2 Synopsis – Including Amendments 1 and 2

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 26-week main treatment period of the trial.

Investigators

A total of 202 principal investigators in 9 countries. Dr. [redacted] and Dr. [redacted], were appointed signatory investigators.

Trial Sites

A total of 202 centres in 9 countries were approved by an Independent Ethics Committee/Institutional Review Board and actively screened and enrolled subjects: Belgium (2), Canada (7), France (19), Germany (37), Italy (18), the Netherlands (16), Spain (14), the United Kingdom (32) and the United States (57).

Publications

None

Trial Period	**Development Phase**
3 Mar 2009 - 19 Apr 2010 (main period of 26 weeks)	Phase 3b

Objectives

The objectives related to the 26-week main part of the trial 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

Secondary Objectives:

- 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 (FPG, 7-point self-monitored 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 26 weeks

Safety Objectives

- To assess and compare clinical and laboratory safety parameters and incidence of hypoglycaemic episodes after 26 weeks

The non-randomised arm was designed to evaluate the sustainability of glycaemic control in subjects who achieved an HbA_{1c} less than 7% 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 26-week extension and with an additional open-label, non-randomised arm carrying 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. This synopsis covers the 12-week run-in phase and the 26-week main treatment period of the trial.

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} greater than or equal to 7.0% after the 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, i.e. 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.
The 'early withdrawal' group was a consequence of the 12-week long run-in period prior to randomisation and accounts for subjects who withdrew prior to the randomisation visit (Week 0).
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. Trial duration was 40 weeks ± visit windows.

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 300 subjects randomised into the 26-week main period of the trial. Based on a planned 20% drop-out rate in the first 12 weeks of the randomised treatment period, 123 subjects in each randomised treatment arm with post-randomisation efficacy data on the primary endpoint was 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 trial products. Subject [redacted] was randomised to liraglutide 1.8 mg+metformin treatment but should not have been randomised as baseline HbA1c was below 7%. 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:

	Lira 1.8		Detemir + Lira 1.8		Non-randomised Lira 1.8		Early WD Lira 1.8		All	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Screened									1658	
Screening failures									670	
Run-in	161		162		498		167		988	
Exposed to Liraglutide	161	(100)	162	(100)	498	(100)	166	(100)	987	(100)
Randomised	161	(100)	162	(100)	0	(0.0)	0	(0.0)	323	(32.7)
Main *	161	(100)	162	(100)	498	(100)	0	(0.0)	821	(83.2)
Exposed to Detemir	0	(0.0)	162	(100)	0	(0.0)	0	(0.0)	162	(16.4)
Withdrawals	34	(21.1)	18	(11.1)	28	(5.6)	167	(101)	247	(25.0)
Adverse Events	6	(3.7)	4	(2.5)	9	(1.8)	92	(55.4)	111	(11.2)
Non-compliance with protocol	3	(1.9)	2	(1.2)	7	(1.4)	14	(8.4)	26	(2.6)
Withdrawal criteria	11	(6.8)	0	(0.0)	3	(0.6)	10	(6.0)	24	(2.4)
Protocol deviations	1	(0.6)	3	(1.9)	0	(0.0)	10	(6.0)	14	(1.4)
Lost to follow up	1	(0.6)	1	(0.6)	2	(0.4)	11	(6.6)	15	(1.5)
Ineffective therapy	5	(3.1)	2	(1.2)	0	(0.0)	6	(3.6)	13	(1.3)
Other	7	(4.3)	6	(3.7)	7	(1.4)	24	(14.5)	44	(4.5)
Completers	127	(78.9)	144	(88.9)	470	(94.4)	0	(0.0)	741	(75.1)
Full analysis set	157	(97.5)	162	(100)	0	(0.0)	0	(0.0)	319	(32.3)
Safety analysis set	159	(98.8)	163	(101)	499	(100)	166	(100)	987	(100)

All subjects also received metformin
Early WD: Withdrawals before randomisation visit (visit 4b)
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.
* 39.3% of subjects entering main period were randomised and 60.7% were non-randomised

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.

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 NYHA class IV), with uncontrolled hypertension or any other clinically significant disorder, which in the investigator's opinion could interfere with trial results, were not to take part in the trial.

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 at a dose of 1.8 mg once-daily s.c. 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, XP52645, XFF0146 and XQ50638) was to be injected s.c., 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-measured fasting plasma glucose measurements (SMPG) and the titration guideline provided.

The titration target during the treatment period was to reach a fasting SMPG of 4.0 to 6.0 mmol/L (72 to 108 mg/dL).

Duration of Treatment

All subjects were to undergo a 12-week run-in period, which included liraglutide dose titration, followed by a 26-week main treatment period. The entire planned trial duration reported here was 40 weeks ± visit windows. The actual mean duration of liraglutide 1.8 mg+metformin treatment was 259.7, 247.7 and 263.2 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 173.2 days.

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}, FPG, self-measured 7-point plasma glucose profiles, body weight, waist and hip circumference and waist to hip ratio, beta-cell function (fasting insulin, fasting C-peptide, fasting pro-insulin, derivation of HOMA-B and HOMA-IR), fasting lipid profile (TC, HDL-C, LDL-C, VLDL-C, TG and FFA), 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 (FAS) was used for analyses of all efficacy endpoints and included all randomised subjects who had been exposed to at least one dose of trial products 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 products.

Primary Endpoint
The primary endpoint was change in HbA_{1c} (%) from baseline (randomisation) to Week 26. The objective was to determine whether the effect (change in HbA_{1c}) of insulin detemir+liraglutide 1.8 mg+metformin was superior to that of liraglutide 1.8 mg+metformin treatment alone.

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%.

The primary endpoint was analysed using an analysis of covariance (ANCOVA) of change in HbA_{1c} from baseline to Week 26 for the randomised treatment groups. Treatment, previous OAD and country were explanatory variables and baseline HbA_{1c} values were included as covariates. This analysis was performed using LOCF. Neither country nor previous OAD, which were included in the ANCOVA model, contributed significantly to the change in HbA_{1c}.

Secondary Endpoints
The secondary endpoints were:
- Proportion of subjects reaching HbA_{1c} targets at Week 26
  - American Diabetes Association (ADA) target <7%
  - American Association of Clinical Endocrinologists (AACE) target ≤6.5%
- Change in glycaemic control parameters from baseline to Week 26
  - 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 26
- Change in waist and hip circumference including waist to hip ratio from baseline to Week 26
- Change in beta-cell function from baseline to Week 26
  - Fasting insulin
  - Fasting pro-insulin
  - Fasting C-peptide
  - Pro-insulin to C-peptide ratio
  - HOMA-B
  - HOMA-IR
- Change in lipid profile (cholesterol, LDL-C, VLDL-C, HDL-C, triglycerides and FFA) from baseline to Week 26
- Change in blood pressure (diastolic and systolic) from baseline to Week 26
- Composite endpoints
  - The proportion of subjects reaching target HbA_{1c} <7%, SBP<130 mmHg and change in body weight ≤ 0 kg at Week 26
  - The proportion of patients reaching target HbA_{1c} <7%, change in body weight ≤0 kg at Week 26 and no major or minor hypoglycaemia during the main period

All secondary analyses, except for the proportion of subjects reaching HbA_{1c} targets of <7% and ≤6.5%, the 7-point SMPG profiles and the composite endpoints, were analysed by an ANCOVA of change from baseline to Week 26 for the randomised treatment groups, with treatment, previous OAD 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 SMPG 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%, SBP <130 mmHg and change in body weight ≤0 kg at Week 26 were analysed using logistic regression with treatment as fixed effect and baseline HbA_{1c} value, baseline SBP and baseline body weight as covariates.

The proportion of subjects reaching target HbA_{1c} <7%, change in body weight ≤0 kg at Week 26 and no major or minor hypoglycaemia during the main period were analysed using logistic regression with treatment, previous OAD and country as fixed effect and baseline HbA_{1c} value and baseline body weight as covariates.

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 (AE), physical examination and laboratory safety parameters (haematology, biochemistry). Statistical analyses were performed for pulse, calcitonin and hypoglycaemic episodes. Pulse was analysed by an ANCOVA of change from baseline to Week 26 for the randomised treatment groups, with treatment, previous OAD 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 (RMA) 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 using a generalised linear model under the assumption that hypoglycaemic episodes per subject-year followed a negative-binomial distribution. The model included treatment as fixed effects. Hypoglycaemic episodes per subject-year by treatment 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.

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). Subject demographics were as follows:

	Lira 1.8	Detemir + Lira 1.8	All Randomised	Non-randomised Lira 1.8	Early WD Lira 1.8
All exposed subjects	161	162	323	498	166
Age (years)					
N	161	162	323	498	166
Mean (SD)	57.3 (9.8)	56.8 (9.4)	57.0 (9.6)	56.5 (9.7)	58.7 (10.8)
Median	58.0	57.0	57.0	57.0	60.0
Min ; Max	33.0 ; 79.0	31.0 ; 77.0	31.0 ; 79.0	18.0 ; 80.0	20.0 ; 80.0
Sex, N (%)					
N	161 (100)	162 (100)	323 (100)	498 (100)	166 (100)
Male	89 (55.3)	88 (54.3)	177 (54.8)	282 (56.6)	91 (54.8)
Female	72 (44.7)	74 (45.7)	146 (45.2)	216 (43.4)	75 (45.2)
Race, N (%)					
N	161 (100)	162 (100)	323 (100)	498 (100)	166 (100)
White	141 (87.6)	144 (88.9)	285 (88.2)	470 (94.4)	146 (88.0)
Black or African American	17 (10.6)	8 (4.9)	25 (7.7)	19 (3.8)	11 (6.6)
Asian	1 (0.6)	4 (2.5)	5 (1.5)	5 (1.0)	4 (2.4)
American Indian or Alaska Native	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)
Other	2 (1.2)	4 (2.5)	6 (1.9)	4 (0.8)	5 (3.0)
Ethnicity, N (%)					
N	161 (100)	162 (100)	323 (100)	498 (100)	166 (100)
Hispanic or Latino	25 (15.5)	22 (13.6)	47 (14.6)	48 (9.6)	28 (16.9)
Not Hispanic or Latino	136 (84.5)	140 (86.4)	276 (85.4)	450 (90.4)	138 (83.1)
Weight (kg)					
N	161	162	323	498	166
Mean (SD)	98.6 (21.3)	99.5 (21.2)	99.1 (21.2)	99.0 (20.8)	90.2 (18.5)
Median	96.6	97.0	96.7	96.2	87.6
Min ; Max	51.8 ; 177.2	50.8 ; 201.0	50.8 ; 201.0	50.0 ; 206.8	53.2 ; 153.
BMI (kg/m^2)					
N	161	162	323	498	166
Mean (SD)	33.9 (6.0)	34.9 (6.3)	34.4 (6.2)	34.4 (6.7)	31.8 (6.0)
Median	33.0	33.5	33.2	33.4	30.6
Min ; Max	22.4 ; 60.6	22.6 ; 56.2	22.4 ; 60.6	20.6 ; 75.9	19.7 ; 54.2
Duration of diabetes (years)					
N	161	162	323	498	166
Mean (SD)	8.5 (6.0)	8.6 (5.8)	8.5 (5.9)	6.6 (5.7)	8.4 (6.4)
Median	7.5	7.7	7.7	5.4	6.9
Min ; Max	0.4 ; 30.5	0.4 ; 30.5	0.4 ; 30.5	0.3 ; 47.3	0.3 ; 33.2
Previous anti-diabetic treatment					
N	161 (100)	162 (100)	323 (100)	498 (100)	166 (100)
Metformin	81 (50.3)	81 (50.0)	162 (50.2)	371 (74.5)	97 (58.4)
Metformin/Sulphonylurea Combination	80 (49.7)	81 (50.0)	161 (49.8)	127 (25.5)	69 (41.6)
HbA_{1c} (%)					
Week -12					
N	161	162	323	498	165
Mean (SD)	8.3 (0.8)	8.2 (0.7)	8.3 (0.8)	7.7 (0.7)	8.0 (0.8)
Median	8.1	8.1	8.1	7.6	7.9
Min ; Max	6.1 ; 11.2	6.7 ; 10.5	6.1 ; 11.2	6.6 ; 10.2	6.6 ; 10.1
Week 0					
N	157	162		498	
Mean (SD)	7.64 (0.66)	7.63 (0.55)		6.37 (0.38)	
Median	7.4	7.50		6.40	
Min ; Max	6.20 ; 10.10	7.00 ; 10.30		4.90 ; 6.90	
FPG (mmol/L)					
Week -12					
N	158	162	320	492	165
Mean (SD)	10.3 (2.5)	10.2 (2.4)	10.2 (2.5)	9.2 (1.8)	9.5 (3.0)
Median	10.0	9.7	9.8	8.9	9.0
Min ; Max	5.0 ; 17.7	3.1 ; 17.6	3.1 ; 17.7	5.3 ; 16.6	4.4 ; 36.5
Week 0					
N	155	160		495	
Mean (SD)	8.81 (2.10)	9.23 (1.86)		7.15 (1.26)	
Median	8.60	9.00		7.00	
Min ; Max	5.20 ; 18.40	6.00 ; 17.10		4.60 ; 14.20	

All subjects also received metformin
Early WD: Withdrawals before randomisation visit (visit 4b)
N: Number of subjects, %: Percentage of exposed subjects, BMI: body mass index, SD: standard deviation

Efficacy Results

After a 12-week run-in period with liraglutide 1.8 mg+metformin treatment, 60.7% of subjects had an adequate response and achieved HbA_{1c} <7%, whereas 39.3% of 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).

Primary Endpoint – Change in HbA_{1c}

- 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. Intensification with insulin detemir led to a further reduction in HbA_{1c} of 0.51% at Week 26, this reduction was clinically relevant and superior to that observed for randomised subjects treated with liraglutide 1.8 mg+metformin (control group) (estimated changes -0.51% and +0.02%, respectively, p<0.0001)

Secondary Endpoints

- The estimated proportions of subjects achieving HbA_{1c} both <7% and ≤6.5% were significantly greater with insulin detemir+liraglutide 1.8 mg+metformin (43.1% and 17.5%) compared to liraglutide 1.8 mg+metformin (control group) (16.8% and 6.0%) (p<0.0001 and p=0.0016, respectively)
- The estimated mean reduction in FPG from baseline to Week 26 was statistically significantly greater with insulin detemir+liraglutide 1.8 mg+metformin treatment compared to liraglutide 1.8 mg+metformin treatment (control group), at -2.12 mmol/L and -0.39 mmol/L, respectively (p<0.0001)
- Treatment with both insulin detemir+liraglutide 1.8 mg+metformin and liraglutide 1.8 mg+metformin alone led to estimated mean decreases in post-prandial glucose at all meal times, with the greatest decrease consistently observed with insulin detemir+liraglutide 1.8 mg+metformin (ranging from -1.18 mmol/L to -2.09 mmol/L and -0.48 mmol/L to -0.97 mmol/L, for the two randomised treatments, respectively). The estimated mean decrease in post-prandial glucose was statistically significantly greater with insulin detemir+liraglutide 1.8 mg+metformin treatment compared to liraglutide 1.8 mg+metformin treatment alone for all meal times
- A greater proportion of subjects (about 10% more) treated with insulin detemir+liraglutide 1.8 mg+metformin had post-prandial glucose measurements below 10 mmol/L at each meal at Weeks 12 and 26 compared to subjects treated with liraglutide 1.8 mg+metformin. This difference was statistically significant at all meal times at Week 26, and all meals but dinner at Week 12
- No statistically significant treatment difference was observed for 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 to 4.3 kg). From baseline (Week 0) to Week 26, the estimated mean reductions in body weight were 0.16 kg and 0.95 kg in the insulin detemir+liraglutide 1.8 mg+metformin and liraglutide 1.8 mg+metformin treatment groups, respectively. This difference in body weight reduction was statistically significant in favour of liraglutide 1.8 mg+metformin (p=0.0283)
- Mean reductions in both hip and waist circumference were observed for both randomised treatment groups from baseline (Week 0) to Week 26. No statistically significant treatment difference with respect to waist and hip ratio was observed
- Due to cross-reactivity between insulin detemir and the insulin assay, an effect of treatment on beta-cell function could not be established in the insulin detemir+liraglutide 1.8 mg+metformin group. Both pro-insulin and C-peptide levels decreased over time, where the decreases were statistically significantly greater for subjects in the insulin detemir+liraglutide 1.8 mg+metformin group compared to subjects in the liraglutide 1.8 mg+metformin group (P=0.0230 and p<0.0001, respectively). No statistically significant treatment difference was observed for pro-insulin to C-peptide ratio
- From baseline (Week 0) to Week 26, there was a statistically significant treatment difference for change in free fatty acids, with estimated decreases of 0.11 mmol/L and 0.03 mmol/L in the insulin detemir+liraglutide 1.8 mg+metformin and liraglutide 1.8 mg+metformin treatment groups, respectively (p=0.0017). No other statistically significant treatment differences with respect to fasting lipid profile were observed from baseline to Week 26
- No statistically significant treatment differences were observed for systolic or diastolic blood pressure

- The proportion of subjects reaching target HbA_{1c} <7%, systolic blood pressure <130 mmHg and change in body weight ≤0kg at Week 26 was 10.5% and 4.1% for subjects treated with insulin detemir+liraglutide 1.8 mg+metformin and liraglutide 1.8 mg+metformin, respectively. This difference was statistically significant (p=0.0126)
- The proportion of subjects reaching target HbA_{1c} <7%, Change in Body Weight ≤0kg at Week 26 and no major or minor hypoglycaemic episodes during the main period was 20.8% and 8.7% for subjects treated with insulin detemir+liraglutide 1.8 mg+metformin and liraglutide 1.8 mg+metformin, respectively. This difference was statistically significant (p=0.0016)
- 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

Safety Results

Adverse Events

- The proportion of subjects reporting adverse events was comparable between the two randomised treatment groups and also for the non-randomised treatment group for the overall trial period
- For the main 26-week trial period, there was a slightly higher frequency of overall adverse events reported by more than 5% of subjects in the insulin detemir+liraglutide 1.8 mg+metformin group compared to the randomised and non-randomised liraglutide+metformin groups (66.9% versus 58.5% and 59.1%, respectively)
- The majority of adverse events in all three treatment groups were mild (68% or more of all adverse events reported in each treatment group) or moderate (33% or more of all adverse events reported in each treatment group) and considered unlikely related to trial product by investigators (more than 67%)
- There were no deaths reported
- The proportion of subjects reporting serious adverse events during the 26-week main trial period was low and comparable for the two randomised treatment groups (5.5% and 3.8%), and the non-randomised treatment group (5.4%). Most of the serious adverse events were evaluated as unlikely related to trial product by the investigator and no clustering of events was observed
- For early withdrawals (17% of total trial population who withdrew during the 12-week run-in period), 45.8% of subjects withdrew due to gastrointestinal symptoms, the most common being nausea and vomiting
- In total, 11.2% of subjects withdrew from the 12-week run-in and 26-week main period due to adverse events. No treatment group difference or clustering in type of adverse event withdrawals were observed
- The most commonly reported adverse events during the 26-week main period were nasopharyngitis, diarrhoea and nausea (reported by 14.1%, 18.9% and 9.0%, 11.7%, 6.9% and 3.8% and 3.7%, 5.7% and 2.8% of subjects treated with insulin detemir+liraglutide 1.8 mg+metformin, liraglutide 1.8 mg+metformin and non-randomised liraglutide 1.8 mg+metformin, respectively)
- Two (2) cases of pancreatitis were reported (acute pancreatitis, early withdrawal (liraglutide 1.8 mg+metformin) and chronic pancreatitis, liraglutide 1.8mg+metformin)
- The overall proportion of subjects reporting thyroid related adverse events was comparable across treatment groups, with 1.2%, 1.9% and 2.4% of subjects reporting an event in the insulin detemir+liraglutide 1.8 mg+metformin, liraglutide 1.8 mg+metformin and the non-randomised liraglutide 1.8 mg+metformin treatment groups, respectively

Clinical Laboratory Evaluation

- There was a slight increase in mean lipase from run-in to Week 26 within normal range in all three treatment groups with no apparent treatment difference. No apparent difference in the frequency of gastrointestinal adverse events reported for subjects with an increase in lipase above 2x UNR versus the total population was observed during the main period
- No other clinically relevant changes, shifts or treatment differences in biochemistry (including calcitonin), 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 across all treatment groups from run-in to Week 26. From baseline to

Week 26, however, mean decreases in pulse were 0.99 and 2.13 beats per minute in the insulin detemir+liraglutide 1.8 mg+metformin and liraglutide 1.8 mg+metformin treatment groups, respectively. No statistically significant treatment difference was observed

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 was low across all treatment groups, at 0.286, 0.029 and 0.129 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 (main 26-week period, outlier excluded). The difference in minor hypoglycaemic episodes reported between the two randomised treatment groups was statistically significant (p=0.0037)

Antibodies

- At Week 26, 5 subjects in total were positive for liraglutide antibodies and no correlation between presence of liraglutide antibodies and change in HbA_{1c} was observed
- At Week 26, overall levels of antibodies specific to insulin detemir remained low (mean 1.59 %B/T at Week 0 and mean 2.20 %B/T at Week 26) and only small increases in antibodies with cross-reacting effect were observed from Week 0 (baseline) to Week 26 (mean -0.10 %B/T at Week 0 and mean 3.89 %B/T at Week 26). 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 trial design support the current ADA treatment cascade, i.e. initiation of basal insulin after OAD/GLP-1 agonist failure, however, no guideline currently mentions the combination use of a GLP-1 agonist and a basal insulin. The results presented support the 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 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 25 May 2010 (database lock) and 28 May 2010 (update of MESI status on 14 adverse events). The synopsis was updated as a consequence of clinical trial report amendment 2.