2 Synopsis

Trial Registration ID-number NCT00700817	**IND Number** 61040 **EudraCT number** 2007-003937-17
Title of Trial The Effect of Liraglutide Compared to Sitagliptin, Both in Combination with Metformin in Subjects with Type 2 Diabetes. A 26-Week, Randomised, Open-Label, Active Comparator, Three-Armed, Parallel-Group, Multi-Centre, Multi-National Trial With a 52-Week Extension. *This Clinical Trial Report Covers the Main and the 52-Week Extension Period (Corresponding to 78 Weeks of Treatment)*	
Investigator(s) A total of 158 principal investigators in 13 countries. Dr. Richard Pratley, University of Vermont College of Medicine, US, was appointed as signatory investigator.	
Trial Site(s) A total of 158 centres in 13 countries participated: Canada (11), Croatia (3), Germany (12), Ireland (5), Italy (8), Netherlands (8), Romania (4), Serbia (3), Slovakia (6), Slovenia (3), Spain (9), United Kingdom (20) and United States (66). Of the 158 sites which were approved by an IEC, 151 actively screened and enrolled subjects for the main trial. Of these 151 sites, a total of 123 sites enrolled subjects into the extension.	
Publications Pratley R.E., Nauck M., Bailey T., Montanya E., Cuddihy R., Filetti S., Thomsen A.B., Søndergaard, R.E. and Davies M.. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet* (375): 1447-56, 2010.	
Trial Period Trial initiated: 16 June 2008 LPLV: 3 June 2010	**Development Phase** Phase 3b
Objectives The primary objective of the entire study pertained to the first 26-week (main) part of the trial and was as follows: To assess and compare the efficacy (as assessed by change from baseline in HbA_{1c}) after 26 weeks of adding liraglutide versus sitagliptin to the pre-trial metformin treatment in subjects with type 2 diabetes inadequately controlled on metformin. All the objectives for the extension were regarded as secondary objectives. **Objectives of the Second 26-Week Extension** • To assess the effect of changing therapy from sitagliptin to liraglutide 1.2 mg/day or 1.8 mg/day on HbA_{1c} and on other parameters of glycaemic control (FPG, 7-point meal-related plasma glucose profile, fraction of subjects reaching target HbA_{1c}), beta cell function, weight and waist and hip circumference, lipid profile and blood pressure. In a subset of subjects: Patient Reported Outcomes (PRO) assessed by Diabetes Treatment Satisfaction Questionnaire (DTSQ). • To assess the sustainability of glycaemic control with liraglutide in combination with metformin over a period of 78 weeks. **Safety objectives** • To assess and compare: – incidence of hypoglycaemic episodes – clinical and laboratory safety parameters	

Methodology

This was a 26-week, randomised, open-label, active comparator, three-armed, parallel-group, multi-centre, multi-national trial with a 52-week extension period (two 26-week extension periods) in subjects with type 2 diabetes. This report describes the results after the 26-week main trial and the second 26-week period of the extension (up to 78 weeks of treatment from randomisation).

Subjects inadequately controlled with metformin monotherapy were randomised into 3 groups (1:1:1) to receive open-labelled 1.2 mg or 1.8 mg q.d. (once-daily) liraglutide (s.c. administration) or 100 mg q.d. sitagliptin (oral administration). Both treatments were added to a background treatment of metformin monotherapy at a stable pre-study dose (≥ 1500 mg, stable for at least 3 months).

After randomisation followed a titration period for subjects treated with liraglutide (2 or 3 weeks for liraglutide 1.2 mg and 1.8 mg, respectively). The dose of 100 mg sitagliptin was not titrated. The initial dose of 0.6 mg of liraglutide was escalated to 1.2 mg and 1.8 mg in weekly increments of 0.6 mg. The titration period was followed by a 23/24-week treatment period with fixed doses of liraglutide. The treatment period of sitagliptin was 26 weeks with the same dose (main part of the trial). Subjects who decided to participate in the 52-week extension signed an informed consent for the entire extension period. For the first 26 weeks of the extension, the subjects continued treatment with the same doses of trial drug and metformin as during the main part of the trial. After 52 weeks of treatment, subjects originally randomised to receive sitagliptin were randomised in a (1:1) manner to liraglutide (1.2 mg or 1.8 mg) where the initial dose of 0.6 mg of liraglutide was escalated to 1.2 mg and 1.8 mg in weekly increments of 0.6 mg. These subjects were treated with liraglutide during the titration period followed by a 23/24-week treatment period with fixed doses of liraglutide. Subjects originally randomised to treatment with liraglutide at baseline continued treatment with liraglutide during the remaining 26 weeks of the extension period for a total of 78 weeks. Dose changes were not allowed at any time during the trial.

Patient reported outcome recordings by use of DTSQs were done in all countries, except for Serbia, Slovakia and Slovenia. These three countries were excluded from the PRO sub-study due to lack of local, linguistically validated PRO measures.

Number of Subjects Planned and Analysed

The sample size was determined for the primary endpoint of the 26-week, randomised portion of the study (main part of the trial). A total of 1085 subjects with type 2 diabetes were planned to be screened in order to be able to randomise 651 subjects. It was anticipated to reach 488 evaluable subjects after 6 months of treatment based on an estimated drop-out rate of 25%.

The actual subject disposition for all subjects was as follows (note that subjects in the sitagliptin+metformin groups were treated with liraglutide from Week 52 to Week 78):

Subjects	Lira 1.2 + Met N (%)	Lira 1.8 + Met N (%)	Sitagliptin + Met N (%)	All N (%)
Screened				1302
Screen failures				637
Randomised in the 26 week trial	225 (100.0)	221 (100.0)	219 (100.0)	665 (100.0)
Exposed in the 26 week trial	221 (98.2)	218 (98.6)	219 (100.0)	658 (98.9)
Completed the 26 week trial	169 (75.1)	191 (86.4)	194 (88.6)	554 (83.3)
Enrolled in the 52 weeks extension period	155 (68.9)	176 (79.6)	166 (75.8)	497 (74.7)
Exposed in the 52 weeks extension period	155 (68.9)	176 (79.6)	166 (75.8)	497 (74.7)
Completed 52 weeks	135 (60.0)	150 (67.9)	151 (68.9)	436 (65.6)
Exposed in the 78 weeks extension period	134 (59.6)	150 (67.9)	135 (61.6)	419 (63.0)
Completed 78 weeks	124 (55.1)	135 (61.1)	122 (55.7)	381 (57.3)
Withdrawals until 26 weeks	56 (24.9)	30 (13.6)	25 (11.4)	111 (16.7)
Adverse Events	14 (6.2)	15 (6.8)	4 (1.8)	33 (5.0)
Non-compliance with protocol	14 (6.2)	4 (1.8)	4 (1.8)	22 (3.3)
Ineffective therapy	4 (1.8)	0 (0.0)	4 (1.8)	8 (1.2)
Withdrawal criteria	10 (4.4)	7 (3.2)	5 (2.3)	22 (3.3)
Other	14 (6.2)	4 (1.8)	8 (3.7)	26 (3.9)
Withdrawals until 52 weeks	76 (33.8)	56 (25.3)	40 (18.3)	172 (25.9)
Adverse Events	19 (8.4)	25 (11.3)	7 (3.2)	51 (7.7)
Non-compliance with protocol	17 (7.6)	6 (2.7)	6 (2.7)	29 (4.4)
Ineffective therapy	6 (2.7)	3 (1.4)	11 (5.0)	20 (3.0)
Withdrawal criteria	16 (7.1)	15 (6.8)	7 (3.2)	38 (5.7)
Other	18 (8.0)	7 (3.2)	9 (4.1)	34 (5.1)
Withdrawals until 78 weeks	87 (38.7)	71 (32.1)	69 (31.5)	227 (34.1)
Adverse Events	19 (8.4)	28 (12.7)	13 (5.9)	60 (9.0)
Non-compliance with protocol	18 (8.0)	8 (3.6)	8 (3.7)	34 (5.1)
Ineffective therapy	9 (4.0)	6 (2.7)	11 (5.0)	26 (3.9)
Withdrawal criteria	20 (8.9)	18 (8.1)	11 (5.0)	49 (7.4)
Other	20 (8.9)	11 (5.0)	10 (4.6)	41 (6.2)
Withdrawn at Week 52	1 (0.4)	0 (0.0)	16 (7.3)	17 (2.6)
Withdrawn from week 26 to week 52	20 (8.9)	26 (11.8)	15 (6.8)	61 (9.2)
Adverse Events	5 (2.2)	10 (4.5)	3 (1.4)	18 (2.7)
Non-compliance with protocol	3 (1.3)	2 (0.9)	2 (0.9)	7 (1.1)
Ineffective therapy	2 (0.9)	3 (1.4)	7 (3.2)	12 (1.8)
Withdrawal criteria	6 (2.7)	8 (3.6)	2 (0.9)	16 (2.4)
Other	4 (1.8)	3 (1.4)	1 (0.5)	8 (1.2)
Withdrawn from week 52 to week 78	10 (4.4)	15 (6.8)	13 (5.9)	38 (5.7)
Adverse Events	0 (0.0)	3 (1.4)	6 (2.7)	9 (1.4)
Non-compliance with protocol	1 (0.4)	2 (0.9)	2 (0.9)	5 (0.8)
Ineffective therapy	3 (1.3)	3 (1.4)	0 (0.0)	6 (0.9)
Withdrawal criteria	4 (1.8)	3 (1.4)	4 (1.8)	11 (1.7)
Other	2 (0.9)	4 (1.8)	1 (0.5)	7 (1.1)
Full analysis set	221 (98.2)	218 (98.6)	219 (100.0)	658 (98.9)
Safety analysis set	221 (98.2)	218 (98.6)	219 (100.0)	658 (98.9)

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.

The actual subject disposition for those subjects who participated in the second 26-week period of the extension (Extension 2 FAS) was as follows:

Subjects	Lira 1.2+Met N	Lira 1.2+Met (%)	Lira 1.8+Met N	Lira 1.8+Met (%)	Sita+Met-> Lira 1.2+Met N	Sita+Met-> Lira 1.2+Met (%)	Sita+Met-> Lira 1.8+Met N	Sita+Met-> Lira 1.8+Met (%)	All N	All (%)
Exposed in week 52 to 78	134	(100.0)	150	(100.0)	67	(100.0)	68	(100.0)	419	(100.0)
Completed 78 weeks	124	(92.5)	135	(90.0)	59	(88.1)	63	(92.6)	381	(90.9)
Withdrawals in week 52 to 78	10	(7.5)	15	(10.0)	8	(11.9)	5	(7.4)	38	(9.1)
Adverse Events	0	(0.0)	3	(2.0)	6	(9.0)	0	(0.0)	9	(2.1)
Non-compliance with protocol	1	(0.7)	2	(1.3)	1	(1.5)	1	(1.5)	5	(1.2)
Ineffective therapy	3	(2.2)	3	(2.0)	0	(0.0)	0	(0.0)	6	(1.4)
Withdrawal criteria	4	(3.0)	3	(2.0)	1	(1.5)	3	(4.4)	11	(2.6)
Other	2	(1.5)	4	(2.7)	0	(0.0)	1	(1.5)	7	(1.7)
Extension 2 Full analysis set	134	(100.0)	150	(100.0)	67	(100.0)	68	(100.0)	419	(100.0)

Withdrawals include subjects withdrawn between weeks 52 and 78 as defined by the Extension 2 Full Analysis Set (which is all subjects who completed 52 weeks of treatment and who were exposed in last extension (week 52 to 78))

Diagnosis and Main Criteria for Inclusion

Male and female subjects diagnosed with type 2 diabetes, stable treatment with metformin for at least 3 months at doses of ≥ 1500 mg, aged 18-80 years inclusive, body mass index (BMI) ≤ 45.0 kg/m^2 and HbA_{1c} 7.5−10.0% (both inclusive).

Test Product, Dose and Mode of Administration, Batch Number

Liraglutide (6.0 mg/mL) in 3 mL pen-injector (Batch no.: VP50196 and VP51426) to be injected once-daily s.c. in the abdomen, thigh or upper arm. Daily dose of liraglutide was 1.2 mg or 1.8 mg, respectively. The expiry date of a part of batch VP51426 was extended by 6 months, based on results demonstrating that the stability of liraglutide was unchanged. Liraglutide with this extended expiry date was only used in the second 26-week part of the extension.

Duration of Treatment

For subjects randomised to treatment with liraglutide, the planned treatment was 26 or 78 weeks and included a forced week dose escalation period with liraglutide (weekly increments of 0.6 mg/day to final dose, 1.2 mg/day or 1.8 mg/day), respectively. The actual mean duration of treatment was 382 days for the liraglutide 1.2 mg+metformin group and 424 days for the liraglutide 1.8 mg+metformin group.

For subjects randomised to treatment with sitagliptin, the planned treatment was 26 or 52 weeks with the same dose of 100 mg sitagliptin. The actual mean duration of treatment with sitagliptin was 304 days (as stated in CTR 2). The actual mean duration of treatment with liraglutide after the switch at Week 52 was 164 days for the liraglutide 1.2 mg+metformin group and 170 days for the liraglutide 1.8 mg+metformin group.

Reference Therapy, Dose and Mode of Administration, Batch Number

Sitagliptin, Januvia®, tablets (Batch no.: S6004 and T5964) for once-daily oral administration. Daily dose of sitagliptin was 100 mg. Sitagliptin was only used during the main and the first 26-week period of the extension. Metformin was not a trial product.

Criteria for Evaluation – Efficacy

- HbA_{1c}, FPG, self-measured 7-point meal-related plasma glucose profiles, body weight, beta-cell function (fasting insulin, fasting C-peptide, fasting pro-insulin), fasting lipid profile (TC, HDL-C, LDL-C, VLDL-C, TG, FFA and ApoB), vital signs (systolic and diastolic blood pressure and pulse), waist circumference and waist to hip ratio, and patient reported outcome (in a subset of subjects).

Criteria for Evaluation – Safety

- Adverse events, physical examination, hypoglycaemic episodes, laboratory safety parameters (standard analyses of haematology, biochemistry and calcitonin) and pregnancy test.

Statistical Methods

Analysis Sets

The **extension 2 full analysis set (Extension 2 FAS)** was used for analyses of all efficacy endpoints (changes from Week 52 to Week 78) as well as safety endpoints and included all subjects from FAS who completed 52 weeks of treatment (26 week main and 26 weeks of extension) and who were exposed in the last extension period (Week 52 to Week 78).

The **full analysis set (FAS)** was used for analyses of all efficacy endpoints (changes from baseline to Week 78) and included all randomised subjects who had been exposed to at least one dose of trial product and, moreover, had at least one post-baseline assessment of efficacy. If a subject had received a different treatment than he/she was randomised to, data for the subject was analysed, tabulated, and/or listed according to the treatment he/she was randomised to.

The **safety analysis set** included all randomised subjects who had been exposed to at least one dose of trial product. If a subject had received a different treatment than he/she was randomised to, data for the subject was analysed, tabulated, and/or listed according to the treatment he/she actually received. The safety analysis set was identical to the safety analysis set defined in the main 26-week trial and identical to the FAS in this trial.

A **completers analysis set** was defined for the statistical analyses of HbA_{1c} and included subjects who completed the 78-week trial period. Completers were subjects included in the extension that performed Visit 11 (at Week 78) within reasonable time limits.

An **extension 2 PRO analysis set** was defined for the analyses of the PRO endpoints (changes from Week 52 to Week 78) and included subjects from the Extension 2 FAS, except for subjects from Serbia, Slovakia and Slovenia.

A **PRO analysis set** was defined for analyses of the PRO endpoints (changes from baseline to Week 78) and included subjects from the FAS, except for subjects from Serbia, Slovakia and Slovenia.

Primary Endpoint

HbA_{1c} (%) was treated as the primary endpoint in this second 26-week extension. In this part of the extension, there was no active control group, as all subjects originally treated with sitagliptin+metformin were randomised to treatment with either 1.2 mg/day or 1.8 mg/day liraglutide for 26 weeks (hereafter called switch groups). Metformin treatment was continued unchanged. The effect of changing therapy (part of first main objective) was assessed by investigating the changes in HbA_{1c} from Week 52 to Week 78, within each treatment group, by a paired t-test on the Extension 2 FAS (using LOCF). The hypothesis was that the change in HbA_{1c} from Week 52 to Week 78 would be different from zero within each treatment group. The analysis is not a controlled comparison and the mean differences are not purely an effect of the treatment in the period from Week 52 to Week 78.

Secondly, the estimated changes from Week 52 to Week 78 in the switch groups were compared by an ANCOVA model on the Extension 2 FAS (LOCF). The statistical hypothesis (H_0) was that the effect of switching therapy from sitagliptin to liraglutide 1.8 mg, assessed as change in HbA_{1c} from Week 52 to Week 78, would be different from the effect of switching therapy from sitagliptin to liraglutide 1.2 mg. A difference between two treatment regimens was to be concluded if H_0 was rejected at a 5% level.

The sustainability of HbA_{1c} with liraglutide in combination with metformin (part of second main objective), over the total trial period of 78 weeks, was investigated by evaluating the mean HbA_{1c} over time during the trial (graphically and by summary tables). In addition, the estimated changes in the two original liraglutide+metformin groups from Week 0 to Week 78 were compared by an ANCOVA model, for the FAS (LOCF), as well as a completer analysis set. The statistical hypothesis (H_0) was that the effect of being treated with liraglutide 1.8 mg, assessed as change in HbA_{1c} from Week 0 to Week 78, would be different from the effect of being treated with liraglutide 1.2 mg. A difference between two treatment regimens was to be concluded if H_0 was rejected at a 5% level.

Secondary Endpoints

For the majority of the secondary endpoints, the same analyses as for HbA_{1c} were to be performed. Analysis of the changes within treatment groups were assessed by a paired t-test and a comparison of the changes within the two

switch groups were done by an ANCOVA using treatment and country as fixed effects and the Week 52 value of the parameter of interest as covariate.

The proportion of subjects achieving HbA_{1c} target (American Diabetes Association, ADA target of HbA_{1c} <7%; American Association of Clinical Endocrinologists, AACE target of $HbA_{1c} \leq 6.5\%$) was compared between treatments using a logistic regression model with treatment and country as fixed effects and baseline HbA_{1c} as covariate.

The sustainability of glycaemic control (HbA_{1c} target, FPG and 7-point post-prandial plasma glucose profiles) with liraglutide in combination with metformin, over the total trial period of 78 weeks, was investigated by evaluating the changes over time during the trial (graphically and by summary tables). In addition, the estimated changes in FPG and in 7-point post-prandial plasma glucose profiles from Week 0 to Week 78 were compared by an ANCOVA model, for the FAS (LOCF). The proportion of subjects (treated with liraglutide from baseline) reaching HbA_{1c} targets at Week 78 were compared by a logistic regression model.

Safety Endpoints

The following safety endpoints were presented for the treatment groups using descriptive statistics: Adverse events (AEs), physical examination, hypoglycaemic episodes and laboratory safety parameters (haematology, biochemistry). No formal statistical analyses between treatment groups were to be performed for the safety endpoints. All analyses and tabulations regarding safety endpoints were performed for both the Extension 2 FAS and the safety analysis set.

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 population participating in the second 26-week period of the extension consisted of male (53.5%) and female (46.5%) subjects with type 2 diabetes. They had a mean age of 54.8 years, a mean weight of 95.0 kg, a mean BMI of 33.0 kg/m^2, a mean duration of diabetes of 5.7 years and a mean baseline HbA_{1c} of 8.4%. The majority of subjects (86.6%) were white with 7.6% of subjects being Black or African American. Approximately 13.6% were of Hispanic or Latino ethnicity.

The baseline demographics of those subjects who participated in the second 26-week period of the extension (Extension 2 FAS) was as follows:

	Lira 1.2 + Met	Lira 1.8 + Met	Sita + Met -> Lira 1.2 + Met	Sita + Met -> Lira 1.8 + Met	Extension 2 Full Analysis Set
Extension 2 Full Analysis Set	134	150	67	68	419
Age (years)					
N	134	150	67	68	419
Mean (SD)	55.2 (9.5)	54.3 (8.3)	55.6 (8.3)	54.3 (9.0)	54.8 (8.8)
Median	54.5	54.0	55.0	55.5	55.0
Min ; Max	26 ; 79	33 ; 76	37 ; 74	37 ; 71	26 ; 79
Sex, N (%)					
N	134 (100)	150 (100)	67 (100)	68 (100)	419 (100)
Male	66 (49.3)	81 (54.0)	38 (56.7)	39 (57.4)	224 (53.5)
Female	68 (50.7)	69 (46.0)	29 (43.3)	29 (42.6)	195 (46.5)
Race, N (%)					
N	134 (100)	150 (100)	67 (100)	68 (100)	419 (100)
White	111 (82.8)	130 (86.7)	62 (92.5)	60 (88.2)	363 (86.6)
Black or African American	16 (11.9)	11 (7.3)	2 (3.0)	3 (4.4)	32 (7.6)
Asian	2 (1.5)	2 (1.3)	0 (0.0)	0 (0.0)	4 (1.0)
American Indian or Alaska Native	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.2)
Other	4 (3.0)	7 (4.7)	3 (4.5)	4 (5.9)	18 (4.3)
Ethnicity, N (%)					
N	134 (100)	150 (100)	67 (100)	68 (100)	419 (100)
Hispanic or Latino	19 (14.2)	22 (14.7)	8 (11.9)	8 (11.8)	57 (13.6)
Not Hispanic or Latino	115 (85.8)	128 (85.3)	59 (88.1)	60 (88.2)	362 (86.4)
Height (m)					
N	134	150	67	68	419
Mean (SD)	1.69 (0.11)	1.70 (0.10)	1.70 (0.11)	1.69 (0.09)	1.70 (0.10)
Median	1.69	1.71	1.71	1.70	1.70
Min ; Max	1.46 ; 2.06	1.50 ; 1.92	1.47 ; 1.89	1.50 ; 1.84	1.46 ; 2.06
Weight (kg)					
N	134	150	67	68	419
Mean (SD)	94.1 (17.5)	97.1 (18.5)	94.3 (20.5)	93.0 (18.0)	95.0 (18.4)
Median	92.3	96.9	94.5	89.6	93.0
Min ; Max	61.2 ; 145.7	57 ; 152.4	59 ; 150.2	54 ; 142.2	54 ; 152.4
BMI (kg/m^2)					
N	134	150	67	68	419
Mean (SD)	33.1 (5.3)	33.4 (5.1)	32.7 (5.6)	32.4 (5.2)	33.0 (5.2)
Median	32.0	33.5	32.3	31.7	32.6
Min ; Max	22.6 ; 44.9	20.9 ; 44.8	22.9 ; 44.9	23.4 ; 44.2	20.9 ; 44.9
HbA1c at screening (%)					
N	134	150	67	68	419
Mean (SD)	8.4 (0.7)	8.5 (0.7)	8.4 (0.7)	8.4 (0.7)	8.5 (0.7)
Median	8.3	8.4	8.3	8.3	8.3
Min ; Max	7.5 ; 10.0	7.5 ; 10.0	7.5 ; 9.8	7.5 ; 10.0	7.5 ; 10.0
Duration of diabetes (years)					
N	134	150	67	68	419
Mean (SD)	5.6 (3.9)	6.0 (5.0)	5.8 (5.1)	5.3 (4.2)	5.7 (4.6)
Median	5.4	4.7	5.2	4.8	5.0
Min ; Max	0.26 ; 23.1	0.39 ; 30.7	0.26 ; 25.6	0.30 ; 20.7	0.26 ; 30.7

BMI: body mass index, SD: standard deviation
All the values used in this table are from screening visit

Efficacy Results

Effect of Changing Therapy from Sitagliptin to Liraglutide (Week 52 to Week 78)

- HbA_{1c}
  - Mean HbA_{1c} value at Week 78 was 7.0% in the sitagliptin+metformin→liraglutide 1.2 mg+metformin group and 7.1% in the sitagliptin+metformin→liraglutide 1.8 mg+metformin group, respectively (using LOCF). In spite of the random allocation to the 1.2 mg or 1.8 mg dose at Week 52, mean HbA_{1c} appeared to be slightly higher in the sitagliptin+metformin→liraglutide 1.8 mg+metformin group (7.6%) as compared to the sitagliptin+metformin→liraglutide 1.2 mg+metformin group (7.2%).
  - Based on a paired t-test, the mean changes from Week 52 to Week 78 in the switch groups were -0.24% and -0.45%, respectively (1.2 mg and 1.8 mg). These changes were statistically significant within both switch groups (p=0.0060 and p=0.0001).
- Glycaemic control parameters
  - The mean changes (based on paired t-test) in FPG from Week 52 to Week 78 were -0.84 mmol/L and -1.42 mmol/L in the switch groups (1.2 mg and 1.8 mg). These reductions were statistically significant within both switch groups (p=0.0004 and p<0.0001). In line with the changes in mean HbA_{1c}, it appears that in spite of the random allocation to the 1.2 mg or the 1.8 mg dose at Week 52, mean FPG at Week 52 appeared to be slightly higher in the sitagliptin+metformin→liraglutide 1.8 mg+metformin group (9.22 mmol/L) as compared to the sitagliptin+metformin→liraglutide 1.2 mg+metformin group (8.62 mmol/).
  - The mean changes (based on paired t-test) in 3-hour postprandial plasma glucose profile (based on AUC) from Week 52 to Week 78 were -2.52 mmol*h/L and -3.46 mmol*h/L in the switch groups (1.2 mg and 1.8 mg). These reductions were statistically significant within both switch groups (p=0.0170 and p=0.0355).
  - After the switch to liraglutide at Week 52, the estimated proportion of subjects achieving the target for HbA_{1c} < 7% (ADA) appeared to increase and at Week 78 they reached 49.2% and 50.0% in the switch groups (1.2 mg and 1.8 mg). There was no statistically significant difference between the 1.2 mg and the 1.8 mg switch groups (p=0.9368).
  - After the switch to liraglutide at Week 52, the estimated proportion of subjects achieving the target for HbA_{1c} ≤ 6.5% (AACE) appeared to increase and at Week 78 they reached 28.7% and 24.5% in the switch groups (1.2 mg and 1.8 mg). There was no statistically significant difference between the 1.2 mg and the 1.8 mg switch groups (p=0.6002).
- Beta-cell function parameters
  - The mean changes (based on paired t-test) from Week 52 to Week 78 in the beta-cell parameters were statistically significant for HOMA-IR (mean change of -1.15 in the sitagliptin+metformin→liraglutide 1.8 mg+metformin group with p=0.0464) and HOMA-B (mean increases of 13.31% and 23.09% with p=0.0006 and p=0.0001 for the 1.2 mg and 1.8 mg dose groups, respectively).
- Body weight
  - The mean changes (based on paired t-test) in body weight from Week 52 to Week 78 were -1.64 kg and -2.48 kg in the switch groups (1.2 mg and 1.8 mg). These changes were statistically significant within both switch groups (both p<0.0001).
- Waist circumference and waist-to-hip ratio
  - The mean changes (based on paired t-test) in waist circumference from Week 52 to Week 78 were -1.33 cm and -2.05 cm (1.2 mg and 1.8 mg). These reductions were statistically significant within both switch groups (p=0.0028 and p=0.0001).
  - The changes in waist-to-hip ratio were not statistically significant.
- Fasting lipid profile
  - The mean changes (based on paired t-test) from Week 52 to Week 78 in the lipid parameters were statistically significant for total cholesterol and TG (reductions in the sitagliptin+metformin→liraglutide 1.8 mg+metformin group), LDL-C (reductions in both switch groups) and ApoB (increases in both switch groups).
- Blood pressure and pulse
  - The mean changes (based on paired t-test) in blood pressure from Week 52 to Week 78 were -2.12 mmHg and 0.35 mmHg for systolic BP and -0.60 mmHg and 0.03 mmHg for diastolic BP (1.2 mg and 1.8 mg). None of

these changes were statistically significant within the treatment groups.
  - The mean changes (based on paired t-test) in pulse from Week 52 to Week 78 were 0.90 beats/min and 2.19 beats/min. The increase was statistically significant in the sitagliptin+metformin→liraglutide 1.8 mg+metformin group (p=0.0224). The increases in pulse were not considered to be clinically relevant.
- Patient reported outcome
  - Following the switch from sitagliptin to liraglutide at Week 52, there was an improvement in the 'overall treatment satisfaction' which was statistically significant in the sitagliptin+metformin→liraglutide 1.2 mg+metformin group (p=0.0170).
  - Interestingly, the DTSQs results generally indicated, that the subjects did not find treatment with liraglutide (an injectable drug) to be less convenient or flexible than treatment with sitagliptin (an orally administered drug).
- For all efficacy endpoints, changes from Week 52 to Week 78 were compared between the two switch dose groups using ANCOVA. It should be kept in mind that the trial was not powered to show a difference between the two switch dose groups. Statistically significant differences between the switch groups (1.2 mg and 1.8 mg) were only observed for two PRO endpoints (in favour of the liraglutide 1.2 mg dose).

Sustainability of Glycaemic Control with Liraglutide in Combination with Metformin over a Period of 78 Weeks

- HbA_{1c}
  - From baseline to Week 12, there was a marked reduction in HbA_{1c} in both original liraglutide+metformin groups, most marked in the liraglutide 1.8 mg+metformin group. The reductions in HbA_{1c} were generally sustained during the trial, although there was a tendency to a slight increase in HbA_{1c} towards Week 78, most pronounced in the liraglutide 1.2 mg+metformin group. The estimated mean changes in HbA_{1c} from baseline to Week 78 (based on ANCOVA) were -0.94% in the liraglutide 1.2 mg+metformin group and -1.28% in the liraglutide 1.8 mg+metformin group.
- Glycaemic control parameters
  - From baseline to Week 4, there was a marked decrease in FPG in both original liraglutide+metformin groups. The reductions in FPG were generally sustained during the trial. The estimated mean changes in FPG from baseline to Week 78 (based on ANCOVA) were -1.30 mmol/L in the liraglutide 1.2 mg+metformin group and -1.65 mmol/L in the liraglutide 1.8 mg+metformin group.
  - The 3-hour postprandial plasma glucose profiles were reduced from Week 0 to Week 52, but with a tendency to an increase again towards Week 78. The estimated mean changes in AUC from baseline to Week 78 were -8.88 mmol*h/L and -6.06 mmol*h/L in the liraglutide 1.2 mg+metformin and the liraglutide 1.8 mg+metformin groups, respectively.
  - For subjects in the original liraglutide+metformin groups, the estimated proportions of subjects reaching the target of $HbA_{1c} < 7\%$ (ADA) at Week 78 were 34.7% and 51.2% and for the target of $HbA_{1c} \leq 6.5\%$ (AACE) were 12.0% and 26.6% (1.2 mg and 1.8 mg).
- A comparison of the two original liraglutide+metformin dose groups (by ANCOVA) with regard to changes in glycaemic control parameters from baseline to Week 78 demonstrated statistically significant differences with regard to HbA_{1c} (estimated treatment difference of -0.33%, the 95% CI for treatment difference was [-0.53; -0.13] and p=0.0011).
- With regard to target HbA_{1c}, the estimated proportion of subjects reaching the targets of $HbA_{1c} < 7\%$ (ADA) and $HbA_{1c} \leq 6.5\%$ (AACE) at Week 78 were statistically significantly greater for subjects in the liraglutide 1.8 mg+metformin as compared to the liraglutide 1.2 mg+metformin group (p=0.0014 and p=0.0002, respectively).

Safety Results

Overall Safety Conclusions

- The most frequently reported TEAEs with liraglutide were gastrointestinal disorders (nausea, diarrhoea and vomiting) with a slightly higher frequency with increasing dose. In general, the events of nausea were transient and mainly categorised as mild. A similar pattern was observed for subjects who were switched from sitagliptin to liraglutide at Week 52.
- A total of 6 deaths were reported during the entire 78-week trial period, of which 2 were in the liraglutide 1.8 mg+metformin group (pancreatic carcinoma and bile duct cancer), 3 were in the sitagliptin+metformin group (cardiac arrest, renal cancer and sudden cardiac death) and 1 was in the sitagliptin+metformin→liraglutide 1.2 mg+metformin group (acute renal failure with diarrhoea, vomiting and septicaemia as contributing factors). All deaths were evaluated as unlikely related to trial product by the investigators.
- One (1) subject treated with liraglutide 1.2 mg+metformin reported 2 episodes of major hypoglycaemia. Rates of minor hypoglycaemia were low throughout the trial and remained low after switching therapy to liraglutide.
- One (1) case of mild non-acute pancreatitis was reported in the liraglutide 1.8 mg+metformin group. The subject did not fulfil the pre-defined criteria for acute pancreatitis in the protocol.
- Thyroid events were reported by a comparable proportion of subjects in the treatment groups and there was not an increase in reports of these events when switching from sitagliptin to liraglutide at Week 52.
- No clinically relevant changes in biochemistry or haematology parameters were observed during the trial, neither for subjects treated with liraglutide from baseline to Week 78 or for subjects switching to liraglutide at Week 52.
- There were no positive pregnancy tests reported during the trial.

Safety Conclusions for the Change of Sitagliptin to Liraglutide (Week 52 to Week 78)

- Adverse events (AE)
  - The overall frequency of TEAEs was 64.2% and 60.3% in the switch groups (1.2 mg and 1.8 mg) and 38.8% and 44.7% for the original liraglutide+metformin groups (1.2 mg and 1.8 mg) during the same period. The most frequently reported TEAEs in the switch groups were gastrointestinal disorders (nausea, diarrhoea and vomiting) and the frequency appeared to increase slightly with increasing dose of liraglutide (32.8% and 36.8% with 1.2 mg and 1.8 mg, respectively). The increased frequency of nausea in the switch groups was transient and the events were mainly mild and moderate.
  - Severe TEAEs were reported by 7.5% and 2.9% of the subjects in the switch groups (1.2 mg and 1.8 mg) and by 1.5% and 5.3% of subjects in the original liraglutide+metformin groups (1.2 mg and 1.8 mg) during the same period. The most commonly reported severe TEAEs in the switch groups were gastrointestinal disorders (4.5% and 0.0% with 1.2 mg and 1.8 mg, respectively) and infections and infestations (3.0% and 1.5% with 1.2 mg and 1.8 mg, respectively). The most commonly reported moderate and mild adverse events in the switch groups were gastrointestinal adverse events.
  - TEAEs assessed by the investigator to be probably or possibly related to trial products were reported by 34.3% and 38.2% of subjects in the switch groups (1.2 mg and 1.8 mg) and by 3.7% and 4.7% in the two original liraglutide+metformin groups (1.2 mg and 1.8 mg) during the same period. The most frequently reported probably or possibly related TEAEs in the two switch groups were gastrointestinal disorders.
  - One (1) death due to acute renal failure was reported in the period from Week 52 to Week 78 in a subject treated with sitagliptin+metformin for 385 days and liraglutide 1.2 mg+metformin for 31 days (see case description under 'Overall Safety Conclusions' above).
  - The proportion of subjects reporting SAEs appeared to be comparable in the four treatment groups (from 1.5% to 6.0%). Overall, the proportion of SAEs reported during Week 52 to Week 78 was low. The majority of the reported SAEs were moderate and severe and showed no consistent pattern with respect to system organ class of events. Four (4) of a total of 7 probably or possibly related SAEs reported during the entire trial occurred between Week 52 and Week 78 (hypoglycaemia and cardiac failure in the original liraglutide+metformin groups and dehydration and gastroenteritis in the switch groups).
  - A total of 9 subjects (1.4%) were withdrawn due to AEs in the period from Week 52 to Week 78. Of these, 6

were in the sitagliptin+metformin→liraglutide 1.2 mg+metformin group and 3 were in the liraglutide 1.8 mg+metformin group. There was no pattern in the TEAEs leading to withdrawal from Week 52 to Week 78.
  - A total of 5 thyroid related TEAEs were reported with no specific pattern (1 event in the sitagliptin+metformin→liraglutide 1.2 mg+metformin group and 4 events in the original liraglutide+metformin groups).
- Laboratory analyses
  - No clinically relevant changes in biochemistry or haematology parameters were observed.
- Physical examination
  - No differences between the treatment groups were observed for changes in physical examination from baseline to Week 78 and shifts in physical examination after baseline were generally infrequent.
- Hypoglycaemic episodes
  - One (1) major hypoglycaemic episode was reported in a subject treated with liraglutide 1.2 mg+metformin. The same subject had also reported a major episode prior to Week 52 (with blood glucose 3.6 mmol/M). For more details on this subject, see 'hypoglycaemic episodes' in the following section ('Safety Conclusions for Long-term Treatment with Liraglutide (Baseline to Week 78)').
  - The proportion of subjects experiencing minor hypoglycaemic episodes appeared to be low and comparable across groups with 3.0% and 4.4% in the switch groups and 6.0% and 2.0% in the original liraglutide+metformin groups during the same period (in 1.2 mg and 1.8 mg dose groups, respectively). The corresponding rates of minor episodes were 0.031 and 0.060 episodes per subject year in the switch groups (1.2 mg and 1.8 mg) and 0.061 and 0.023 episodes per subject year in the original liraglutide+metformin groups (1.2 mg and 1.8 mg). The proportion of subjects experiencing symptoms only episodes was low in all four treatment groups (1.5% and 0.0% in the switch groups and 1.5% and 3.3% in the original liraglutide+metformin groups (in the 1.2 mg and 1.8 mg dose groups, respectively)

Safety Conclusions for Long-term Treatment with Liraglutide (Baseline to Week 78)
- Adverse events (AE)
  - The overall frequency of TEAEs was 74.2% and 81.2% in the two original liraglutide+metformin groups (1.2 mg and 1.8 mg). The most frequently reported TEAEs in these groups were gastrointestinal disorders (nausea, diarrhoea and vomiting) and the frequency appeared to increase with increasing dose of liraglutide (38.0% and 43.6% with 1.2 mg and 1.8 mg, respectively).
  - The majority of TEAEs were mild in severity and to a lesser extent moderate and assessed by the investigator to be unlikely related to trial products. Severe TEAEs were reported by 6.3% and 9.6% of the subjects, respectively (1.2 mg and 1.8 mg). The most commonly reported severe TEAEs were gastrointestinal disorders in the liraglutide 1.2 mg+metformin group (1.8%) and infections and infestations in the liraglutide 1.8 mg+metformin group (2.8%).
  - TEAEs assessed by the investigator to be probably or possibly related to trial products were reported by 34.8% and 46.8% of subjects, respectively (1.2 mg and 1.8 mg). The most frequently reported TEAEs being possibly or probably related to trial products were gastrointestinal disorders in both groups (27.1% and 36.2% with 1.2 mg and 1.8 mg, respectively).
  - Six (6) deaths were reported during the entire 78-week trial period. Two (2) of these deaths occurred in subjects from the original liraglutide 1.8 mg+metformin group, in whom the following SAEs were reported after 8 and 316 days of treatment, respectively; pancreatic carcinoma and bile duct cancer. Three (3) deaths occurred in subjects from the sitagliptin+metformin group, in whom the following SAEs were reported after 48, 100 and 282 days of treatment, respectively; cardiac arrest, renal cancer and sudden cardiac death. The last death occurred in a subject initially randomised to sitagliptin+metformin and then switched to liraglutide 1.2 mg+metformin at Week 52; acute renal failure (see case description under 'Overall Safety Conclusions' above).
  - The proportion of subjects reporting SAEs was comparable in the two original liraglutide+metformin groups (5.4% and 8.7% with 1.2 mg and 1.8 mg, respectively). The majority of the reported SAEs were moderate and severe and the most frequently reported SAEs in these two treatment groups belonged to the system organ class

of infections and infestations. A total of 4 SAEs in 4 subjects in the original liraglutide+metformin groups were judged by the investigator as being probably or possibly related to the trial product (liraglutide 1.2 mg+metformin: thyroid disorder and hypoglycaemia; liraglutide 1.8 mg+metformin: cardiac failure and pancreatitis). For details on the thyroid disorder and the pancreatitis, see 'thyroid related TEAEs' and 'pancreatitis' below.

- Overall, a total of 60 subjects (9.0%) were withdrawn due to AEs. The percentage of subjects withdrawn from the trial due to TEAEs was slightly higher in the liraglutide 1.8 mg+metformin group (12.8%) as compared to the liraglutide 1.2 mg+metformin (8.6%) group. In the original liraglutide+metformin groups, the majority of the TEAE withdrawals were caused by gastrointestinal disorders leading to withdrawal within the first months of randomised treatment.
- One (1) case of mild non-acute pancreatitis was reported (after treatment for 227 days in the liraglutide 1.8 mg+metformin group). The event was upgraded to serious due to 'medical significance' and was considered to be possibly related by the investigator. The subject did not fulfil the pre-defined criteria for acute pancreatitis in the protocol.
- The frequency of clinical thyroid events reported was comparable between treatment groups and none of the events were malignant.

- Laboratory analyses
  - From baseline to Week 78, no clinically relevant changes in biochemistry or haematology parameters were observed.
- Physical examination
  - No differences between the original liraglutide+metformin treatment groups were observed for changes in physical examination from baseline to Week 78 and shifts in physical examination after baseline were generally infrequent.
- Hypoglycaemic episodes
  - One (1) subject reported 2 major hypoglycaemic episodes (after treatment with liraglutide 1.2 mg+metformin for 40 and 486 days, respectively). Blood glucose at the first episode was 3.6 mmol/L but the subject required third-party assistance (food and drink) and the episode was evaluated as a non-serious TEAE. At the second episode, the subject had to be hospitalised for treatment with intravenous dextrose and glucagon (blood glucose unknown) and the episode was classified as an SAE of hypoglycaemia. No convulsions or loss of consciousness were reported.
  - From baseline to Week 78, the proportion of subjects experiencing minor hypoglycaemic episodes (confirmed plasma glucose < 3.1 mmol/L) appeared to be comparable in the two original liraglutide+metformin groups (10.0% and 9.6% with 1.2 mg and 1.8 mg, respectively). The corresponding rates of minor episodes were 0.156 and 0.221 episodes per subject year (1.2 mg and 1.8 mg). When excluding an extreme outlier (Subject 786017), the rate of minor episodes decreased to 0.130 episodes per subject year in the liraglutide 1.8 mg+metformin group. The proportion of subjects experiencing symptoms only episodes was low in the two original liraglutide+metformin groups (5.9% and 7.8% with 1.2 mg and 1.8 mg), respectively.

Conclusions

The change of treatment from sitagliptin to liraglutide (1.2 mg or 1.8 mg) after 52 weeks appeared safe and well tolerated. The change to liraglutide improved the glycaemic control, assessed by glycaemic parameters such as HbA_{1c}, FPG and the proportion of subjects reaching the ADA and AACE HbA_{1c} targets. Body weight was further reduced. The changes in HbA_{1c} and body weight from the switch at Week 52 to Week 78 were statistically significant within each dose group. There was an increase in incidence of gastrointestinal adverse events (especially nausea) in the switch groups when changing therapy from sitagliptin to liraglutide, but these events were generally transient and mild or moderate in severity. The rates of minor hypoglycaemia remained low after the switch in therapy and no major episodes were reported in the two switch groups.

For the two groups treated with liraglutide and metformin from baseline, sustained and clinically relevant reductions in HbA_{1c}, FPG and body weight were shown for the total trial period. The changes in HbA_{1c} as well as the proportion of subjects reaching the ADA and AACE targets increased markedly from baseline to Week 26 and remained generally stable when reaching Week 52 and Week 78. The safety profile of liraglutide was confirmed and the risk of hypoglycaemia remained low.

This clinical trial confirmed that the change in therapy from sitagliptin to liraglutide as well as the long-term use of liraglutide (both in combination with metformin), were effective and safe treatment options for subjects with type 2 diabetes.

The trial was conducted in accordance with the Declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Last amended with Note of Clarification on Paragraph 30 by the WMA General Assembly, Tokyo 2004) and ICH Good Clinical Practice (1 May 1996).

The results presented reflect data available in the clinical database as of 1 July 2010.