CTR synopsis

Clinical Trial Report synopsis - ICH E3 Section 2

Trial registration ID-number NCT01272232	**UTN** – U1111-1118-7963 **IND number** – 73,206 **EudraCT number** – 2008-002199-88

TITLE OF TRIAL

Effect of liraglutide on body weight in overweight or obese subjects with type 2 diabetes - A 56 week randomised, double-blind, placebo-controlled, three armed parallel group, multi-centre, multinational trial with a 12 week observational follow-up period

INVESTIGATORS

One principal investigator was appointed at each of the 126 trial sites in the trial. The following investigators was designated signatory investigators for the trial, and were responsible for reviewing and approving the Clinical Trial Report:

Professor [redacted], MD
[redacted]

TRIAL SITES

The trial was conducted at 126 sites in 9 countries as follows:

France: 7 sites; Germany: 10 sites; Israel: 5 sites; South Africa: 6 sites; Spain: 8 sites; Sweden: 5 sites; Turkey: 3 sites; United Kingdom: 15 sites; United States: 67 sites

PUBLICATIONS

No publications were available at the time of this clinical trial report synopsis.

TRIAL PERIOD	**DEVELOPMENT PHASE**
Initiation date: 1 June 2011 Completion date: 25 January 2013	Phase 3a

DATA CUT-OFF DATE

The results presented reflect the data available in the clinical database as of 21 February 2013. Data on mental health questionnaires were queried due to errors, and the data cut-off date was 23 May 2013.

OBJECTIVES

Primary objective:

- To investigate the efficacy of liraglutide compared to liraglutide placebo in inducing and maintaining weight loss in overweight or obese subjects with type 2 diabetes after 56 weeks.

Secondary objectives:

- To compare liraglutide and liraglutide placebo regarding the effect on:
- Parameters of glycaemic control
- Waist circumference
- Cardiovascular risk factors
- Attaining treatment targets of risk factors for subjects with type 2 diabetes
- Patient reported outcomes (PRO)
  Weight maintenance in the 12-week observational follow-up period

Safety objective:

- To evaluate the safety and tolerability of liraglutide.

METHODOLOGY

This was a 56-week, randomised, double-blind, placebo-controlled, three-armed, parallel-group, multi-centre, multi-

national trial comparing once daily administration of 3.0 mg and 1.8 mg of liraglutide with liraglutide placebo in overweight or obese subjects with type 2 diabetes. The duration of the trial from screening to follow up was 70 weeks per subject with a liraglutide/ liraglutide placebo treatment duration of 56 weeks.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

A total of 800 subjects were planned for enrolment, and 846 were actually enrolled.

Table 1. Subject disposition – Full analysis Set

	Lira 3.0 mg N (%)	Lira 1.8 mg N (%)	Placebo N (%)	Total N (%)
Screened				1361 (160.9)
Screening Failures				515 (60.9)
Withdrawn before Randomisation				0 (0.0)
Randomised	423 (100.0)	211 (100.0)	212 (100.0)	846 (100.0)
Exposed	422 (99.8)	210 (99.5)	212 (100.0)	844 (99.8)
Completer w56	324 (76.6)	164 (77.7)	140 (66.0)	628 (74.2)
Withdrawn w56	99 (23.4)	47 (22.3)	72 (34.0)	218 (25.8)
Adverse Event	39 (9.2)	18 (8.5)	7 (3.3)	64 (7.6)
Ineffective therapy	0 (0.0)	0 (0.0)	3 (1.4)	3 (0.4)
Non-compliance with protocol	12 (2.8)	8 (3.8)	13 (6.1)	33 (3.9)
Withdrawal criteria	32 (7.6)	14 (6.6)	37 (17.5)	83 (9.8)
Withdrawn consent	27 (6.4)	10 (4.7)	28 (13.2)	65 (7.7)
Target dose not tolerated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy or pregnancy intent	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.2)
Use of insulin, GLP1RA or DPP4i	0 (0.0)	2 (0.9)	1 (0.5)	3 (0.4)
Unacceptable hyperglycaemia	5 (1.2)	2 (0.9)	9 (4.2)	16 (1.9)
Unacceptable hypoglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psych disorder (INV/MHP opinion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Calcitonin >=50 ng/L (France)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	16 (3.8)	7 (3.3)	12 (5.7)	35 (4.1)
Withdrawn during first 56 weeks but attended Visit 16x	36 (36.4)	12 (25.5)	23 (31.9)	71 (32.6)
Entered off drug period	324 (76.6)	164 (77.7)	140 (66.0)	628 (74.2)
Completer w68	310 (95.7)	154 (93.9)	135 (96.4)	599 (95.4)
Withdrawn w68	14 (4.3)	10 (6.1)	5 (3.6)	29 (4.6)
Adverse Event	1 (0.3)	1 (0.6)	0 (0.0)	2 (0.3)
Ineffective therapy	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Non-compliance with protocol	1 (0.3)	0 (0.0)	1 (0.7)	2 (0.3)
Withdrawal criteria	9 (2.8)	7 (4.3)	4 (2.9)	20 (3.2)
Withdrawn consent	3 (0.9)	4 (2.4)	2 (1.4)	9 (1.4)
Target dose not tolerated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy or pregnancy intent	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Use of insulin, GLP1RA or DPP4i	6 (1.9)	3 (1.8)	2 (1.4)	11 (1.8)
Unacceptable hyperglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unacceptable hypoglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psych disorder (INV/MHP opinion	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Calcitonin >=50 ng/L (France)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (0.6)	2 (1.2)	0 (0.0)	4 (0.6)

N = Number of Subjects, %=Proportion of randomised subjects, disc.=Discontinuation.
Number of withdrawn subjects at w68: Only subjects withdrawn in the follow up period.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Inclusion Criteria:

- Informed consent obtained
- Subjects diagnosed with type 2 diabetes and treated with either diet and exercise alone, metformin, SU, glitazone as single agent therapy or any combination of the previously mentioned compounds (metformin+SU,

metformin+glitazone, SU+glitazone, metformin+SU+glitazone)
- Glycosylated haemoglobin (HbA_{1c}) 7.0-10.0% (both inclusive)
- Body Mass Index (BMI) of 27.0 kg/m^2
- Stable body weight
- Preceding failed dietary effort

Exclusion Criteria:
- Treatment with glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors or insulin within the last 3 months
- Known proliferative retinopathy or maculopathy
- History of acute or chronic pancreatitis
- Obesity induced by drug treatment
- Use of approved weight lowering pharmacotherapy
- Previous surgical treatment of obesity
- History of major depressive disorder or suicide attempt
- Uncontrolled hypertension (systolic blood pressure of 160 mmHg or above and/or diastolic blood pressure of 100 mmHg or above)
- Screening calcitonin of 50 ng/L or above
- Familial or personal history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma (FMTC)
- Personal history of non-familial medullary thyroid carcinoma

INVESTIGATIONAL MEDICINAL PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Liraglutide 6.0 mg/mL, 3 mL FlexPen® for subcutaneous (s.c.) injection. Batch number: AP50018, AP50534

DURATION OF TREATMENT

The trial consisted of a screening visit (visit 1, up to 2 weeks before randomisation), a 2- to 4-week dose escalation period, a 52-54 weeks maintenance period and a 12-week observational follow-up period after last treatment.

REFERENCE THERAPY , DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Placebo 3 mL FlexPen® for s.c. injection. Batch number: AP50557, YP52304

CRITERIA FOR EVALUATION – EFFICACY

Primary efficacy endpoints:
- Change from baseline in body weight (fasting body weight) at 56 weeks
- Proportion of subjects losing at least 5% of baseline body weight at 56 weeks
- Proportion of subjects losing more than 10% of baseline body weight at 56 weeks

Secondary efficacy endpoints:
- Parameters of glycaemic control: change from baseline (week 0) to week 56 in HbA_{1c}, FPG, 7-point self-measured plasma glucose (SMPG) profile, glucose metabolism related parameters including fasting glucagon, fasting insulin, fasting C-peptide, pro-insulin/insulin ratio and homeostasis model assessment (HOMA) parameters (HOMA-B, HOMA-IR)
- Parameters of glycaemic control: proportion of subjects reaching target HbA_{1c} (< 7% or ≤ 6.5% at week 56)
- Proportion of subjects with change in concomitant medication from baseline to week 56 in: anti-hypertensives, lipid lowering agents, and oral antidiabetic drugs
- Waist circumference
- Cardiovascular risk factors: change from baseline (week 0) to week 56 in systolic and diastolic blood pressure (SBP and DBP), lipids (total cholesterol [TC], low density lipoprotein [LDL] cholesterol, high density lipoprotein [HDL] cholesterol, very low density lipoprotein [VLDL] cholesterol, triglycerides [TG], free fatty acids [FFA]), cardiovascular biomarkers (high sensitivity C reactive protein [hsCRP], adiponectin, fibrinogen, [PAI-1]), and urinary albumin-to-creatinine ratio
- Cardiovascular risk factors: proportion of subjects reaching American Diabetes Association (ADA) treatment

targets for LDL cholesterol (< 100 mg/dL) and TG (< 150 mg/dL); proportion of subjects reaching ADA treatment targets for SBP/DBP (< 130/80 mmHg)

- PRO assessed by Impact of Weight on Quality of Life – Lite (IWQoL-Lite) questionnaire and Diabetes Treatment Satisfaction Questionnaire status version (DTSQs)

CRITERIA FOR EVALUATION – SAFETY

Safety endpoints:

- Physical examination (cardiovascular system, respiratory system, abdomen, central and peripheral nervous system, musculo-skeletal system and the thyroid gland)
- Hypoglycaemic episodes
- Electrocardiogram (ECG)
- Adverse events (AEs)
- Haematology and biochemistry including amylase, lipase and calcitonin
- Vital signs (pulse, rate pressure product [RPP])
- Formation of anti-liraglutide antibodies
- Mental health assessed by Columbia Suicidality Severity Rating Scale (C-SSRS) and Patient Health Questionnaire (PHQ-9)
- Binge eating scale (BES)

STATISTICAL METHODS

A sample size of 400 subjects randomised to liraglutide 3.0 mg treatment, 200 subjects randomised to liraglutide 1.8 mg treatment and 200 subjects randomised to placebo was chosen. The power for the primary endpoint weight change was calculated based on a two sided t-test with a significance level of 5%. The power with regards to the 3 co-primary dichotomous endpoints was calculated based on a two-sided chi-square test. The sample size provided sufficient power for the primary efficacy endpoints weight change, the proportion of subjects with a weight loss of at least 5% and the proportion of subjects with a weight loss more than 10%.

Full analysis set (FAS) – All randomised subjects exposed to at least one dose of the trial product and with at least one post-baseline assessment of any efficacy endpoint. Subjects in the FAS were analysed according to randomised treatment.

Safety analysis set (SAS) – All randomised subjects who have been exposed to at least one dose of trial product. Subjects in the SAS were analysed "as treated".

The continuous primary endpoint, fasting body weight loss, analysed as change in fasting body weight from week 0 to week 56 was compared between liraglutide and placebo using an analysis of covariance (ANCOVA) model with treatment (liraglutide 3.0 mg, liraglutide 1.8 mg, placebo), country, HbA_{1c} stratification factor, background treatment stratification factor, interaction between stratification factors and gender as fixed effects and with baseline body weight (at week 0) as a covariate.

For categorical primary endpoints, a logistic regression model with treatment (liraglutide 3.0 mg, liraglutide 1.8 mg, placebo), country, HbA_{1c} stratification factor, background treatment stratification factor, interaction between stratification factors and gender as fixed effects and with baseline fasting body weight (at week 0) as a covariate, was used to compare the proportion of subjects who lost at least 5% (or more than 10%) of their baseline fasting body weight at week 56 in the three groups.

The tests of equality between liraglutide 3.0 mg and placebo for each of the endpoints were conducted in a hierarchical manner in the order in which the endpoints are presented. If superiority of the liraglutide 3.0 mg dose was demonstrated for all three co-primary endpoints, the tests of equality between liraglutide 1.8 mg and placebo were to be performed in a similar hierarchical manner.

Continuous secondary endpoints were analysed and presented similarly to the primary analysis of weight change. Baseline values were included as covariates in the analyses of the corresponding response variables.

Categorical secondary endpoints were analysed and presented similarly to the primary analysis of proportion of subjects losing at least 5% of baseline body weight. Continuous baseline values were included as covariates in the analyses of the corresponding response variables unless otherwise specified.

All analyses and tabulations regarding safety endpoints were done using the SAS. AEs were summarised by treatment emergent (weeks 0-58), follow-up period (weeks 56-68). Due to the definition of treatment-emergent (14 days after last

dose), AEs with an onset during weeks 56-58 were included in both periods. The proportion of subjects with AEs, and the rate of AEs were compared between the treatment arms (no formal statistic analyses were performed). Pulse and RPP were analyses in the same manner as SBP and DBP. Descriptive statistics and shift tables were prepared for other safety parameters.

DEMOGRAPHY OF TRIAL POPULATION

Table 2. Demographics and baseline characteristics

	Lira 3.0 mg	Lira 1.8 mg	Placebo	Total
Number of Subjects	423	211	212	846
Age (years)				
N	423	211	212	846
Mean (SD)	55.0 (10.8)	54.9 (10.7)	54.7 (9.8)	54.9 (10.5)
Median	56.0	56.0	54.5	55.5
Min ; Max	18.0 ; 79.0	25.0 ; 82.0	28.0 ; 78.0	18.0 ; 82.0
Height (m)				
N	423	211	212	846
Mean (SD)	1.69 (0.11)	1.69 (0.10)	1.69 (0.10)	1.69 (0.10)
Median	1.69	1.70	1.69	1.69
Min ; Max	1.32 ; 1.98	1.45 ; 1.95	1.45 ; 1.91	1.32 ; 1.98
HbA1c (%)				
N	423	211	212	846
Mean (SD)	7.9 (0.8)	8.0 (0.8)	7.9 (0.8)	7.9 (0.8)
Median	7.8	7.9	7.7	7.8
Min ; Max	6.4 ; 10.3	6.7 ; 10.0	6.5 ; 10.1	6.4 ; 10.3
Fasting BW (kg)				
N	422	210	212	844
Mean (SD)	105.7 (21.9)	105.8 (21.0)	106.5 (21.3)	105.9 (21.5)
Median	102.4	101.7	105.4	102.5
Min ; Max	60.1 ; 199.4	66.8 ; 193.3	65.0 ; 187.9	60.1 ; 199.4
BMI (kg/m^2)				
N	423	211	212	846
Mean (SD)	37.1 (6.5)	37.0 (6.9)	37.4 (7.1)	37.1 (6.8)
Median	36.1	35.6	36.0	36.0
Min ; Max	27.0 ; 61.3	27.1 ; 67.6	27.1 ; 67.4	27.0 ; 67.6
FPG (mmol/L)				
N	418	209	212	839
Mean (SD)	8.8 (1.9)	8.9 (2.0)	8.6 (1.8)	8.8 (1.9)
Median	8.5	8.6	8.4	8.5
Min ; Max	5.6 ; 17.3	4.2 ; 16.2	4.9 ; 16.1	4.2 ; 17.3
Duration of Diabetes (years)				
N	423	211	212	846
Mean (SD)	7.54 (5.65)	7.43 (5.16)	6.71 (5.07)	7.30 (5.39)
Median	6.3	6.5	5.6	6.1
Min ; Max	0.36 ; 36.46	0.31 ; 25.87	0.19 ; 28.57	0.19 ; 36.46

BMI= Body Mass Index, N= Number of subjects, SD= Standard Deviation
FPG= Fasting Plasma Glucose

EFFICACY RESULTS

After 56 weeks of treatment with liraglutide 3.0 mg, liraglutide 1.8 mg or placebo as add on to background diabetes treatment in conjunction with diet and exercise, the following was concluded:

Overall, liraglutide treatment resulted in statistically significant and clinically relevant improvements in almost all efficacy endpoints (primary as well as secondary) and for most endpoints, the treatment effect of liraglutide 3.0 mg was statistically significantly greater than that of liraglutide 1.8 mg, thus showing a consistent better effect with the higher dose compared to the lower dose.

Primary endpoints:

- Both liraglutide doses succeeded on all 3 confirmatory primary endpoints (change from baseline in fasting body weight, proportion of subjects losing ≥5% of baseline fasting body weight, proportion of subjects losing >10% of baseline fasting body weight) compared to placebo.
- For all 3 endpoints, the treatment effect of liraglutide 3.0 mg was statistically significantly greater than that of liraglutide 1.8 mg.
- Consistent results were observed with each of the 6 sensitivity analyses, confirming the robustness of the primary analysis.
- The treatment effect was independent of baseline BMI category.

Change from baseline in fasting body weight (%, kg):

- Fasting body weight was reduced in all 3 groups; observed mean weight loss was 5.9% (6.2 kg) for liraglutide 3.0 mg, 4.6% (4.8 kg) for liraglutide 1.8 mg and 2.0% (2.2 kg) for placebo.
- Both liraglutide doses reduced body weight statistically significantly more than placebo and liraglutide 3.0 mg was better than 1.8 mg. The estimated treatment differences were −3.97% (p<0.0001) for liraglutide 3.0 mg vs. placebo, −2.62% (p<0.0001) for liraglutide 1.8 mg vs. placebo, and −1.35% (p=0.0024) for liraglutide 3.0 mg vs. 1.8 mg. The corresponding values in kg were −4.11 kg (p<0.0001), −2.65 kg (p<0.0001), and −1.45 kg (p=0.0029).

Proportion of subjects losing ≥5% of baseline fasting body weight:

- Statistically significantly more subjects on liraglutide achieved a weight loss of ≥5% of baseline fasting body weight compared to placebo, and more on liraglutide 3.0 mg compared to 1.8 mg (49.9% for liraglutide 3.0 mg, 35.6% for liraglutide 1.8 mg, and 13.8% for placebo; odds ratios of 6.81 (p<0.0001) for liraglutide 3.0 mg/placebo, 3.69 (p<0.0001) for liraglutide 1.8 mg/placebo and 1.84, (p=0.0008) for liraglutide 3.0 mg/1.8 mg).

Proportion of subjects losing >10% of baseline fasting body weight:

- Statistically significantly more subjects on liraglutide achieved a weight loss of >10% of baseline fasting body weight compared to placebo, and more on liraglutide 3.0 mg than on 1.8 mg (23.4% for liraglutide 3.0 mg, 14.4% for liraglutide 1.8 mg, and 4.3% for placebo; odds ratios of 7.10 (p<0.0001) for liraglutide 3.0 mg/placebo, 3.84 (p= 0.0008) for liraglutide 1.8 mg/placebo, and 1.85, (p =0.0099) for liraglutide 3.0 mg/1.8 mg).

Secondary weight-related efficacy endpoints (waist circumference, BMI, excess body weight)

- Consistent with its effects on body weight reduction, liraglutide treatment also statistically significantly reduced waist circumference, BMI, and excess body weight compared to placebo. The treatment effect was greater with liraglutide 3.0 mg compared to 1.8 mg.

Secondary efficacy endpoints related to glycaemic control:

- Compared to placebo, both liraglutide doses statistically significantly improved HbA_{1c}, proportion of subjects achieving target HbA_{1c}<7% and ≤6.5%, fasting and postprandial glycaemia, as well as fasting glucagon, fasting pro-insulin, pro-insulin to insulin ratio, and HOMA-B (a measure of beta-cell function), and reduced the concomitant use of OADs. For most of these endpoints, liraglutide 3.0 mg was statistically significantly better than 1.8 mg, and only liraglutide 3.0 mg reduced HOMA-IR (a measure of hepatic insulin resistance). Liraglutide treatment had no effect on fasting insulin and C-peptide concentrations.
  - HbA_{1c} was reduced by −1.32%-point with liraglutide 3.0 mg, −1.13%-point with liraglutide 1.8 mg, and −0.38%-points with placebo (estimated change from baseline to week 56), resulting in treatment differences in change from baseline of −0.93% (p<0.0001) for liraglutide 3.0 mg vs. placebo, −0.74% (p<0.0001) for liraglutide 1.8 mg vs. placebo, and −0.19% (p=0.0125) for liraglutide 3.0 mg vs. 1.8 mg.
  - The proportion of subjects achieving HbA_{1c} <7% after 56 weeks of treatment was 69.2% for liraglutide 3.0 mg, 66.7% for liraglutide 1.8 mg, and 27.2% for placebo, with odds ratios for the HbA_{1c}<7% target of 8.79 (p<0.0001) for liraglutide 3.0 mg/placebo, and 7.71 (p<0.0001) for liraglutide 1.8 mg/placebo, but no difference between liraglutide 3.0 mg and 1.8 mg.
  - The proportion of subjects achieving HbA_{1c} ≤6.5% after 56 weeks of treatment was 56.5% for liraglutide 3.0 mg, 45.6% for liraglutide 1.8 mg, and /15.0% for placebo, with odds ratios for the HbA_{1c} ≤ 6.5% target of 9.61 (p<0.0001) for liraglutide 3.0 mg/placebo, and 5.98 (p<0.0001) for liraglutide 1.8 mg/placebo, and 1.61 (p=0.0142) for liraglutide 3.0 mg/1.8 mg.
  - FPG decreased by −1.89 mmol/L with liraglutide 3.0 mg and −1.40 mmol/L with liraglutide 1.8 mg, but was unchanged in the placebo group (estimated change from baseline to week 56), resulting in treatment difference in

change from baseline of −1.77 mmol/L (p<0.0001) for liraglutide 3.0 mg vs. placebo, −1.28 mmol/L (p<0.0001) for liraglutide 1.8 mg vs. placebo, and −0.49 mmol/L (p=0.0061) for liraglutide 3.0 mg vs. 1.8 mg.
- Prandial plasma glucose increment was reduced by −0.85 mmol/L with liraglutide 3.0 mg, −0.74 mmol/L with liraglutide 1.8 mg, and −0.30 mmol/L with placebo (estimated difference from baseline at week 56), resulting in treatment difference of −0.55 mmol/L (p=0.0003) for liraglutide 3.0 mg vs. placebo, −0.44 mmol/L (p=0.0088) for liraglutide 1.8 mg vs. placebo, and −0.11 mmol/L (p=0.4536) for liraglutide 3.0 mg vs. 1.8 mg.
- Liraglutide treatment resulted in statistically significantly lower use of OADs compared to placebo, and the OAD use was lower with liraglutide 3.0 mg compared to 1.8 mg, as seen by fewer subjects in the liraglutide groups increased their OADs use (5.1%, 9.3%, 27.0% for liraglutide 3.0 mg, 1.8 mg, and placebo, respectively), and more subjects in the liraglutide groups decreased their OADs use (13.1%, 8.3%, 5.7% respectively), compared to placebo.

Secondary efficacy endpoints related to cardiovascular risk:

- Liraglutide treatment reduced SBP from baseline to week 56 (estimated treatment differences vs. placebo: −2.59 mmHg, and −2.68 mmHg, respectively). No difference in SBP was found between liraglutide 3.0 mg and 1.8 mg. No treatment differences were observed for DBP.
- Liraglutide 3.0 mg treatment was associated with statistically significant reductions in total cholesterol (4%), VLDL-cholesterol (13%), and triglycerides (14%), and an increase in HDL-cholesterol (3%) at week 56, compared to placebo. No differences were observed between liraglutide 1.8 mg and placebo in any lipid parameters.
- Both liraglutide doses reduced hsCRP (25%−27%), while only liraglutide 3.0 mg reduced PAI-1 (24%) and urinary albumin to creatinine ratio (20%), compared to placebo. A slight increase (5%) in fibrinogen was seen with liraglutide 3.0 mg compared to placebo, with a similar trend for liraglutide 1.8 mg.

Secondary efficacy endpoints related to patient reported outcomes:

- For IWQoL-Lite, liraglutide 3.0 mg treatment resulted in a higher (better) total score (estimated treatment difference: 2.75, p=0.0136), and higher score in 'physical function' (estimated treatment difference 4.92, p=0.0006) at week 56 compared with placebo. No differences were observed between liraglutide 1.8 mg and placebo in any IWQoL-Lite domains.
- For DTSQ, liraglutide 3.0 mg treatment was associated with a higher total score (estimated treatment difference: 1.44, p=0.0066) compared with placebo. No difference was observed between liraglutide 1.8 mg and placebo.

SAFETY RESULTS

After 56 weeks of treatment with liraglutide 3.0 mg, liraglutide 1.8 mg or placebo as add on to background diabetes treatment in conjunction with diet and exercise, the following was concluded:

Overall treatment with liraglutide 3.0 mg and liraglutide 1.8 mg was well-tolerated by overweight or obese subjects with type 2 diabetes. The overall AE and tolerability profile observed in this trial was consistent with previous findings with liraglutide 1.8 mg in subjects with type 2 diabetes and apart from GI events no dose relation was evident for safety.

The safety conclusions for each of the investigated areas are summarised below:

Overall adverse event profile:

- One CV death was reported during the follow-up period, [redacted] days after the subject had completed treatment with liraglutide 1.8 mg.
- The proportion of subjects reporting AEs and the rate of AEs was higher with liraglutide than with placebo (3.0 mg: 92.9%, 981 event per 100 PYE; 1.8 mg: 90.5%, 876 events per 100 PYE; placebo: 85.8%, 578 events per 100 PYE). The treatment difference was mainly driven by GI events reported by a higher proportion of subjects and at higher rates with liraglutide than with placebo and more so with liraglutide 3.0 mg than with 1.8 mg (3.0 mg: 65.2%, 224 events per 100 PYE; 1.8 mg: 56.2%, 148 events per 100 PYE; placebo: 39.2%, 83 events per 100 PYE). Most GI events were transient, and occurred within the first 4–8 weeks of treatment.
- The most frequent AEs (reported by ≥5% of subjects) with liraglutide were reported within the SOCs of GI disorders (e.g. nausea, diarrhoea, constipation, and vomiting) and metabolism and nutritional disorders (e.g. hypoglycaemia).
- The proportion of subjects with SAEs was higher with liraglutide than with placebo whereas the rate of SAEs was similar across treatments (3.0 mg: 8.8%, 13 events per 100 PYE; 1.8 mg: 8.6%, 12 events per 100 PYE; placebo: 6.1%, 11 events per 100 PYE). Generally the events occurred as single events in single subjects with no evident clustering.

- AE withdrawal was more frequent with liraglutide 3.0 mg (9.2%) and 1.8 mg (8.5%) than with placebo (3.3%). The most common AEs leading to withdrawals with liraglutide were GI AEs.
- Hypoglycaemic episodes were more frequently reported with liraglutide than with placebo. For ADA documented symptomatic hypoglycaemic episodes, the proportion of subjects with episodes and rates were 23.0% / 87 events per 100 PYE for liraglutide 3.0 mg, 22.4% / 95 events per 100 PYE for liraglutide 1.8 mg compared to 12.7% / 31 events per 100 PYE for placebo. A total of 8 severe treatment emergent hypoglycaemic episodes were reported, 5 events by 3 subjects (0.7%) with liraglutide 3.0 mg, and 3 events were reported by 2 subjects (1.0%) with liraglutide 1.8 mg; all subjects were taking SU as background diabetes medication. All events were non-serious and all subjects recovered. No dose relation for hypoglycaemic events was evident for liraglutide.

Medical events of special interest:

- The proportion of subjects with EAC confirmed treatment-emergent CV events and event rates were similar for liraglutide and placebo (3.0 mg: 1.2%, 2 events per 100 PYE; 1.8 mg: 1.9%, 3 events per 100 PYE; placebo: 1.9%, 3 events per 100 PYE). Eight (8) treatment-emergent MACE were confirmed by the EAC and the rates were low and similar with liraglutide and placebo (3.0 mg: 0.5%, 1 event per 100 PYE; 1.8 mg: 1.4%, 2 events per 100 PYE; placebo: 1.4%, 2 events per 100 PYE).
- More subjects on liraglutide reported AEs related to cardiac arrhythmia compared to placebo (3.0 mg: 3.8%; 1.8 mg: 4.8%; placebo: 1.4%), primarily driven by more non-serious mild events of tachycardia in the liraglutide groups. No difference between liraglutide doses was evident.
- There were no reported events of pancreatitis.
- Serum amylase activity remained relatively stable during treatment with liraglutide, except for a small increase in serum amylase during the first 4 weeks of treatment compared to placebo. There was, however, no difference in the proportions or rates for AEs of 'amylase increased' between liraglutide (3.0 or 1.8 mg) and placebo treated subjects.
- Serum lipase activity increased during liraglutide treatment compared with placebo, primarily during the first 4 weeks of treatment, but returned to baseline levels after treatment stop. No difference between the two doses of liraglutide was seen. The proportion of subjects reporting AEs of 'lipase increased' as well as the rates were higher in the liraglutide groups compared with placebo group (15, 14, and 9 events per 100 PYE for liraglutide 3.0 mg, 1.8 mg, and placebo, respectively).
- More events of gallbladder related diseases (primarily cholecystitis and cholecystitis acute) were reported with liraglutide compared to placebo, but the incidence was low in all 3 treatment groups (2, 2, and 1 events per 100 PYE for liraglutide 3.0 mg, 1.8 mg, and placebo, respectively).
- The rate of EAC confirmed neoplasm events was similar between liraglutide and placebo (3.0 mg: 4 events per 100 PYE; 1.8 mg: 2 events per 100 PYE; placebo: 4 events per 100 PYE). The rate of malignant neoplasms was similar between liraglutide and placebo (3.0 mg: 1 event per 100 PYE; 1.8 mg: no events; placebo: 2 events per 100 PYE).
- No differences in proportion or rate of thyroid disease events were seen with liraglutide treatment as compared to placebo (3.0 mg: 2.6% subjects, 3 events per 100 PYE; 1.8 mg: 3.3% subjects, 4 events per 100 PYE; placebo: 4.7% subjects, 6 events per 100 PYE subjects). Two treatment-emergent events of thyroid disease requiring thyroidectomy were confirmed by the EAC. One subject in the placebo group was found to have medullary thyroid carcinoma. Another subject in the liraglutide 3.0 mg group was found to have a benign follicular adenoma and malignant micropapillary carcinoma.
- No increase of mean calcitonin level was seen with liraglutide in this trial and there was no indication of any increased occurrence of reported events of 'increased calcitonin' with liraglutide treatment compared to placebo.
- Very few events (5 events in 4 subjects [0.9%] with liraglutide 3.0 mg, and 2 events in 2 subjects [1.0%] with liraglutide 1.8 mg) were identified by the predefined MedDRA search for 'acute renal failure' and the identified events were primarily 'blood creatinine increased'. One non-serious, mild event of preferred term 'renal failure' was reported by a [redacted] in the liraglutide 3.0 mg group. [redacted] and the investigator rated the event as unlikely related to trial product.
- More subjects in liraglutide 1.8 mg group reported allergic reactions compared to liraglutide 3.0 mg and placebo group (3.0 mg: 0.7% subjects, 1 event per 100 PYE; 1.8 mg: 4.3% subjects, 8 events per 100 PYE; placebo: 2.4% subjects, 5 events per 100 PYE subjects). This was primarily driven by a few subjects in the liraglutide 1.8 mg group with repeated asthma and urticaria events.
- No events of immune complex diseases were seen in this trial.

- Similar proportions of subjects reported AEs of injection site reactions with liraglutide (3.0 mg: 9.2% subjects; 1.8 mg: 8.1% subjects) compared to placebo (8.5% subjects). The rate of injection site reaction was higher in the liraglutide 3.0 mg group (25 events per 100 PYE) compared with the liraglutide 1.8 mg group (12 events per 100 PYE) and the placebo group (11 events per 100 PYE) primarily driven by 1 subject with a large number ([redacted] events) of injection site haemorrhage.
- The proportion of subjects reporting AEs of psychiatric disorders and the rate of psychiatric disorders were higher in the 2 liraglutide groups (3.0 mg: 11.4%, 14 events per 100 PYE; 1.8 mg: 11.9%, 15 events per 100 PYE) compared with the placebo group (6.1%, 8 events per 100 PYE). This was primarily driven by more subjects reporting non-serious events of insomnia (11 events in 11 subjects [2.6%] with liraglutide 3.0 mg, 8 events in 8 subjects [3.8%] with liraglutide 1.8 mg, and 2 events in 2 subjects [0.9%] with placebo) and depression (6 events in 6 subjects [1.4%] with liraglutide 3.0 mg, 6 events in 6 subjects [2.9%] with liraglutide 1.8 mg, and 2 events in 2 subjects [0.9%] with placebo) with liraglutide compared to placebo.
- No important differences were seen between treatment groups in the outcome of the mental health questionnaires. During the treatment period, the mean PHQ-9 total scores decreased (improvement) in all groups with no clinically relevant difference between liraglutide (3.0 mg and 1.8 mg) and placebo. No suicidal behaviour was reported on the C-SSRS during the trial and no subjects attempted suicide.
- Discontinuation of liraglutide treatment did not result in withdrawal or rebound effects as assessed by the BES.

Clinical laboratory evaluation

- Liver enzymes (ALAT and ASAT) were improved in liraglutide groups compared to placebo. No other clinically relevant changes in biochemistry or haematology were observed.
- No clinically relevant liraglutide-specific antibody development was seen during the trial.

Pulse

- A mean increase in pulse was observed with both liraglutide 3.0 mg and liraglutide 1.8 mg with no difference between doses whereas a small decline was seen with placebo (estimated treatment differences vs. placebo of 3.40 beats/min and 3.70 beats/min after 56 weeks for liraglutide 3.0 mg and liraglutide 1.8 mg, respectively). The increase in pulse after 56 weeks of treatment with liraglutide 3.0 mg and liraglutide 1.8 mg was statistically significant compared to placebo but was reversed within 2 weeks upon trial drug cessation. No subjects withdrew from the trial due to pulse increase.

Physical examination, ECG and pregnancies

- No clinically relevant treatment differences in physical examination or ECG were observed.
- Two pregnancies occurred during the trial (3.0 mg: [redacted]; placebo: [redacted]).

CONCLUSIONS

After 56 weeks of treatment with liraglutide 3.0 mg, liraglutide 1.8 mg or placebo as add on to background diabetes treatment in conjunction with diet and exercise, the following was concluded:

- Fasting body weight was reduced by 5.9% (6.2 kg) for liraglutide 3.0 mg, 4.6% (4.8 kg) for liraglutide 1.8 mg and 2.0% (2.2 kg) for placebo; 49.9% of subjects on liraglutide 3.0 mg, 35.6% on liraglutide 1.8 mg, and 13.8% on placebo achieved a weight loss ≥5% target; 23.4% of subjects on liraglutide 3.0 mg, 14.4% on liraglutide 1.8 mg, and 4.3% on placebo achieved a weight loss > 10% target.
- Both liraglutide 3.0 mg and liraglutide 1.8 mg succeeded on all 3 confirmatory primary endpoints (% change in fasting body weight from baseline, proportion of subjects losing ≥ 5% of baseline fasting body weight, and proportion of subjects losing > 10% of baseline fasting body weight) and it was confirmed that liraglutide 3.0 mg and liraglutide 1.8 mg are superior to placebo in terms of reducing fasting body weight and body weight related parameters (BMI, waist circumference, and excess body weight) from baseline to week 56.
- Both liraglutide 3.0 mg and liraglutide 1.8 mg were superior to placebo on glycaemic control as measured by HbA_{1c}, proportions of subjects reaching HbA_{1c}<7% or ≤ 6.5%, FPG, 7-point SMPG. Liraglutide 3.0 mg was significantly better than liraglutide 1.8 mg in mean reduction of HbA_{1c}, proportion of subjects reaching HbA_{1c} ≤ 6.5%, and FPG after 56 weeks of treatment.
- Liraglutide 3.0 mg also demonstrated benefits on improvement of insulin sensitivity, reduced CV risk (SBP, hsCRP, PAI-1, CV biomarkers, urinary albumin to creatinine ratio, total cholesterol, VLDL, and triglyceride), and improved quality of life compared to placebo.

- Liraglutide treatment was generally safe and well-tolerated in overweight and obese individuals with type 2 diabetes.
- No difference between the 2 doses was noted in safety/tolerability, except for gastrointestinal adverse events. A mean increase in pulse was observed with liraglutide with no difference between the dosages of liraglutide 3.0 mg and 1.8 mg.
- Liraglutide 3.0 mg was superior to liraglutide 1.8 mg for all three primary body weight related endpoints, and showed improvements in secondary efficacy endpoints confirming the additional benefits associated with liraglutide 3.0 mg. No differences between the 2 doses were noted with regards to adverse events pattern and frequency apart from more GI events seen with liraglutide 3.0 mg, and no differences were noted for other safety related assessments including vital signs.
- The efficacy and safety results obtained in this trial confirm that the intended liraglutide 3.0 mg dose was the optimal clinical dose compared to 1.8 mg in weight management for overweight or obese subjects with type 2 diabetes.

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice and FDA 21 Code of Federal Regulations (CFR), parts 312, 50, and 56 were followed.