2 Synopsis

Trial Registration ID-number NCT00856986	**IND Number –** 61040 **EudraCT number –** 2007-005317-19
Title of Trial The effect of insulin detemir in combination with liraglutide and metformin compared to liraglutide and metformin in subjects with type 2 diabetes. A 26-week, randomised, open-label, parallel-group, multicentre, multinational trial with a 26-week extension. *This Synopsis covers the 12-week run in period, the 26-week Main Treatment Period and the 26-week Trial Extension Period.*	
Investigators A total of 202 principal investigators in 9 countries. Of these, 192 participated in the trial extension period. Dr. [redacted] and Dr. [redacted], were signatory investigators.	
Trial Sites A total of 202 centres in 9 countries were approved by an Independent Ethics Committee and actively screened and enrolled subjects. Of these, 192 sites participated in the trial extension period: Belgium (2), Canada (7), France (19), Germany (35), Italy (18), the Netherlands (13), Spain (14), the United Kingdom (32) and the United States (52).	
Publications None as of the date of the final clinical trial report.	
Trial Period 3 March 2009 to 01 November 2010	**Development Phase** Phase 3b
Objectives The objectives relevant for the 52-week (12-week run-in, 26-week main treatment period and 26-week extension period) randomised treatment period were as listed: **Primary Objective:** • To assess and compare the efficacy (as assessed by HbA_{1c}) of insulin detemir in combination with liraglutide and metformin versus liraglutide and metformin in subjects with type 2 diabetes after 26-weeks of randomised treatment. The primary objective was presented and described in detail in the clinical trial report covering the 26-week main treatment period. **Secondary Objectives:** • To assess and compare the efficacy (as assessed by HbA_{1c}) of insulin detemir in combination with liraglutide and metformin versus liraglutide and metformin and with the possibility of intensified treatment with insulin detemir from Week 26, in subjects with type 2 diabetes, after a total of 52 weeks of randomised treatment. • To assess and compare the effects of insulin detemir in combination with liraglutide and metformin versus liraglutide and metformin on other descriptors of glycaemic control (fasting plasma glucose, 7-point self-monitored plasma glucose profiles, proportion of subjects reaching target HbA_{1c}), C-peptide, proinsulin to C-peptide ratio, body weight, waist and hip circumference including the waist to hip ratio, lipids and blood pressure after 52 weeks. **Safety Objectives** • To assess and compare clinical and laboratory safety parameters and incidence of hypoglycaemic episodes after 52 weeks. The non-randomised arm was designed to evaluate the sustainability of glycaemic control in subjects who achieved an HbA_{1c} less than 7.0% at randomisation over a subsequent period of 26 and 52 weeks and further to evaluate the safety profile of liraglutide. The non-randomised arm is presented using descriptive statistics only.	
Methodology This was a 26-week, randomised, open-label, two-armed, parallel-group, multi-centre, multi-national trial with a 12-week run-in period, a 26-week extension period and with an additional open-label, non-randomised arm with subjects	

who achieved target glycaemic control after the run-in period. The non-randomised arm was designed to evaluate the long-term sustainability of glycaemic control and safety data.

Subjects with type 2 diabetes treated with metformin monotherapy (≥ 1500 mg/day for ≥ 3 months prior to screening) or metformin (≥ 1500 mg/day) and a sulphonylurea (less than or equal to ½ of the maximum approved dose) underwent screening, and if eligible, entered a 12-week run-in period with liraglutide (1.8 mg/day). When entering run-in, sulphonylurea treatment was discontinued, while treatment with metformin remained unchanged (same dose and dosing regimen). Treatment with liraglutide was initiated in 0.6 mg/day weekly increments to allow a final dose of 1.8 mg/day.

Subjects with an HbA_{1c} ≥ 7.0% after the 12-week run-in period were randomised in a 1:1 manner to intensification of treatment with insulin detemir added to the combination of liraglutide and metformin, or to continue with liraglutide and metformin treatment as a randomised control group. The randomisation of subjects to treatment groups was stratified by previous treatment with metformin or a combination of metformin and a sulphonylurea. Subjects with an adequate response to liraglutide, that is, with an HbA_{1c} less than 7.0% after the run-in period, were not randomised, but continued the metformin and liraglutide treatment as in the run-in period.

After the initial dose titration period, liraglutide was to be administered at a constant dose of 1.8 mg throughout the entire trial period. Insulin detemir was initiated at a dose of 10 U per day, with further titration depending on subjects' self-measured glucose values. The maximum duration of the trial, including screening and follow-up was approximately 67 weeks per subject. The maximum treatment duration was 64 weeks.

Subjects (n=166) who withdrew before the randomisation visit ('early withdrawals') were described in the 26-week main treatment period clinical trial report and were only presented in certain sections of the safety evaluation of the extension clinical trial report: in the description of medical events of special interest and in some adverse event summary tables, where considered helpful to the overall description of adverse events.

Number of Subjects Planned and Analysed

A total of 1570 subjects with type 2 diabetes were to be screened in order to have 940 subjects entering the run-in phase and 150 subjects randomised into each of the two randomised treatment arms. Based on a planned 20% drop-out rate in the first 12 weeks of the randomised treatment period, a total of 123 subjects in each randomised treatment arm with post-randomisation efficacy data on the primary endpoint were anticipated.

Two subjects received the wrong trial treatments; subject [redacted] was randomised to liraglutide 1.8 mg+metformin treatment but received trial products from the insulin detemir+liraglutide 1.8 mg+metformin treatment group. The subject withdrew from the trial before taking any insulin detemir. Subject [redacted] was randomised to liraglutide 1.8 mg+metformin treatment but should not have been randomised as baseline HbA_{1c} was below 7.0%. The subject continued in the trial. For the full analysis set, these subjects appear in the treatment arm they were randomised to, whereas for the safety analysis set, these subjects appear in the treatment arm according to drug actually taken and baseline HbA_{1c} value used for randomisation. The actual subject disposition (including analysis sets) was as follows:

	Liraglutide 1.8 mg	**Detemir +Liraglutide 1.8 mg**	**Non-randomised Liraglutide 1.8 mg**	**Intensified***	**Early Withdrawals**	**All**
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Screened						1658
Screening failures						670
Run-in	161	162	498		167	988
Exposed to Lira	161 (100)	162 (100)	498 (100)		166 (100)	987 (100)
Randomised	161 (100)	162 (100)	0 (0.0)			323 (32.7)
Completers Main	127 (78.9)	144 (88.9)	470 (94.4)	24 (100)		741 (75.1)
Exposed to Detemir	17 (10.6)	162 (100)	7 (1.4)	24 (100)		186 (18.8)
Extension	122 (75.8)	140 (86.4)	461 (92.6)	24 (100)		723 (73.3)

Withdrawals	53 (32.9)	32 (19.8)	66 (13.3)	2 (8.3)	167 (101)	318 (32.2)
Adverse Events	9 (5.6)	7 (4.3)	19 (3.8)	0 (0.0)	92 (55.4)	127 (12.9)
Ineffective therapy	9 (5.6)	4 (2.5)	2 (0.4)	0 (0.0)	6 (3.6)	21 (2.1)
Non-compliance with protocol	7 (4.3)	4 (2.5)	11 (2.2)	1 (4.2)	14 (8.4)	36 (3.6)
Withdrawal criteria	13 (8.1)	0 (0.0)	11 (2.2)	0 (0.0)	10 (6.0)	34 (3.4)
Protocol Deviations	3 (1.9)	3 (1.9)	1 (0.2)	0 (0.0)	10 (6.0)	17 (1.7)
Lost to follow up	1 (0.6)	6 (3.7)	4 (0.8)	1 (4.2)	11 (6.6)	22 (2.2)
Other	11 (6.8)	8 (4.9)	18 (3.6)	0 (0.0)	24 (14.5)	61 (6.2)
Intensified at week 26	16 (9.9)		3 (0.6)	19 (79.2)		19 (1.9)
Intensified at week 38	1 (0.6)		4 (0.8)	5 (20.8)		5 (0.5)
Completers**	92 (57.1)	130 (80.2)	426 (85.5)	22 (91.7)		670 (67.9)
Full analysis set	157 (97.5)	162 (100)	0 (0.0)	17 (70.8)		319 (32.3)
Safety analysis set***	159 (98.8)	163 (101)	499 (100)	24 (100)	166 (100)	987 (100)

All subjects also received metformin. Early withdrawals are those who withdrew during the run-in period and before randomisation
The full analysis set is based on the treatment the subjects were randomised to
The safety analysis set is based on the actual treatment the subjects received
*Intensified subjects are tabulated both the initial treatment group and the intensified treatment group
** Intensified completer subjects are tabulated in the intensified treatment group only
*** One subject received other treatment than randomised to and one subjects was randomised by error

Diagnosis and Main Criteria for Inclusion

Male and female subjects aged 18 to 80 years (both inclusive), diagnosed with type 2 diabetes, insulin naïve, previously treated with either metformin monotherapy (≥ 1500 mg/day) for ≥ 3 months or metformin (≥ 1500 mg/day) and a sulphonylurea (less than or equal to ½ of the maximum approved dose) prior to screening and HbA_{1c} 7.0 to 10.0% (both inclusive) for subjects on previous metformin monotherapy or HbA_{1c} 7.0 to 8.5% (both inclusive) for subjects on previous metformin and sulphonylurea combination therapy.

Key exclusion criteria included subjects previously treated with insulin or glucose-lowering agents not specified by the protocol, with impaired liver and/or renal function as defined by the protocol, with a history of known pancreatitis or cardiac disease (including Heart failure New York Heart Classification class IV), with uncontrolled hypertension or any other clinically significant disorder, which in the investigators' opinion could interfere with trial results.

Test Product, Dose and Mode of Administration, Batch Number

Liraglutide (6.0 mg/mL) in a 3 mL pen-injector (batch no.: VP52200, VP52200, VP52201 and VP52201) was to be injected subcutaneously at a dose of 1.8 mg once-daily in the abdomen, thigh or upper arm and irrespective of meal times. The injection could be administered at any time of the day and irrespective of meals, although subjects were encouraged to inject liraglutide at the same time of the day during the entire treatment period.

Insulin detemir (100 U/mL) in a 3 mL FlexPen® (batch no.: VP52055, XP51639 (US only), XP52645, YP50232 (CA only) and YP50152 (EU only) was to be injected subcutaneously once daily, in the upper arm, abdomen or thigh. The area chosen was to remain unchanged throughout the trial. The injection was to be administered with the evening meal or at bedtime and at approximately the same time each day. The starting dose was 10 U, whereas the dose could be adjusted at trial visits by the investigator based upon the subject's self-monitored plasma glucose measurements and the titration guideline provided. The titration target during the treatment period was to reach a fasting self-monitored plasma glucose of 4.1 to 6.0 mmol/L (73 to 108 mg/dL). For the 26-week extension period, subjects who received intensification of treatment with insulin detemir were presented separately where relevant.

Duration of Treatment

All subjects were to undergo a 12-week run-in period, which included liraglutide dose titration, followed by a 26-week open-labelled randomised treatment period and a 26-week extension period. The maximum duration of the trial, including screening and follow-up was approximately 67 weeks per subject. The maximum treatment duration was 64 weeks. The actual mean duration of liraglutide 1.8 mg+metformin treatment was 411.3, 369.3 and 426.5 days

for subjects treated with insulin detemir+liraglutide 1.8 mg+metformin, liraglutide 1.8 mg+metformin and non-randomised liraglutide 1.8 mg+metformin, respectively. The actual mean duration of insulin detemir treatment was 325.7 days. A total of 24 subjects received intensification of therapy with insulin detemir during the trial.

Reference Therapy, Dose and Mode of Administration, Batch Number

The reference therapy in this trial was liraglutide 1.8 mg (both randomised and non-randomised treatment groups). Batch numbers used were identical to those mentioned above for test product. All subjects also received metformin (not considered a trial product).

Criteria for Evaluation – Efficacy

- HbA_{1c}, fasting plasma gkucose, self-measured 7-point plasma glucose profiles, body weight, waist and hip circumference and waist to hip ratio, beta-cell function (fasting insulin[1], fasting C-peptide, fasting pro-insulin, derivation of HOMA-B[1] and HOMA-IR[1]), fasting lipid profile (cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, very low-density lipoprotein-cholesterol, triglycerides and free fatty acids), systolic and diastolic blood pressure.

Criteria for Evaluation – Safety

- Adverse events (including events of special interest: pancreatitis, thyroid and neoplasm related adverse events, major hypoglycaemic episodes, medication errors), hypoglycaemic episodes, physical examination, electrocardiograms (ECGs), standard laboratory safety parameters (haematology, biochemistry including calcitonin, lipase and amylase, urinalysis and liraglutide and insulin detemir antibodies) and pregnancy tests.

Statistical Methods

Analysis Sets

The full 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 trial product and who provided post-baseline HbA_{1c} efficacy data.

The safety analysis set included all randomised subjects who had been exposed to at least one dose of trial product.

Primary Endpoint

The primary endpoint of the entire trial was change in HbA_{1c} from randomisation to Week 26. This endpoint was analysed and presented in the clinical trial report for the main 26-week period. There was no primary endpoint of the 26-week extension period.

Secondary Endpoints

The secondary endpoints were:

- Change in HbA_{1c} (%) from baseline (randomisation and Week 0) to Week 52
- Proportion of subjects reaching HbA_{1c} targets at Week 52
  - American Diabetes Association target < 7%
  - American Association of Clinical Endocrinologists (AACE) target ≤ 6.5%
- Change in glycaemic control parameters from baseline to Week 52
  - Fasting plasma glucose (FPG)
  - Self-measured 7-point (meal-related) glucose profiles, taken before and 90 minutes after the start of breakfast, lunch and dinner, and at bedtime
- Change in body weight from baseline to Week 52
- Change in waist and hip circumference including waist to hip ratio from baseline to Week 52
- Change in beta-cell function from baseline to Week 52[1]

[1] Fasting insulin, HOMA-B and HOMA-IR are not presented for subjects treated with insulin detemir as the assay used by the central laboratory demonstrated cross-reactivity with insulin detemir.

- Fasting insulin
- Fasting pro-insulin
- Fasting C-peptide
- Pro-insulin to C-peptide ratio
- HOMA-B
- HOMA-IR

- Change in lipid profile (cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, very low-density lipoprotein-cholesterol, triglycerides and free fatty acid) from baseline to Week 52
- Change in blood pressure (diastolic and systolic) from baseline to Week 52
- Composite endpoints
  - The proportion of subjects reaching target $HbA_{1c} < 7.0\%$, change in body weight ≤ 0 kg at Week 52 and no major or minor hypoglycaemia during the main period and extension period.

Change in HbA_{1c} from randomisation to Week 52 was analysed using the full analysis set and by an analysis of covariance (ANCOVA) for the randomised treatment groups with treatment, previous oral antidiabetic drug and country as fixed effects, and baseline HbA_{1c} value as covariate. Superiority of insulin detemir + liraglutide 1.8 mg+metformin was concluded if the upper limit of the two-sided 95% confidence intervals for the treatment difference between insulin detemir+liraglutide 1.8 mg+metformin and liraglutide 1.8 mg+metformin was below 0%. In one analysis, and as in the primary analysis of the 26-week main trial, values for intensified subjects were kept in the initial treatment arm and the last observation carried forward (LOCF) method was applied. In another analysis, an ANCOVA including values before intensification as LOCF for intensified subjects was performed using the same model as described above. No transformation of HbA_{1c} data was performed. Neither country nor previous oral antidiabetic drug, which were included in the ANCOVA model, contributed significantly to the change in HbA_{1c}.

All other secondary endpoints were analysed including values before intensification as LOCF for intensified subjects. All secondary analyses, except for the proportion of subjects reaching HbA_{1c} targets of <7% and ≤6.5%, the 7-point self-monitored plasma glucose profiles and the composite endpoints, were analysed by an ANCOVA of change from baseline to Week 52 for the randomised treatment groups, with treatment, previous oral antidiabetic drug and country as explanatory variables, and baseline value as a covariate. A log-transformation was performed for HOMA-B, HOMA-IR and fasting insulin.

The proportion of subjects reaching HbA_{1c} targets of <7% and ≤6.5% were analysed using a logistic regression with treatment as fixed effect and baseline HbA_{1c} value as a covariate. The 7-point self-monitored plasma glucose profiles were investigated by plasma glucose prandial increments (i.e., difference between post and pre-prandial) for each meal and post-prandial plasma glucose by meal. Both derived endpoints were analysed using the ANCOVA model described above for the other secondary endpoints.

For the composite endpoints, the proportion of subjects reaching target $HbA_{1c} < 7\%$, and change in body weight ≤ 0 kg at Week 52 and no major or minor hypoglycaemia during the main period was analysed using logistic regression with treatment, previous oral antidiabetic drug and country as fixed effect and baseline HbA_{1c} value and baseline body weight as covariates.

For the non-randomised treatment group, only descriptive statistics were provided.

Safety Endpoints
All safety analyses and tabulations were performed on the safety analysis set. The following safety endpoints were compared between the treatment groups using descriptive statistics: adverse events, physical examination and laboratory safety parameters (haematology, biochemistry, urinalysis). Statistical analyses were performed for pulse, calcitonin and hypoglycaemic episodes. Pulse was analysed by an ANCOVA of change from baseline to Week 52 for the randomised treatment groups, with treatment, previous oral antidiabetic drug and country as explanatory variables, and baseline value as a covariate.

Calcitonin was evaluated as a censored response. The analysis of calcitonin was conducted as a repeated measures analysis 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 and

compound symmetric covariance structure.

Treatment emergent hypoglycaemic episodes were analysed in a generalised linear model, under the assumption that the number of hypoglycaemic episodes per subject from baseline to Week 52 followed a negative-binomial distribution with treatment and previous oral antidiabetic drug as fixed effects.

Hypoglycaemic episodes per subject-year by treatment were 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.

Demography of Trial Population

The treatment groups (both randomised and non-randomised) were overall well matched with respect to baseline demographics and characteristics. For randomised subjects, 14.6% of subjects were of Hispanic/Latino ethnicity, whereas 9.6% of non-randomised subjects were of Hispanic/Latino ethnicity. A slightly higher proportion of randomised subjects receiving liraglutide 1.8 mg+metformin were Black/African American (10.6%) compared to randomised subjects receiving insulin detemir+liraglutide 1.8 mg+metformin and non-randomised liraglutide 1.8 mg+metformin (4.9% and 3.8%, respectively). Randomised subjects receiving either insulin detemir+liraglutide 1.8 mg+metformin or liraglutide 1.8 mg+metformin had a slightly longer mean duration of diabetes compared to the non-randomised subjects (8.5 years versus 6.6 years, respectively). The randomised treatment groups had an even balance of subjects previously treated with either metformin or metformin and sulphonylurea combination therapy, whereas 75% of non-randomised subjects were previously treated with metformin alone.

Subjects intensified with insulin detemir treatment during the extension period (N=24) had comparable demographics and characteristics to the rest of the subject population, although were generally somewhat younger and heavier and with a greater Hispanic/Latino ethnic representation. Subject demographics were as follows:

	Liraglutide 1.8 mg	**Detemir + Liraglutide 1.8 mg**	**All Randomised**	**Non-randomised**	**Intensified***	**All**
All exposed subjects	161	162	323	498	24	821
Age (yrs), mean (SD)	57.5 (9.8)	57.0 (9.5)	57.2 (9.6)	56.7 (9.7)	54.3 (10.3)	56.9 (9.7)
Sex, N (%)						
Male	89 (55.3)	88 (54.3)	177 (54.8)	282 (56.6)	13 (54.2)	459 (55.9)
Female	72 (44.7)	74 (45.7)	146 (45.2)	216 (43.4)	11 (45.8)	362 (44.1)
Race, N (%)						
White	141 (87.6)	144 (88.9)	285 (88.2)	470 (94.4)	22 (91.7)	755 (92.0)
Black or African American	17 (10.6)	8 (4.9)	25 (7.7)	19 (3.8)	1 (4.2)	44 (5.4)
Asian	1 (0.6)	4 (2.5)	5 (1.5)	5 (1.0)	0 (0.0)	10 (1.2)
American Indian or Alaska Native	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Other	2 (1.2)	4 (2.5)	6 (1.9)	4 (0.8)	1 (4.2)	10 (1.2)

Ethnicity, N (%)						
Hispanic or Latino	25 (15.5)	22 (13.6)	47 (14.6)	48 (9.6)	5 (20.8)	95 (11.6)
Not Hispanic or Latino	136 (84.5)	140 (86.4)	276 (85.4)	450 (90.4)	19 (79.2)	726 (88.4)
Height (m), mean (SD)	1.70 (0.10)	1.69 (0.11)	1.69 (0.10)	1.70 (0.10)	1.72 (0.09)	1.69 (0.10)
Weight (kg),mean(SD)	98.6 (21.3)	99.5 (21.2)	99.1 (21.2)	99.0 (20.8)	109 (25.7)	99.0 (21.0)
BMI(kg/m^2),mean(SD)	33.9 (6.0)	34.9 (6.3)	34.4 (6.2)	34.4 (6.7)	36.5 (7.7)	34.4 (6.5)
Duration of diabetes(y)						
Mean (SD)	8.5 (6.0)	8.6 (5.8)	8.5 (5.9)	6.6 (5.7)	6.8 (5.4)	7.4 (5.8)
Previous anti-diabetic treatment, N (%)						
Metformin	81 (50.3)	81 (50.0)	162 (50.2)	371 (74.5)	10 (41.7)	533 (64.9)
Metformin/Sulphonylurea	80 (49.7)	81 (50.0)	161 (49.8)	127 (25.5)	14 (58.3)	288 (35.1)

BMI: body mass index, SD: standard deviation, N = Number of subjects, % = Percentage of exposed subjects
*Intensified subjects are tabulated both in the initial treatment group and in the intensified treatment group

Efficacy Results

After a 12-week run-in period with liraglutide 1.8 mg+metformin treatment, 60.7% of run-in completers had an adequate response and achieved HbA_{1c} <7.0%, whereas 39.3% of these subjects needed further intensification and were randomised to either insulin detemir+liraglutide 1.8 mg+metformin or continued liraglutide 1.8 mg+metformin treatment (control group).

Change in HbA_{1c} from Randomisation to Week 52

- Subjects in the randomised groups had a mean screening HbA_{1c} of 8.3%, which decreased to 7.6% after the 12-week run-in period. In the analysis including values for the 17 randomised of 24 intensified subjects in their original treatment groups after Week 26, intensification with insulin detemir led to a further mean estimated reduction in HbA_{1c} of 0.51% at Week 52. This reduction was clinically relevant and statistically significantly greater than the estimated mean reduction of -0.10% observed for control group subjects treated with liraglutide 1.8 mg+metformin (estimated mean difference of -0.41%, p<0.0001).
- Results of the analysis including values before intensification as LOCF for intensified subjects were comparable to the analysis including values for intensified subjects in their original treatment groups. The analysis demonstrated that treatment with insulin detemir+liraglutide 1.8 mg+metformin was superior to treatment with liraglutide 1.8 mg+metformin in terms of change in HbA_{1c} from randomisation to Week 52 (estimated mean difference of -0.51%, p<0.0001).

Other Secondary Endpoints

- The estimated proportions of subjects achieving HbA_{1c} both <7.0% and ≤6.5% at Week 52 were significantly greater with insulin detemir+liraglutide 1.8 mg+metformin (51.9% and 22.4%) compared to control group subjects treated with liraglutide 1.8 mg+metformin (including values before intensification as LOCF for intensified subjects; 21.5% and 6.8%) (p<0.0001 for both analyses).
- The estimated mean reduction in fasting plasma glucose from randomisation to Week 52 was statistically significantly greater with insulin detemir+liraglutide 1.8 mg+metformin treatment compared to control group subjects treated with liraglutide 1.8 mg+metformin treatment (including values before intensification as LOCF for intensified subjects), at 1.91 mmol/L and -0.14 mmol/L, respectively (p<0.0001).
- Treatment with both insulin detemir+liraglutide 1.8 mg+metformin and liraglutide 1.8 mg+metformin alone (including values before intensification as LOCF for intensified subjects) led to estimated mean decreases in post-prandial glucose (obtained from the self-measured blood glucose profiles) at all meal times, with the greatest

decrease consistently observed with insulin detemir+liraglutide 1.8 mg+metformin (ranging from -1.14 mmol/L to -2.43 mmol/L and -0.51 mmol/L to -0.96 mmol/L, for the two randomised treatments, respectively).

- A greater proportion of subjects treated with insulin detemir+liraglutide 1.8 mg+metformin had post-prandial plasma glucose measurements below 10 mmol/L at breakfast, lunch and dinner for all timepoints (the proportion difference between the 2 groups was between 10 and 20% for breakfast and lunch, with a slightly smaller difference at dinner).
- A mean decrease from randomisation to Week 52 was observed in prandial glucose increments with liraglutide 1.8 mg + metformin treatment (including values before intensification as LOCF for intensified subjects) at all meal-times, whereas a mean decrease with insulin detemir + liraglutide 1.8 mg + metformin was observed at breakfast and dinner. However, no statistically significant treatment difference was observed for change in prandial glucose increments at either breakfast, lunch or dinner.
- A mean reduction in body weight was observed in all treatment groups during the 12-week run-in period (3.5–4.4 kg). Similarly, a decrease in mean body weight from randomisation to Week 52 was observed for all treatment groups, and was sustained over this period. From randomisation (Week 0) to Week 52, the estimated mean reductions in body weight were 0.05 kg and 1.02 kg in the insulin detemir+liraglutide 1.8 mg+metformin and liraglutide 1.8 mg+metformin treatment groups (including values before intensification as LOCF for intensified subjects), respectively. This difference in body weight reduction was statistically significant in favour of liraglutide 1.8 mg+metformin (p=0.0416).
- Mean reductions in both hip and waist circumference were observed for both randomised treatment groups (including values before intensification as LOCF for intensified subjects) from randomisation (Week 0) to Week 52. No statistically significant treatment difference with respect to waist or hip circumference or waist to hip ratio was observed.
- Due to cross-reactivity between insulin detemir and the insulin assay, an effect of treatment on fasting insulin, HOMA-B and HOMA-IR parameters could not be established in the insulin detemir+liraglutide 1.8 mg+metformin group. Both pro-insulin and C-peptide levels decreased over time in subjects treated with insulin detemir + liraglutide 1.8 mg + metformin, whereas slight increases were observed for subjects treated with liraglutide 1.8 mg + metformin (including values before intensification as LOCF for intensified subjects). No difference was observed for pro-insulin to C-peptide ratio.
- From randomisation to Week 52, there was a statistically significant treatment difference for change in HDL-cholesterol in favour of insulin detemir + liraglutide 1.8 mg + metformin, with increases observed for both treatment groups (including values before intensification as LOCF for intensified subjects). Other statistically significant treatment differences with respect to fasting lipid profile from randomisation to Week 52 were not observed. Mean triglyceride concentrations decreased in all groups from randomisation to Week 52 by 0.10–0.35 mmol/L.
- Mean systolic blood pressure decreased in all groups during the 12-week run-in period. A decrease in both systolic and diastolic blood pressure from randomisation to Week 52 was observed for subjects in the liraglutide 1.8 mg + metformin treatment group, with little change in the insulin detemir + liraglutide 1.8 mg + metformin group. No statistically significant treatment differences were observed from randomisation to Week 52.
- The proportion of subjects reaching target HbA_{1c} <7.0%, with change in body weight ≤0kg at Week 52 and with no major or minor hypoglycaemic episodes during the main and extension trial periods was 25.9% and 16.8% for subjects treated with insulin detemir+liraglutide 1.8 mg+metformin and liraglutide 1.8 mg+metformin (including values before intensification as LOCF for intensified subjects), respectively. This difference was not statistically significant (p=0.06).
- For subjects randomised to insulin detemir+liraglutide 1.8 mg+metformin, insulin detemir was initiated at 10 U at Week 0 with a mean prescribed dose of 0.41 U/kg at Week 26 and 0.45 U/kg at Week 52.
- During the 26-week trial extension period, 24 subjects treated with liraglutide 1.8 mg + metformin (randomised or non-randomised) who had HbA_{1c} levels ≥8.0% at Week 26 or 38 chose to intensify treatment with insulin detemir and had a mean prescribed dose of 0.41 U/kg at end of trial.

Safety Results

Adverse Events

- The proportion of subjects reporting adverse events for the entire trial period was overall comparable between the

two randomised treatment groups and the non-randomised treatment group, and the most commonly reported events were within the system organ classes infections and infestations (mostly nasopharyngitis) and gastrointestinal disorders (mostly nausea, diarrhoea and vomiting).

- The majority of adverse events in all three treatment groups were mild (70% or more of all adverse events reported in each treatment group) or moderate (42% or more of all adverse events reported in each treatment group) and considered unlikely to be related to trial product by investigators (more than 69%).
- There were no deaths reported during the main period of the trial. Two deaths were reported during the 26-week extension, both within the system organ class neoplasms benign, malignant and unspecified. One death was due to metastases to the central nervous system [redacted] (randomised liraglutide 1.8 mg + metformin) and the other was due to gallbladder cancer [redacted] (non-randomised liraglutide 1.8 mg + metformin). Both were considered unlikely to be related to treatment by the investigator.
- The overall proportion of subjects reporting serious adverse events for the entire trial period was 10.4%, 6.9% and 12.4% for subjects treated with insulin detemir+liraglutide 1.8 mg+metformin and randomised and non-randomised liraglutide 1.8 mg+metformin, respectively. No serious adverse events with suspected trial drug causality were reported in the insulin detemir+liraglutide 1.8 mg+metformin treatment group. Of the 11 events rated as possibly related to trial treatment in the trial, all had outcome recovered or recovering at the time of reporting, except for 2: one event of chronic pancreatitis (outcome unknown) and one of benign intracranial hypertension (not recovered), both in the liraglutide 1.8 mg+metformin group.
- In total, 127/987 (12.9%) of subjects withdrew from the entire trial period due to adverse events: 7 subjects (4.3%) treated with insulin detemir+liraglutide 1.8 mg+metformin, 9 subjects (5.6%) in the randomised liraglutide 1.8 mg+metformin group, 19 subjects (3.8%) in the non-randomised group and 92 subjects (55.4%) who withdrew before randomisation (early withdrawals). Apart from early withdrawals due to gastrointestinal disorders, no treatment group difference or clustering in type of adverse event withdrawals were observed.
- Four (4) cases of pancreatitis were reported during the entire trial duration (2 cases of acute pancreatitis, 1 case of chronic pancreatitis and 1 pancreatitis undefined).

Clinical Laboratory Evaluation

- A small and most likely clinically insignificant increase in median lipase concentrations from run-in to Week 26 within normal range was observed in all three treatment groups, with no apparent treatment group difference. From Week 26 to Week 52, no further change or a trend towards a decrease in median lipase levels was observed for all treatment groups.
- No other clinically relevant changes, shifts or treatment differences in biochemistry (including calcitonin and amylase), haematology and urinalysis were apparent.

Vital Signs and Physical Findings

- No clinically relevant treatment differences or shifts in physical examination or ECG were observed.
- A mean increase in pulse was observed in all treatment groups from run-in to randomisation of 4.67 to 5.66 beats per minute, whereas a mean decrease from randomisation to Week 52 was observed (estimated mean decreases of 1.90 and 2.52 beats per minute in the insulin detemir+liraglutide 1.8 mg+metformin and liraglutide 1.8 mg+metformin treatment groups, respectively).

Hypoglycaemic episodes

- One subject (early withdrawal, liraglutide 1.8 mg+metformin) reported a major hypoglycaemic episode (blood glucose [redacted] mmol/L) [redacted].
- The rate of minor hypoglycaemic episodes during the 26-week main trial and 26-week extension period was low across all treatment groups, at 0.228, 0.034 and 0.115 events per subject years for insulin detemir+liraglutide 1.8 mg+metformin, liraglutide 1.8 mg+metformin and non-randomised liraglutide 1.8 mg+metformin, respectively. The difference in minor hypoglycaemic episodes reported between the two randomised treatment groups was statistically significant (p=0.0011), when excluding an outlier in the liraglutide 1.8 mg+metformin group with a medical history of hypoglycaemia .

Antibodies

- At Week 53, and for subjects off drug between Weeks 52 and 53, 4 (3.7%), 2 (2.1%) and 15 (4.0%) subjects were positive for liraglutide antibodies in the insulin detemir+liraglutide 1.8 mg + metformin, liraglutide

1.8 mg+metformin and non-randomised liraglutide 1.8 mg+metformin treatment groups, respectively. No correlation between presence of liraglutide antibodies and change in HbA_{1c} was observed.

- For insulin detemir antibodies, a slight increase was observed from randomisation to Week 53 (subjects off drug between Weeks 52 and 53) in antibodies with cross-reacting effect (mean -0.08% B/T at Week 0 and mean 11.74% B/T at Week 53). No correlation between change in insulin detemir antibody titres and change in HbA_{1c} for subjects treated with insulin detemir + liraglutide 1.8 mg + metformin was observed.

Conclusions

The results presented support the sustained efficacious and well tolerated use of insulin detemir in combination with liraglutide and metformin, when liraglutide and metformin treatment is no longer sufficient to achieve adequate glycaemic control. The trial was designed in accordance with the current ADA treatment sequence for people with type 2 diabetes, recommending that OAD/GLP-1 treatment may precede initiation of basal insulin.

The trial was conducted in accordance with the Declaration of Helsinki (World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 59th WMA Assembly, Seoul, October 2008) and ICH Good Clinical Practice (1 May, 1996).

The results presented reflect data available in the clinical database as of 10 December 2010 (database lock).