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.

Note: This report covers data as of 21 February 2008 for subjects entering the extension period of the trial.

Investigators

A total of 139 centres in 20 countries included subjects into the extension period of the trial.

Prof. Dr. [redacted] from Germany was appointed as Signatory Investigator.

Trial Sites

143 centres participated in the extension period of the trial.

Publications

No publications specifically covering data for the subset of subjects continuing into the extension period are available.

Trial Period	**Development Phase**
30 May 2006 to 21 February 2008	Phase 3a

Objectives

The main purpose of the extension period is to obtain long-term safety and efficacy data, and to analyse the β-cell sparing effect in all subjects as the slope of increase in HbA_{1c} per year after nadir. The evaluation of β-cell sparing effect will be assessed after completion of the full extension period of the trial.

The extension report 1 aims to fulfil the FDA request to present data following extended exposure in more subjects. This report summarises safety and efficacy data for subjects continuing into the extension period. All data including adverse events and hypoglycaemic episodes for the period from time of enrolment into the main trial and until the cut-off date of 21 February 2008 are included except for visit-related data pertaining to visits after Visit 18 at 78 weeks.

Methodology

This was a 6-month double-blind, double-dummy, randomised, active control, parallel-group, multi-centre, multi-national trial with an 18-month extension period investigating the safety and efficacy of liraglutide as add-on to metformin. This report includes data from the completed six-month trial period and from the ongoing extension period as of 21 February 2008 for the subset of subjects who continued into the extension period.

Subjects were randomised in five 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).

Randomisation occurred after a three-week initial forced metformin titration period followed by a maintenance period of another 3 weeks. During the titration period, doses of metformin were increased up to 2000 mg/day. Subjects already on metformin at enrolment could go through a modified titration period or advance directly to the maintenance period at the discretion of the investigator. After randomisation, a two-week titration period commenced followed by a 24-week maintenance treatment period with fixed doses of liraglutide/glimepiride. 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.

After a 6-month main trial period, 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.

Number of Subjects Planned and Analysed

The safety analysis set included the 780 subjects of the main trial who continued into the extension period.

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% (inclusive) in subjects on OAD combination therapy and 7.0-11.0% (inclusive) in subjects on OAD monotherapy.

Test Product, Dose and Mode of Administration, Batch Number (During Extension Period)

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

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

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

Duration of Treatment

Six-month main trial period followed by an open-label treatment extension period, with data included as of the cut-off date of 21 February 2008 (or at 18 month for efficacy data as applicable).

Reference Therapy, Dose and Mode of Administration, Batch Number (During Extension Period)

Liraglutide placebo in 3 mL FlexPen® (Batch no. SP51130) to be injected subcutaneously in the upper arm, abdomen or thigh. Daily liraglutide placebo injection volumes were similar to the volumes of activeliraglutide.

Glimepiride tablets: 1 mg (Batch no. , E479) or 2 mg (Batch nos. E560, E407, E407, 40E524) for oral administration. Daily glimepiride dose was 1-4 mg during the three-week titration period and 4 mg during the rest of the trial.

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

Criteria for Evaluation – Efficacy

HbA_{1c}, body weight, fasting plasma glucose (FPG), mean prandial increments of plasma glucose based on self-measured 7-point plasma glucose profiles, β-cell function (mean prandial increments of plasma glucose, fasting insulin, pro-insulin to insulin ratio, HOMA Indices of beta cell function and insulin resistance), fasting glucagon, systolic and diastolic blood pressure, fasting lipid profile (total cholesterol, low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C) and high density lipoprotein cholesterol (HDL-C), triglycerides, free fatty acids, apolipoprotein B), cardiovascular biomarkers (highly sensitive C-reactive protein (hsCRP), plasminogen activator inhibitor-1 (PAI-1), N-terminal B-type natriuretic peptide (NT-proBNP), urine albumine-to-creatinine ratio, 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

Data are presented for all subjects of the NN2211-1572 intention-to-treat (ITT) population who continued into the extension period. All data including adverse events and hypoglycaemic episodes for the period from time of enrolment into the main trial and until the cut-off date of 21 February 2008 are included except for visit-related data pertaining to visits after Visit 18 at 78 weeks.

Statistical Analyses

The statistical analyses were similar to those performed on data from the main trial in order to facilitate comparisons. A last observation carried forward (LOCF) approach was applied whenever applicable. The following LOCF rules were applied:

- 18-month data: If a subject was on trial product for less than 18 months (defined as <532 days) by 21 February 2008, the measurements from the last visit before 21 February 2008 (ordinary visit or pre mature termination visit as

applicable) were carried forward to 78 weeks. Similarly, the last non-missing measurement prior to the 78-week visit was carried forward in case of missing 78 week measurements due to other reasons. LOCF for 78-week measurements was only performed for subjects who completed the 12-month treatment (350 days).

- 12-month data: If a subject was withdrawn before Week 52 and has a result from the pre-mature termination visit, then this measurement was used for the LOCF measurement at 52 weeks. If a Week 52 measurement was missing and there was no pre-mature termination visit measurement before Week 52, then the last non-missing and usable measurement before Week 52 was carried forward.

Baseline values were never carried forward.

Presentations and analyses were made for 18-month and 12-month data separately.

One un-planned post-hoc analysis was performed. In order to explore the effect of the selection bias introduced by the high rate of withdrawals due to ineffective therapy, particularly in the metformin group, a post-hoc exploratory analysis of HbA1c was performed. The exploratory analysis was identical to the main analysis, however, LOCF for 78-week measurements was performed for all subjects with data in the 18-month trial period and not only for subjects who completed the 12-month treatment (350 days) as in the planned analysis.

Demography of Trial Population

There were 58.1% male subjects and 41.9% female subjects. Subjects had a mean age of 56.3 years, a mean BMI of 31.2 kg/m^2, a mean duration of diabetes of 7.3 years and a mean HbA_{1c} of 8.4% (at screening). The majority of subjects (87%) were white with 9% of subjects being Asian or Pacific Islanders. The five treatment arms were well matched with only minor differences in baseline characteristics.

Efficacy Results

- The frequency of withdrawal due to ineffective therapy (i.e. inadequate glycaemic control) during the 18-month trial period was higher in the groups receiving metformin monotherapy (approximately 31%) and glimiperide+metformin (approximately 17%) as compared with subjects in the liraglutide+metformin groups (approximately 11%). This selection bias is to be taken into account in the interpretation of the trial results.
- The results tabulated below represent data after 78 weeks of treatment. Missing values after the 52-week visit were replaced using the last observation carried forward (LOCF) approach.

	Liraglutide 0.6 mg+ metformin	Liraglutide 1.2 mg +metformin	Liraglutide 1.8 mg +metformin	Metformin	Glimepiride +metformin
N	184	178	174	61	183
HbA_{1c} (%)					
Baseline (Mean)	8.32	8.26	8.41	8.09	8.40
Change from baseline (LSMean)[a]	-0.59	-0.68	-0.66	-0.35	-0.60
Subjects (%) achieving HbA_{1c} <7%	21.2	34.3	32.8	18.0	27.3
Subjects (%) achieving HbA_{1c} ≤6.5%	10.3	18.5	19.5	11.5	15.8
Body weight (kg)					
Baseline (Mean)[a]	86.4	91.1	89.6	91.1	89.3
Change from baseline (LSMean)	-1.90	-2.83	-2.78	-2.37	1.08
FPG (mmol/L)					
Baseline (Mean)	9.96	9.84	10.09	9.20	9.88
Change from baseline (LSMean)[a]	-1.13	-1.45	-1.47	-0.73	-0.81
(mg/dL)					
Baseline (Mean)	179.33	177.17	181.81	165.65	177.89
Change from baseline (LSMean)[a]	-20.43	-26.19	-26.39	-13.20	-14.58
Systolic Blood Pressure (mmHg)					
Baseline (Mean)	131.2	132.2	130.9	133.7	131.8
Change from baseline (LSMean)[a]	-1.06	-1.31	-1.09	-0.87	0.84

a: estimated based on ANCOVA model. N = number of subjects enrolled in the extension trial

HbA1c

- Mean decreases in HbA1c from baseline to 78 weeks were observed for the for all treatment groups. Non-inferiority relative to the main comparator (glimepiride + metformin) was indicated for all liraglutide+metformin treatment groups. Superiority relative to comparator treatments was not demonstrated for any of the liraglutide+metformin treatment groups, although estimated treatment differences were in favour of the liraglutide+metformin groups except for the comparison of liraglutide 0.6 mg+metformin versus glimepiride+metformin.
- The withdrawal rates due to ineffective therapy (i.e. inadequate control) were high in the comparator groups, particularly in the metformin group (approximately 31%), which resulted in a considerable selection bias. In order to explore the effect of the selection bias a post-hoc exploratory analysis of HbA1c was performed using LOCF for all patients with data in the 18 month treatment period. Superiority relative to metformin monotherapy was demonstrated for all of the liraglutide+metformin groups and for the glimiperide+metformin group. In addition, non-inferiority of liraglutide+metformin to glimiperide+metformin was indicated for all liraglutide+metformin groups, while superiority of liraglutide+metformin relative to glimiperide+metformin was not demonstrated for any of the liraglutide+metformin groups.
- A corresponding analysis of change in HbA1c from baseline to 52 weeks demonstrated superiority relative to metformin monotherapy and non-inferiority relative to the main comparator for all liraglutide+metformin treatment groups.
- The percentages of subjects reaching the ADA target of <7% and AACE target of ≤6.5% at 52 and 78 weeks were slightly higher in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups relative to either comparator at both time points.

Body weight

- A mean weight loss from baseline to 78 weeks was observed for the liraglutide+metformin and metformin monotherapy groups, while the mean weight increased in the glimeriride+metformin group. The weight loss in the liraglutide+metformin treatment groups tended to occur primarily during the initial months of treatment and was sustained for the duration of the exposure period. Superiority relative to glimepiride+metformin treatment was demonstrated for all liraglutide+metformin treatment groups. No difference in weight loss relative to metformin monotherapy was determined. Similar results were obtained for the 52-week observation period.

Glycaemic control parameters

- A mean reduction in fasting plasma glucose (FPG) from baseline to 78 weeks was observed for all treatment groups. Analysis of change in FPG from baseline to 78 weeks showed that the reduction in FPG from baseline to 78 weeks in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups were statistically significantly larger compared with the glimepiride+metformin group. No statistically significant differences were noted for the comparisons with metformin monotherapy, although estimated treatment differences were consistently in favour of liraglutide+metformin treatment groups. Similar results were obtained for the 52-week observation period, except that the estimated treatment differences between liraglutide+metformin groups and metformin monotherapy reached statistical significance.
- Mean prandial increment of plasma glucose indicated improved postprandial glycaemic control relative to comparator treatments particularly in the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups. Similar results were obtained for the 52-week observation period.

β-cell function

- Trends towards improvements in the liraglutide+metformin treatment groups relative to glimepiride+metformin treatment were observed for both the HOMA index of β-cell function and the HOMA index of insulin resistance. No consistent effects of treatment were found for fasting insulin or pro-insulin to insulin ratio.
- For fasting glucagon, a reduction of levels in the liraglutide-metformin treatment groups relative to the glimepiride+metformin group was indicated.

Blood pressure

- Small differences in change in systolic blood pressure from baseline to 78 weeks were noted it favour of liraglutide+metformin groups relative to the glimepiride+metformin group but not when comparing with metformin monotherapy. Results of analysis of change in systolic blood pressure from baseline to 78 weeks showed no statistically significant differences between treatment groups, although estimated treatment differences were consistently in favour of liraglutide+metformin treatment groups. The change from baseline as well as the estimated

treatment differences relative to comparator treatments were overall more favourable at 52 weeks compared with 78 weeks. Results on diastolic blood pressure showed no noticeable differences between treatment groups.

Fasting lipid profile

- No major differences between treatment groups were noted for changes in total cholesterol, low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides, free fatty acids or apolipoprotein B from baseline to 52 and 78 weeks.

Cardiovascular biomarkers including urine albumin-to-creatinine ratio

- A minor trend towards a reduction of mean values in the liraglutide+metformin groups relative to glimepiride+metformin treatment was noted for highly sensitive C-reactive protein (hsCRP) and plasminogen activator inhibitor-1 (PAI-1), but differences were small.
- No noticeable changes across treatment groups were seen for N-terminal B-type natriuretic peptide (NT-proBNP) or urine albumine-to-creatinine ratio.

Waist circumference and waist-to-hip ratio

- The origin of the body weight changes was assessed by determining changes in waist ratio and waist-to-hip ratio. Results on change in waist circumference indicated that subjects of the liraglutide+metformin treatment groups on average had a waist reduction relative to baseline of approximately 2-3 cm at both 52 and 78 weeks, which was comparable to the reduction observed in the metformin group but greater than that observed in the glimepiride+metformin group, where mean changes from baseline were below or equal to an increase of 0.5 cm.
- Mean change in waist-to-hip ratio at 52 and 78 weeks relative to baseline ranged from -0.02 to 0.00 across treatment groups, with mean values below 0.00 observed in the liraglutide+metformin treatment groups only.

DEXA scan

- Although based on a limited subset of subjects, fat tissue mass and fat percentage tended to decrease across treatment groups, whereas lean tissue mass remained relatively unchanged.

CT scan

- Although based on a limited subset of subjects, trends towards reductions in visceral and subcutaneous adipose tissue areas were noted, whereas no effect on visceral-to-subcutaneous adipose tissue ratio was apparent.
- No major differences between treatment groups were noted for liver to spleen attenuation ratio.

Patient-reported outcome

- No noticeable differences between treatment groups in DTSQs and DTSQc scores of overall treatment satisfaction were apparent.
- Mean DTSQs scores for perceived frequency of hypoglycaemia were more favourable in the liraglutide+metformin treatment groups relative to the glimepiride+metformin group at all post-baseline time points. The same applied for the corresponding mean DTSQc scores of the 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups relative to the glimepiride+metformin group.
- The scoring of perceived frequency of hyperglycaemia was similar to or slightly more favourable in the liraglutide+metformin treatment groups relative to the glimepiride+metformin group for the DTSQs score. Similar results were obtained for the DTSQc score.
- No major differences between treatment groups were observed for the total IWQOL-Lite score (reflecting impact of weight on quality of life) or corresponding subscores.

Safety Results

A total of 780 subjects entered the extension period and thus constitute the safety analysis set.

- The incidence and distribution of adverse events were overall comparable to what was observed for the main trial comprising the six-month blinded treatment period.
- Infections and infestations were the most frequently reported TEAEs within 18 months in all treatment groups. Gastrointestinal disorders were more frequently reported within 18 months in the liraglutide+metformin treatment groups compared with the metformin and glimepiride+metformin groups. A similar observation was made in the main trial comprising the six-month blinded treatment period, in which gastrointestinal disorders were the most frequently reported type of TEAE in the liraglutide+metformin treatment groups. As for the main trial, the higher frequencies of gastrointestinal disorders in the liraglutide+metformin groups were, in particular, among the preferred terms diarrhoea, nausea, dyspepsia and vomiting.
- The most frequently reported TEAEs within 18 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+metformin groups compared with the metformin and glimepiride+metformin groups.

- The proportion of subjects with treatment emergent SAEs within 18 months tended to decrease with increasing liraglutide dose, the proportion of subjects with events being similar for the liraglutide 1.2 mg+metformin, liraglutide 1.8 mg+metformin and metformin treatment groups. The majority of events were rated as severe. The distribution of treatment emergent SAEs showed no consistent pattern across treatment groups with respect to system organ class of events. Four subjects experienced treatment emergent SAEs that were judged by the investigator as being possibly or probably related to trial products. All 4 subjects received liraglutide.
- No deaths were recorded as of the cut-off date of 21-February-2008 for subjects entering the extension period.
- A minority of subjects (6 cases in liraglutide+metformin groups at week 78) had samples that were positive for liraglutide antibodies. Overall, cross-reactivity to native GLP-1 was determined for approximately half of these cases. No neutralising antibodies were detected in any subject at any time point. Data should be interpreted with caution, however.
- No clinically significant effects were noted for laboratory parameters or vital signs.
- No consistent nor clinically significant changes were observed in calcitonin levels during the trial and calcitonin levels at 78 weeks did not differ significantly between treatment groups.

Conclusions

In this subset of subjects, the outcome for safety and efficacy following extended exposure appeared similar to that observed for the main six-month trial period.

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