated. Dr [redacted] was appointed Principal and Signatory Investigator for the trial.

Trial Sites

A total of 21 countries and 116 centres participated:

Argentina (7), Australia (9), Bulgaria (6), Croatia (3), Czech Republic (7), Finland (10), France (8), Hong Kong (1), India (4), Israel (3), Italy (5), Korea (3), Malaysia (3), Philippines (4), Poland (15), Romania (5), South Africa (5), Switzerland (5), Taiwan (4), Thailand (3) and Turkey (6)

Publications

None

Trial Period	**Development Phase**
29 May 2006 to 07 May 2007	Phase 3a

Objectives

Primary Objective:

- To assess and compare the effect on glycaemic control (HbA_{1c}) of once daily administration of three doses of liraglutide in combination with glimepiride versus glimepiride monotherapy versus rosiglitazone 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) 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 glimepiride.
- 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.

Methodology

This was a 6-month double-blind, double-dummy, randomised, active control, parallel-group, multi-centre, multi-

national trial investigating the safety and efficacy of liraglutide as add-on to glimepiride.

Subjects were randomised into 5 groups (2:2:2:1:2) to receive liraglutide 0.6 mg+glimepiride once-daily, liraglutide 1.2 mg+glimepiride once-daily, liraglutide 1.8 mg+glimepiride once-daily, glimepiride monotherapy or rosiglitazone+glimepiride.

At randomisation, subjects were stratified with respect to their previous treatment (OAD monotherapy or OAD combination therapy). Randomisation took place after a glimepiride run-in period of 2 weeks followed by a maintenance period of 2 weeks. During the run-in period, the dose level of glimepiride was increased up to 4 mg/day. Subjects already on glimepiride therapy at enrolment could go through a modified titration period or advance directly to the maintenance period at the discretion of the investigator. Treatment with glimepiride was open-label. Rosiglitazone was to be given as either active drug or placebo at a fixed dose of 4mg/day.

After randomisation, subjects in the liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride groups underwent a 1-2 week period of forced titration with liraglutide. After this titration period, the treatment period commenced, during which dose levels of liraglutide and rosiglitazone were fixed, while the glimepiride dose level could be adjusted to between 2 mg and 4 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) and rosiglitazone (active or placebo) and glimepiride (open-label) were to be taken orally once daily.

Number of Subjects Planned and Analysed

Assuming a drop out rate of 25%, the total number of subjects to be randomised was 1026 (228 in both the liraglutide plus glimepiride and rosiglitazone plus glimepiride treatment groups and 114 in the glimepiride monotherapy group).

The actual subject disposition (including analysis sets) was as follows:

	LIRA 0.6 + Glim N (%)	LIRA 1.2 + Glim N (%)	LIRA 1.8 + Glim N (%)	Glim N (%)	Rosi + Glim N (%)	All N (%)
Screened						1712
Screening failures						671
Randomized	233 (100)	228 (100)	234 (100)	114 (100)	232 (100)	1041 (100)
Exposed	233 (100)	228 (100)	234 (100)	114 (100)	231 (99.6)	1040 (99.9)
Withdrawn	25 (10.7)	32 (14.0)	21 (9.0)	31 (27.2)	38 (16.4)	147 (14.1)
Adverse Events	5 (2.1)	11 (4.8)	9 (3.8)	6 (5.3)	7 (3.0)	38 (3.7)
Ineffective therapy	12 (5.2)	8 (3.5)	7 (3.0)	20 (17.5)	16 (6.9)	63 (6.1)
Non-compliance with protocol	3 (1.3)	5 (2.2)	3 (1.3)	2 (1.8)	6 (2.6)	19 (1.8)
Other	5 (2.1)	8 (3.5)	2 (0.9)	3 (2.6)	9 (3.9)	27 (2.6)
Completers	208 (89.3)	196 (86.0)	213 (91.0)	83 (72.8)	194 (83.6)	894 (85.9)
ITT analysis set	233 (100)	228 (100)	234 (100)	114 (100)	231 (99.6)	1040 (99.9)
PP analysis set	189 (81.1)	187 (82.0)	202 (86.3)	74 (64.9)	182 (78.4)	834 (80.1)
Safety analysis set	233 (100)	228 (100)	234 (100)	114 (100)	231 (99.6)	1040 (99.9)

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 glimepiride and rosiglitazone treatment), BMI ≤ 45.0 kg/m^2 and HbA_{1c} values of 7.0-10.0% (both incl.) in subjects on OAD combination therapy and 7.0-11.0% (both 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. SP51131, SP51133, SP50161) to be injected subcutaneously (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.

Rosiglitazone placebo capsules (Batch nos. PBBK040) for once-daily oral administration.
Glimepiride tablets (1 mg) (Batch nos. E479, E482, E486) for oral administration. Daily dose was 2 to 4 mg.

Duration of Treatment

A glimepiride run-in period of 2 weeks and a glimepiride maintenance period of 2 weeks followed by a 26-weeks treatment period during which subjects in the liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride 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. SP51129, SP51130, RP51976) to be injected subcutaneously (s.c.) in the upper arm, abdomen or thigh. Daily liraglutide placebo injection volumes were identical to the volumes of active liraglutide.

Rosiglitazone capsules (4 mg) (Batch nos. SBBL026, 63231G076) for oral administration. Daily rosiglitazone dose was 4 mg throughout the entire trial period

Glimepiride tablets as described above.

Criteria for Evaluation – Efficacy

HbA_{1c}, body weight, fasting plasma glucose (FPG), self-measured 7-point plasma glucose profiles, β-cell function (fasting insulin, fasting pro-insulin, fasting C-peptide), 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.

Criteria for Evaluation – Safety

Adverse events, physical examination, pulse, ECG, opthalmoscopy and hypoglycaemic episodes. Laboratory analyses of standard haematology, biochemistry and urine parameters, calcitonin, liraglutide antibody levels and pregnancy test.

Statistical Methods

Analysis Sets

- The ITT analysis set was used for analyses of all efficacy endpoints and included all 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 no protocol deviations with potential impact on the primary efficacy assessment
  - completed the double-blind part of the trial
  - fulfilled the first three 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
  - had an evaluable HbA_{1c} observation at Visits 3 and 10 collected within the allowed window (5 days before the visit until 7 days after the visit) and
  - had at least 151 days between first and last dose on randomised treatment.
- The safety analysis set included all 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+glimepiride was superior to glimepiride. If so, it was tested whether liraglutide 1.8 mg+glimepiride was non-inferior to rosiglitazone+glimepiride. If so, it was tested whether liraglutide 1.8 mg+glimepiride was superior to rosiglitazone+glimepiride. The same testing sequence applied for the 2 lower liraglutide dose levels in combination with glimepiride. Furthermore, a given liraglutide dose level, in combination with glimepiride, was only tested for superiority to glimepiride if the liraglutide dose level immediately above the dose level considered had shown non-inferiority to rosiglitazone+glimepiride. A test for superiority of rosiglitazone+glimepiride to glimepiride 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 (liraglutide+glimepiride – comparator) 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 proportion of subjects achieving HbA_{1c} target (ADA target: < 7%; AACE target ≤ 6.5%) was compared between treatments using a logistic regression model with treatment and baseline HbA_{1c}.

Secondary Endpoints

Change in body weight was analysed using the same model as for the primary endpoint. Superiority of each liraglutide dose level, in combination with glimepiride, to both glimepiride and rosiglitazone+glimepiride was tested. 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.
- The change in body weight was evaluated for different nausea subgroups (subjects were categorised based on how many days they reported nausea in the early phase (up to 8 weeks) and in the late phase (after 8 weeks of treatment) of the trial.

FPG was analysed using the same model as for the primary endpoint. For each liraglutide dose level, in combination with glimepiride, it was tested whether liraglutide+glimepiride was different from rosiglitazone+glimepiride and glimepiride, respectively. Moreover, the proportion of subjects reaching the FPG target of 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, fasting C-peptide, 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
- 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:

- 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 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 calcitonin was the (censored) response. The model included time, treatment and gender 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 trial subjects had a mean age of 56.1 years (± 9.8 years), a mean weight of 81.6 kg (± 17.4) at randomisation, a mean BMI of 29.9 kg/m^2 (± 5.1) at randomisation, a mean duration of diabetes of 7.9 years (± 5.4)) and a mean HbA_{1c} of 8.4% (± 0.9) at screening. The majority of subjects (64.4%) were white, while 32.4% of subjects were Asian/Pacific Islanders and 2.8% of subjects were black.

Approximately one third of the randomised subjects had been using OAD monotherapy prior to participation in the trial, while the other two thirds had been using OAD combination therapy.

Efficacy Results

Primary Endpoint

- The mean estimated changes in HbA_{1c} from baseline to end of treatment were -0.60% in the liraglutide 0.6 mg+glimepiride, -1.08% in the liraglutide 1.2 mg+glimepiride, -1.13% in the liraglutide 1.8 mg+glimepiride, 0.23% in the glimepiride and -0.44% in the rosiglitazone+glimepiride treatment groups. The mean estimated changes in HbA_{1c} at end of treatment for all 3 liraglutide+glimepiride groups were shown to be superior to glimepiride monotherapy (95% CIs for treatment differences (liraglutide+glimepiride – glimepiride) were [-1.07;-0.60], [-1.54;-1.08] and [-1.60;-1.13] for liraglutide 0.6 mg+glimepiride, liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride, respectively). Liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride treatment also demonstrated superiority to rosiglitazone+glimepiride (95% CIs for treatment differences (liraglutide+glimepiride – rosiglitazone+glimepiride) were [-0.82;-0.45] and [-0.88;-0.51], respectively), whereas liraglutide 0.6 mg+glimepiride was non-inferior to rosiglitazone+glimepiride treatment (95% CIs for treatment difference was [-0.35; 0.02]).
- The percentages of subjects achieving HbA_{1c} targets of < 7% (ADA) and ≤ 6.5% (AACA) were 23.2% and 12.0% for liraglutide 0.6 mg+glimepiride, 33.8% and 21.1% for liraglutide 1.2 mg+glimepiride, 40.2% and 20.5% for liraglutide 1.8 mg+glimepiride, 7.0% and 3.5% for glimepiride and 21.2% and 9.5% for rosiglitazone+glimepiride. All treatments were significantly better than the glimepiride treatment in this respect ($p \leq 0.0001$), whereas both liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride, in a dose-dependent manner, were also significantly better than the rosiglitazone+glimepiride treatment ($p=0.0003$ and ≤ 0.0001, respectively).

Secondary Endpoints

- Treatment of subjects with liraglutide 1.8 mg+glimepiride resulted in a mean estimated weight reduction of 0.2 kg, whereas subjects on glimepiride lost an average of 0.1 kg. Mean estimated weight increases of 0.7 kg, 0.3 kg and 2.1 kg were seen with liraglutide 0.6 mg+glimepiride, liraglutide 1.2 mg+glimepiride and rosiglitazone+glimepiride combination treatments, respectively. Differences in weight change between all 3

liraglutide doses in combination with glimepiride and rosiglitazone+glimepiride were statistically significant ($p \leq 0.0001$).

- The percentage of subjects achieving a weight loss ≥ 5% at end of treatment was significantly higher in the liraglutide 1.8 mg+glimepiride treatment group compared with the rosiglitazone+glimepiride treatment group ($p=0.0013$). No other statistically significant differences between liraglutide+glimepiride treatment and rosiglitazone+glimepiride or glimepiride were observed.
- Mean estimated changes in FPG from baseline to end of treatment were -0.72 mmol/L in the liraglutide 0.6 mg+glimepiride group, -1.57 mmol/L in the liraglutide 1.2 mg+glimepiride group, -1.59 mmol/L in the liraglutide 1.8 mg+glimepiride group, +1.01 mmol/L in the glimepiride group and -0.88 mmol/L in the rosiglitazone+glimepiride group. The dose-dependent changes in FPG in the 3 liraglutide+glimepiride groups were all statistically different from the glimepiride group ($p<0.0001$ for all 3 comparisons), whereas liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride were also statistically different from the rosiglitazone+glimepiride group ($p=0.0036$ and 0.0056, respectively).
- There was a dose-dependent increase across all 3 liraglutide dose levels, in combination with glimepiride, for percentage of subjects achieving FPG values between 5.0 and 7.2 mmol/L. This was significantly higher in the 3 liraglutide+glimepiride groups compared with the glimepiride group ($p<0.0001$ and $= 0.002$ for liraglutide 1.8 mg+glimepiride, liraglutide 1.2 mg+glimepiride and liraglutide 0.6 mg+glimepiride, respectively), whereas both liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride were also significantly better compared with the rosiglitazone+glimepiride treatment ($p=0.0071$ and 0.0123, respectively).
- There was a dose-dependent reduction in mean post-prandial plasma glucose in the 3 liraglutide+glimepiride groups, all of which were significantly greater than in the glimepiride group ($p<0.001$). Moreover, the decreases in the liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride treatment groups were also significantly greater than in the rosiglitazone+glimepiride group ($p=0.0022$ and 0.0434, respectively).
- The percentage of subjects with 2 or 3 post-prandial glucose measurements below 10 mmol/L was dose-dependent for liraglutide+glimepiride, and significantly higher in all 3 liraglutide+glimepiride groups compared with the glimepiride treatment group ($p=0.0337$, 0.0024 and 0.0008 for liraglutide 0.6 mg+glimepiride, liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride, respectively). No statistically significant differences between liraglutide+glimepiride and rosiglitazone+glimepiride were observed.
- A statistically significant greater increase in fasting insulin was observed with liraglutide 1.8 mg+glimepiride treatment compared to rosiglitazone+glimepiride treatment ($p=0.0273$). No other statistically significant differences between treatment groups were observed.
- β-cell function (as assessed by fasting C-peptide, pro-insulin to insulin ratio and HOMA-β), was significantly increased with liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride treatments compared to rosiglitazone+glimepiride treatment ($p=0.0033$ and 0.0313, respectively), whereas only liraglutide 1.2 mg+glimepiride demonstrated a statistically significant increase in β-cell function compared to glimepiride treatment ($p=0.0105$).
- Changes in blood pressure from baseline to end of treatment were generally small and no statistically significant differences between any of the 3 liraglutide+glimepiride treatments and glimepiride and rosiglitazone+glimepiride were observed.
- A significantly greater reduction in total cholesterol was observed with liraglutide+glimepiride treatment at all 3 liraglutide doses and in a dose-dependent manner, compared to rosiglitazone+glimepiride treatment ($p \leq 0.003$ for all doses), whereas a statistically significant reduction compared to the glimepiride treatment was only observed for the liraglutide 1.8 mg+glimepiride treatment ($p=0.0079$). Statistically significant and dose-dependent LDL-C reductions in all liraglutide+glimepiride groups were also seen compared with rosiglitazone+glimepiride treatment ($p \leq 0.03$ for all doses).
- The percentage of subjects achieving the following lipid targets (LDL-C < 2.6 mmol/L, TG < 1.7 mmol/L and HDL-C > 1.0 mmol/L) was comparable in all 5 treatment groups.
- A statistically significant increase in hsCRP levels was seen for the liraglutide 1.8 mg+glimepiride compared to the rosiglitazone+glimepiride group ($p=0.0121$). A statistically significant decrease in NT-proBNP levels were observed in both the liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride groups compared with the rosiglitazone+glimepiride group ($p=0.0135$ and 0.0480, respectively). A statistically significant decrease in PAI-1

levels were observed in both the liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride groups compared with the rosiglitazone+glimepiride group ($p= 0.02$ and $p<0.01$, respectively).

- The decrease in mean waist circumference was significantly reduced for the liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride groups, in a dose-dependent manner, compared to the rosiglitazone+glimepiride group at the end of the trial ($p\leq0.0002$ for both).
- No statistically significant difference in the percentage of subjects having metabolic syndrome at the end of the trial period was observed between the treatment groups.

Safety Results

- Treatment emergent adverse events were reported by 69.5%, 69.3%, 70.1%, 64.0% and 61.9% of subjects in the liraglutide 0.6 mg+glimepiride, liraglutide 1.2 mg+glimepiride, liraglutide 1.8 mg+glimepiride, glimepiride and rosiglitazone+glimepiride treatment groups, respectively. The most commonly reported treatment emergent adverse events in the liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride treatment groups were gastrointestinal disorders, whereas the most commonly reported adverse events in the liraglutide 0.6 mg+glimepiride, glimepiride and rosiglitazone+glimepiride treatment groups were in the system organ class of infections and infestations.
- The majority of adverse events were mild (ca. 50% in all treatment groups) or moderate (≥ 22% in all treatment groups). The number of subjects reporting severe adverse events was low and comparable across all treatment groups (6 to 8 subjects for liraglutide+glimepiride and rosiglitazone+glimepiride and 3 subjects for glimepiride treatment).
- The number of treatment emergent adverse events evaluated by the investigator to be possibly or probably related to trial treatment was generally higher in the 3 liraglutide+glimepiride treatment groups ((27.5%, 30.7% and 33.8% for increasing dose) compared to the glimepiride and rosiglitazone+glimepiride treatment groups (18.4% and 18.6%), respectively). The majority of these were gastrointestinal adverse events.
- Thirty-nine (39) serious adverse events were reported by 35 subjects. Of these 1, 1, 3, and 2 events in the liraglutide 0.6 mg+glimepiride, liraglutide 1.2 mg+glimepiride, liraglutide 1.8 mg+glimepiride and glimepiride treatment groups, respectively were evaluated by the investigator as possibly or probably related to trial treatment (aggravation of tachycardia, overdose of liraglutide causing gastritis, acute diarrhoea, carcinoma of the prostate, papillary thyroid cancer, myocardial infarction and hyperglycaemia).
- A total of 38 (3.7%) subjects were withdrawn due to adverse events. Twenty-five (25) of these were in the 3 liraglutide+glimepiride treatment groups and were mostly due to gastrointestinal adverse events.
- Gastrointestinal disorders (mainly diarrhoea, nausea, dyspepsia and constipation) were more common in the 3 liraglutide+glimepiride treatment groups than in the glimepiride and rosiglitazone+glimepiride treatment groups but were transient in nature. The relative presence of diarrhoea, nausea, dyspepsia and constipation increased during the first 4 weeks of treatment and then decreased to a lower level seen in the period from 4 to 26 weeks of treatment.
- No clinically relevant differences or shifts were observed for haematology, biochemistry or urinalysis laboratory analyses.
- No statistically significant differences in calcitonin between the 3 liraglutide+glimepiride treatment groups and glimepiride and rosiglitazone+glimepiride treatments were observed at the end of the trial period (Week 26).
- No clinically relevant treatment differences or shifts in physical examination, ECG or ophthalmoscopy were observed.
- Treatment of subjects with liraglutide 0.6 mg+glimepiride, liraglutide 1.2 mg+glimepiride, liraglutide 1.8 mg+glimepiride and rosiglitazone+glimepiride resulted in mean estimated pulse increases of 3.1, 2.3, 3.8 and 1.0 beats per minute, respectively, while treatment with glimepiride resulted in a pulse reduction of 0.7 beats per minute. All doses of liraglutide in combination with glimepiride were statistically significantly different compared to glimepiride ($p\leq0.0016$), whereas liraglutide 0.6 mg+glimepiride and liraglutide 1.8 mg+glimepiride also demonstrated a statistically significant increase compared with rosiglitazone+glimepiride treatment ($p\leq0.0055$). The observed increases in pulse were not considered clinically relevant.
- One subject receiving liraglutide 1.8 mg+glimepiride reported a major hypoglycaemic episode (blood glucose 3.0 mmol/L) 9 days after start of treatment and 13 hours and 5 hours after liraglutide injection and glimepiride administration, respectively. No hypoglycaemic episodes reported fulfilled the definition of a serious adverse

event. The proportion of subjects experiencing minor hypoglycaemic episodes was lowest in the glimepiride treatment group (2.6%), comparable between the liraglutide 0.6 mg+glimepiride and the rosiglitazone+glimepiride treatment groups at 5.2% and 4.3%, and comparable between the liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride treatment groups at 9.2% and 8.1%.

- Two (2) confirmed pregnancies were reported during the trial. [redacted]
- At end of treatment, 10.9%, 12.7% and 9.3% of subjects were positive for liraglutide antibodies in the liraglutide 0.6 mg+glimepiride, liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride treatment groups, respectively. No subjects in the glimepiride or rosiglitazone+glimepiride treatment groups were positive for liraglutide antibodies at end of treatment.

Conclusions

- Liraglutide 0.6 mg, 1.2 mg and 1.8 mg/day in combination with glimepiride resulted in superior glycaemic control (based on change in HbA_{1c}) compared with glimepiride monotherapy. The two highest liraglutide dose levels, in combination with glimepiride, furthermore resulted in superior glycaemic control compared to rosiglitazone+glimepiride. Liraglutide 0.6 mg+glimepiride was demonstrated to be non-inferior to rosiglitazone+glimepiride treatment. Results on FPG supported the results seen for HbA_{1c}.
- Treatment of subjects with liraglutide 1.8 mg+glimepiride and glimepiride for 26 weeks resulted in mean weight reductions of 0.2 kg and 0.1 kg, respectively, whereas mean weight increases of 0.7 kg, 0.3 kg and 2.1 kg were seen with liraglutide 0.6 mg+glimepiride, liraglutide 1.2 mg+glimepiride and rosiglitazone+glimepiride combination treatments, respectively.
- β-cell function, based on fasting C-peptide, pro-insulin to insulin ratio and HOMA-β, was significantly increased with liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride treatments compared to rosiglitazone+glimepiride treatment, wheras only liraglutide 1.2 mg+glimepiride demonstrated a statistically significant increase in β-cell function compared to glimepiride treatment.
- Effects of liraglutide+glimepiride on cardiovascular risk factors did not show any consistent trends.
- Liraglutide at all 3 doses in combination with glimepiride was generally well tolerated.
- One subject receiving liraglutide 1.8 mg+glimepiride reported a major hypoglycaemic episode (blood glucose 3.0 mmol/L and need for third party assistance). The proportion of subjects experiencing minor hypoglycaemic episodes during the trial was comparable between the liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride treatment groups at 9.2% and 8.1%, comparable between the liraglutide 0.6 mg+glimepiride and the rosiglitazone+glimepiride treatment groups at 5.2% and 4.3%, and the lowest in the glimepiride treatment group (2.6%).
- The proportion of subjects reporting treatment emergent adverse events was comparable within the 5 treatment groups, although the total number of treatment emergent adverse events reported was generally higher in the 3 liraglutide+glimepiride treatment groups compared to the glimepiride and rosiglitazone+glimepiride treatment groups. The majority of events were mild and assessed to be unlikely related to trial product. A higher incidence of gastrointestinal adverse events (particularly diarrhoea, nausea, dyspepsia and constipation) was observed in the 3 liraglutide+glimepiride treatment groups. These appeared to be liraglutide dose dependent, occurred mainly during the first 4 weeks of treatment and were transient in nature.
- At end of treatment, between 9.3% and 12.7% of subjects in the 3 liraglutide+glimepiride groups were positive for liraglutide antibodies, whereas no subjects in the glimepiride or rosiglitazone+glimepiride treatment groups tested positive.

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