2 Synopsis

Trial Registration ID-number: NCT00696657	**EudraCT number:** 2007-003956-12

Title of Trial

Investigation of safety and efficacy of five doses of semaglutide (NNC 0113-0217) versus placebo and open-label liraglutide, as add on therapy, in subjects diagnosed with type 2 diabetes currently treated with metformin or controlled with diet and exercise.

A 12 week multi-centre, multi national, double-blind placebo-controlled, randomised, nine-armed parallel group dose finding trial.

Investigators

A total of 80 principal investigators in 14 countries. Prof. Dr. med. [redacted], [redacted], [redacted] was appointed as signatory investigator.

Trial Sites

A total of 80 centres in 14 countries were planned to participate: AT (8), BG (6), FI (6), FR (5), DE (7), HU (5), IN (4), IT (6), CS (3), ZA (3), ES (6), CH (4), TR (5) and GB (12). Of the 80 centres, 74 were approved by an independent ethics committee, 67 actively screened subjects and 63 enrolled subjects.

Publications

Not applicable

Trial Period	**Development Phase**
3 June 2008 – 5 February 2009	2

Objectives

Primary Objective:

- To assess and compare the dose-response of five doses (6 treatment arms) of semaglutide versus placebo on glycaemic control in the treatment of type 2 diabetes as assessed by change from baseline to end of treatment in HbA_{1c}

Secondary Objectives:

- To assess and compare the effect on change from baseline to end of treatment in HbA1c of five dose levels (6 treatment arms) of semaglutide versus 2 doses of open label liraglutide
- To assess and compare the effect on additional glycaemic control parameters (homeostasis model assessment (HOMA), FPG, insulin, C-peptide, insulin/pro-insulin ratio, and glucagon)
- To assess and compare the effect on change from baseline to end of treatment in body weight
- To assess and compare the effect on change from baseline to end of treatment in waist and hip circumference
- To assess and compare lipid profiles: total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), high density lipoprotein cholesterol (HDL-C) and triglyceride (TG)
- To assess and compare the subjective feelings of appetite following a standard meal
- To assess and compare postprandial plasma glucose, insulin and C-peptide levels
- To assess and compare rates of gastric emptying as assessed by paracetamol kinetics

Safety Objectives

- To assess the safety and tolerability of multiple doses of semaglutide in subjects with type 2 diabetes
- To assess the tolerability of higher doses (0.8 and 1.6 mg) using weekly dose titration to mitigate nausea and heartburn.
- To evaluate the effect of titration versus no titration for the 0.8 mg semaglutide treatment arms
- To assess formation of semaglutide antibodies
- To assess and compare incidences of hypoglycaemic episodes

Methodology

This was a 12-week multi-centre, multi national, double-blind (semaglutide), placebo-controlled, open-label (liraglutide) randomised, stratified, parallel group, dose response trial.

Subjects with type 2 diabetes were randomised in a 1:1:1:1:1:1:1:1:1 manner to one of the following treatment arms:

- semaglutide 0.1 mg (sema 0.1 mg) once weekly
- semaglutide 0.2 mg (sema 0.2 mg) once weekly
- semaglutide 0.4 mg (sema 0.4 mg) once weekly
- semaglutide 0.8 mg (sema 0.8 mg) once weekly
- semaglutide 0.8 mg with titration (sema 0.8 mg T) once weekly
- semaglutide and 1.6 mg with titration (sema 1.6 mg T) once weekly
- semaglutide placebo (placebo) once weekly
- open-label liraglutide 1.2 mg (lira 1.2 mg) once daily
- open-label liraglutide 1.8 mg (lira 1.8 mg) once daily

For all treatment groups trial product was given in adjunct to previous metformin therapy on a stable dose (minimum 1.5 g daily) or as monotherapy in case the diabetes was controlled by diet and exercise alone. Dose reduction or increase of metformin was not allowed. If subjects could not tolerate the assigned semaglutide, they were withdrawn.

Subject randomised to 0.1 mg, 0.2 mg, 0.4 mg or 0.8 mg semaglutide/placebo administered the trial product once a week throughout the 12-week treatment period. Subjects randomised to 0.8 mg semaglutide with titration received 0.4 mg semaglutide the first week (one dose), followed by 11 weeks of treatment with 0.8 mg semaglutide administered once a week. Similarly, subjects randomised to 1.6 mg semaglutide with titration received one week of treatment with 0.4 mg semaglutide (one dose), then one week of treatment with 0.8 mg semaglutide (one dose), followed by 10 weeks of treatment with 1.6 mg semaglutide once a week. Subjects randomised to open-label liraglutide were titrated to final dose (1.2 mg or 1.8 mg, respectively) in weekly increments of 0.6 mg (i.e., 0.6, 1.2 and 1.8 mg).

The 12-week treatment period was followed by a 5-week follow-up period and a follow-up visit (Visit 9). Thus, the maximum duration of the trial including visit windows, from screening to follow-up was 19 weeks.

Meal Tests

A meal test was performed in order to evaluate postprandial glucose excursions and insulin secretion. In addition, the effect of semaglutide and liraglutide on gastric emptying was evaluated by assessment of paracetamol absorption and sensations of appetite, nausea, thirst and well being assessed using a visual analogue scale (VAS). Meal tests (standardised breakfast meals) were performed at Visits 2 and 8.

Number of Subjects Planned and Analysed

A total of 517 subjects were planned to be screened in order to be able to randomise 362 subjects and reach the planned 290 completers in the trial. A screening failure rate of 30% and a drop-out rate of 20% were anticipated. Actual screening failure rate was 42% (296/711) and the drop-out rate was 22.7%. A total of 415 subjects were randomised. Four subjects were randomised but not exposed to treatment. These subjects were not included in any of the analysis sets. Two subjects were randomised to semaglutide 0.8 mg but mistakenly titrated, so actual treatment was semaglutide 0.8 mg T. Two subjects were randomised to semaglutide 0.8 mg T but were mistakenly titrated to 1.6 mg T (actual treatment). The subject disposition (including analysis sets) was as follow where actual treatment is presented for the safety analysis set only:

	Placebo N (%)	Sema 0.1 mg N (%)	Sema 0.2 mg N (%)	Sema 0.4 mg N (%)	Sema 0.8 mg N (%)
Screened					
Screening Failures					
Non-fulfillment of inclusion/exclusion criteria					
Other reason					
Randomised	46 (100.0)	47 (100.0)	44 (100.0)	49 (100.0)	44 (100.0)
Exposed	46 (100.0)	47 (100.0)	43 (97.7)	48 (98.0)	44 (100.0)
Withdrawals	1 (2.2)	5 (10.6)	8 (18.2)	11 (22.4)	10 (22.7)
Adverse event	0 (0.0)	0 (0.0)	3 (6.8)	7 (14.3)	6 (13.6)
Non-compliance with protocol	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ineffective therapy	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal criteria	1 (2.2)	3 (6.4)	2 (4.5)	2 (4.1)	0 (0.0)
Other	0 (0.0)	1 (2.1)	3 (6.8)	2 (4.1)	4 (9.1)
Completed	45 (97.8)	42 (89.4)	36 (81.8)	38 (77.6)	34 (77.3)
Safety Analysis Set #	46 (100.0)	47 (100.0)	43 (97.7)	48 (98.0)	42 (95.5)
Full Analysis Set	46 (100.0)	47 (100.0)	43 (97.7)	48 (98.0)	44 (100.0)
PP Analysis Set	42 (91.3)	37 (78.7)	32 (72.7)	33 (67.3)	31 (70.5)
Meal Test PP Analysis Set	31 (67.4)	35 (74.5)	28 (63.6)	33 (67.3)	29 (65.9)

	Sema 0.8 mg T N (%)	Sema 1.6 mg T N (%)	Lira 1.2 mg N (%)	Lira 1.8 mg N (%)	Total N (%)
Screened					711
Screening Failures					296
Non-fulfillment of inclusion/exclusion criteria					276
Other reason					20
Randomised	45 (100.0)	45 (100.0)	45 (100.0)	50 (100.0)	415 (100.0)
Exposed	43 (95.6)	45 (100.0)	45 (100.0)	50 (100.0)	411 (99.0)
Withdrawals	12 (26.7)	15 (33.3)	3 (6.7)	9 (18.0)	74 (17.8)
Adverse event	9 (20.0)	14 (31.1)	2 (4.4)	5 (10.0)	46 (11.1)
Non-compliance with protocol	1 (2.2)	0 (0.0)	0 (0.0)	1 (2.0)	2 (0.5)
Ineffective therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Withdrawal criteria	0 (0.0)	1 (2.2)	1 (2.2)	2 (4.0)	12 (2.9)
Other	2 (4.4)	0 (0.0)	0 (0.0)	1 (2.0)	13 (3.1)
Completed	33 (73.3)	30 (66.7)	42 (93.3)	41 (82.0)	341 (82.2)
Safety Analysis Set #	43 (95.6)	47 (104.4)	45 (100.0)	50 (100.0)	411 (99.0)
Full Analysis Set	43 (95.6)	45 (100.0)	45 (100.0)	50 (100.0)	411 (99.0)
PP Analysis Set	30 (66.7)	27 (60.0)	39 (86.7)	39 (78.0)	310 (74.7)
Meal Test PP Analysis Set	27 (60.0)	23 (51.1)	33 (73.3)	37 (74.0)	276 (66.5)

Diagnosis and Main Criteria for Inclusion

Men and women-not-of-childbearing-potential (i.e., permanently sterilised or post-menopausal) who have been diagnosed with type 2 diabetes for at least three months and who had been treated with either diet and exercise alone or have been on stable doses of metformin (at least 1.5 g) for at least three months prior to trial, aged ≥ 18 years, HbA_{1c} 7.0–10.0 % (both inclusive), 60.0 kg < body weight <110.0 kg.

Key exclusion criteria:

- Treatment with insulin, GLP-1 receptor agonists (including liraglutide), dipeptidyl peptidase-4 inhibitors, sulphonylurea, thiazolidinediones or Alpha-GIs within the last three months prior to the trial
- Impaired liver (ALAT ≥ 2.5 times upper limit of normal) or renal function (serum-creatinine ≥ 135 µmol/L [≥ 1.53 mg/dL] for males and ≥ 120 µmol/L [≥ 1.23 mg/dL] for females)
- Proliferative retinopathy or maculopathy requiring acute treatment
- Clinically significant active cardiovascular disease (myocardial infarction within the last 6 months prior to trial, NYHA III-IV) and uncontrolled treated/untreated hypertension (systolic blood pressure [SBP] ≥ 160 mmHg, diastolic blood pressure [DBP] ≥ 100 mmHg)

Test Product, Dose and Mode of Administration, Batch Number

All trial products were supplied by Novo Nordisk A/S, Denmark:

- Semaglutide 1.0 mg/mL and 10 mg/mL solutions in 1.5 mL Penfill® cartridges (batch numbers VLDP002 and VLDP003) for once-weekly s.c. injection in the upper arm, abdomen or thigh with the NordiPen® pen-injector (batch number TSCY406). Once-weekly doses were 0.1 mg, 0.2 mg, 0.4 mg (semaglutide 1.0 mg/mL solution used), 0.8 mg or 1.6 mg semaglutide (semaglutide 10 mg/mL solution used)
- Semaglutide placebo solution in 1.5 mL Penfill® cartridges (batch number VLDP001) for once-weekly s.c. injection in the upper arm, abdomen or thigh with the NordiPen® pen-injector (batch number TSCY406). Once-weekly doses were 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg or 1.6 mg.

Duration of Treatment

A 12-week treatment period including a fixed 1 to 2-week dose escalation period for the two highest doses of semaglutide and corresponding placebo arms (0.8 mg T, 1.6 mg T) and for both doses of liraglutide (1.2 mg, 1.8 mg). Please refer to methodology section for details.

Reference Therapy, Dose and Mode of Administration, Batch Number

- Liraglutide (6.0 mg/mL pH 8.15) in 3 mL Flexpen® pen-injectors (batch number TP51313) to be injected once-daily in the upper arm, abdomen or thigh. Daily doses were 1.2 mg or 1.8 mg.

Criteria for Evaluation – Efficacy

- HbA_{1c}
- FPG
- additional fasting glycaemic control parameters:
  - insulin, C-peptide, glucagon, HOMA-B, HOMA-IR and pro-insulin to insulin ratio
  - postprandial beta-cell function: plasma glucose, insulin and C-peptide following a standardised breakfast meal, including C_{max}, t_{max}, area under the curve [$AUC_{0\text{-}240min}$] and incremental AUC of glucose [$iAUC_{0\text{-}240min,\ glucose}$]
- body weight
- waist and hip circumference
- fasting lipid profile (TC, LDL-C, VLDL-C, HDL-C and TG)
- sensations of appetite (hunger, fullness, satiety, prospective food consumption), thirst, well-being and nausea rated by visual analogue scales (VAS) following a standardised breakfast meal
- gastric emptying as measured by paracetamol concentrations ($AUC_{0\text{-}60min}$, $AUC_{0\text{-}240min}$, C_{max} and t_{max}) following a standardised breakfast meal

Criteria for Evaluation – Safety

- adverse events (AE)
- physical examination
- vital signs: SBP, DBP and pulse
- electrocardiogram (ECG)
- fundoscopy
- gastrointestinal adverse events (GIAEs) in the period from start of treatment until two weeks later
- hypoglycaemic episodes
- laboratory safety parameters: haematology, biochemistry, calcitonin, urinalysis and semaglutide antibodies

Statistical Methods

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 the trial products. The randomised treatment was applied regardless of the treatment actually received.

The per-protocol (PP) analysis set was used for analysis of the primary endpoint and included all randomised and exposed subjects who had signed informed consent before any trial-related activities, had no protocol deviations with potential impact on the primary efficacy assessment, did not meet any withdrawal criteria and had an evaluable HbA_{1c} observation at Visit 8 (end of randomised 12 week treatment period).

The meal test PP analysis set was used for analysis of the gastric emptying endpoints and included all randomised and exposed subjects who had signed informed consent before any trial-related activities, did not meet any withdrawal criteria, had eaten at least half of the meal at both Visits 2 and 8, had the Visit 8 meal test performed no later than 14 days after date of last drug dose for semaglutide/placebo treated subjects and had the Visit 8 meal test

performed no later than 1 day after date of last drug dose for the liraglutide treated subjects (checked after database release (DBR) and documented in post DBR minutes) and had taken the planned dose of paracetamol.

The safety analysis set included all randomised subjects who were exposed to at least one dose of trial product. Actual treatment was applied regardless of which treatment the subject was randomised to.

For the primary endpoint the FAS analysis was the primary analysis and the PP analysis the supportive whereas for the tests of equivalence and non-inferiority for the gastric emptying endpoints the FAS analysis and the meal test PP analysis were of equal importance.

Primary Endpoint

The primary endpoint was the change from baseline in HbA_{1c} after 12 weeks of treatment. The change in HbA_{1c} was analysed using a linear normal model (analysis of variance (ANOVA)) with treatment, country, pre-trial anti-diabetic treatment (diet and exercise or metformin) as fixed effects and baseline HbA_{1c} as a covariate. In this analysis, missing values of HbA_{1c} at Visit 8 were replaced using last observation carry forward (LOCF) of the last post-baseline measurement of HbA_{1c} (i.e., the Visit 7 value). The analysis was made for the FAS. A similar analysis was made for the PP analysis set (however, not using LOCF) as supportive evidence.

Superiority of the six semaglutide doses (0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg T and 1.6 mg T) versus placebo was tested. Based on the ANOVA model, the estimated treatment differences for each of the semaglutide dose groups compared to placebo were calculated with 2-sided 95% confidence intervals (CIs). In order to protect the overall type I error, simultaneous pair-wise comparisons were done using Dunnett's method.

The change from baseline in HbA_{1c} for semaglutide doses was compared to that of the 1.2 mg and 1.8 mg liraglutide dose groups, respectively, using the same model as for the primary endpoint. No formal hypotheses were tested for the comparison as the trial was not designed and powered for this. The pair-wise semaglutide–liraglutide comparisons were therefore not adjusted for multiple testing. Likewise, no hypothesis was tested for the pair-wise liraglutide–placebo comparisons and these were therefore not adjusted for multiple testing.

In an exploratory analysis the proportion of subjects achieving HbA_{1c} target (ADA target < 7% and AACE target ≤ 6.5%) was compared between treatments using a logistic regression model with treatment, country and pre-trial antidiabetic treatment (diet and exercise or metformin) as fixed effects and baseline HbA_{1c} as a covariate. Semaglutide–placebo comparisons were corrected for multiple testing using Dunnett's method whereas the semaglutide–liraglutide and liraglutide–placebo comparisons were not corrected for multiple testing.

Secondary Efficacy Endpoints

For FPG, additional glycaemic control parameters, change from baseline in body weight, sensations of appetite, thirst, well-being and nausea rated by VAS and postprandial plasma glucose, insulin and C-peptide, the aims of the analyses were to show superiority of the semaglutide doses versus placebo and to estimate the difference between the semaglutide and liraglutide doses and liraglutide doses versus placebo. The analyses were made for the FAS. Superiority was tested using the same approach as described for the primary endpoint and as no formal hypotheses were tested for the semaglutide–liraglutide and liraglutide–placebo comparisons for the secondary endpoints these were not corrected for multiple testing.

- FPG was analysed using the same model as for the primary endpoint but with baseline FPG as a covariate. LOCF was applied using the last post-baseline measurement of FPG
- Fasting insulin, fasting C-peptide, fasting glucagon, HOMA-B, HOMA-IR and fasting insulin to pro-insulin ratio were analysed using the same model as for the primary endpoint but with the Visit 2 value of the endpoint as a covariate. LOCF was applied using the last post-baseline measurement (i.e., the Visit 7 value)
- Change from baseline in body weight was analysed using the same model as for the primary endpoint but with baseline body weight as a covariate. LOCF was applied using the last post-baseline measurement of body weight
- Change from baseline in waist and hip circumference were summarised by descriptive statistics only.
- Fasting lipids were summarised by descriptive statistics only.
- Sensations of appetite (hunger, fullness, satiety and prospective food consumption), thirst, well-being and nausea rated by VAS: The pre-meal rating and the average post-meal rating at Visit 8 were analysed using the same

model as for the primary endpoint but with the Visit 2 value of the endpoint as a covariate.

- Postprandial plasma glucose, insulin and C-peptide:
  - $AUC_{0\text{-}240min}$ and C_{max} for glucose, insulin and C-peptide were log-transformed and analysed using the same model as for the primary endpoint but with and the Visit 2 value of the endpoint as a covariate. The results were back-transformed to the original scale and thus presented as the ratio and not the difference between treatments.
  - $iAUC_{0\text{-}240min}$ for glucose was analysed using the same model as for the primary endpoint but with the Visit 2 value of the endpoint as a covariate.
- Gastric emptying (assessed by paracetamol). The aims of the analyses were to investigate if semaglutide doses and placebo were equivalent with respect to gastric emptying and whether delay of gastric emptying was comparable between semaglutide doses and 1.2 and 1.8 mg liraglutide (non-inferiority if delay not more pronounced). The analyses were made for the FAS and meal test PP analysis set with equal importance with no adjustment for multiple testing. No adjustment for meal size at Visit 8 was made. $AUC_{0\text{-}60min,\ paracetamol}$ and $AUC_{0\text{-}240min,\ paracetamol}$ and $C_{max,\ paracetamol}$ at Visit 8 were log-transformed and analysed using an ANOVA model with treatment, pre-trial anti-diabetic treatment (diet and exercise or metformin) and country as fixed effects and the Visit 2 value of the endpoint as a covariate. The results were back-transformed to the original scale. The ratio between each semaglutide dose and placebo were presented with the corresponding 90% CI (for assessment of equivalence: equivalence declared if CI was fully contained within the limits [0.80, 1.25]) and the ratio between each semaglutide and liraglutide doses was presented with the corresponding 95% CI (for assessment of non-inferiority: non-inferiority declared if the lower limit of CI was above 0.8).

Safety Endpoints

The safety endpoints were compared between treatment groups using descriptive statistics.

No formal statistical hypothesis was tested except for SBP, DBP and pulse (exploratory) where the aims of the analyses were to show superiority of the semaglutide doses versus placebo and to estimate the difference between the semaglutide doses and the liraglutide doses. The analyses were made for the safety analysis set using LOCF of the last post-baseline measurement. The endpoints were analysed using an ANOVA model similar to the ANOVA model applied for the primary endpoint but with baseline value of the endpoint as a covariate.

As a substantial amount of calcitonin data were below the lower limit of quantification (LLOQ), this parameter was evaluated as a censored response. The exploratory analysis was conducted as a repeated measures model for normal censored data where the logarithm of calcitonin was the (censored) response. The model included treatment, sex and treatment by time interaction as fixed effects and subject was included as random effect.

Demography of Trial Population

	Placebo	**Semaglutide**						**Liraglutide**		**All**
		0.1 mg	**0.2 mg**	**0.4 mg**	**0.8 mg**	**0.8 mg T**	**1.6 mg T**	**1.2 mg**	**1.8 mg**	
Exposed, N (Safety Analysis Set)	46	47	43	48	44	43	45	45	50	411
Diet and exercise: Metformin	22:78	23:76	14:86	23:77	19:81	16:84	19:81	18:82	24:76	20:80
Female:Male, %	39:61	34:66	30:70	23:77	48:52	37:63	45:55	31:69	30:70	35:65
Ethnicity %										
• Hispanic/latino	13.0	4..3	9..3	12.5	9..5	7	4..3	8.9	2	7.8
• Not applicable	6..5	6.4	14.0	6..3	2.4	7	8.5	11.1	8	7.8
• Not hispanic/latino	78.3	83.0	74.4	75.0	81.0	81.4	72.3	75.6	84	78.3
• Unknown (*)	2.2	6.4	2..3	6..3	7.1	4.7	14.9	4.4	6	6.1
Race										
• Asian (Indian)	13.0	12.8	16.3	22.9	14.3	14	17	13.3	22	16.3
• Black/African American	0	2.1	4.7	2.1	0	0	2.1	4.4	2	1..9
• White	84.8	78.7	76.7	68.8	78.6	81.4	66	77.8	70	75.7
• Unknown (*)	2.2	6.4	2.3	6.3	7.1	4.7	14.9	4.4	6	6.1
Duration of diabetes (years)	2.4 (3.3)	3.6 (5.0)	2.3 (2.7)	2.0 (2.3)	3.0 (3.0)	2.6 (2.1)	1.8 (2.0)	3.3 (3.4)	2.5 (2.6)	2.6 (3.1)

Age (years)	55.3 (10.6)	55.2 (10.1)	54.7 (10.0)	53.8 (10.2)	55.0 (9.7)	55.9 (7.9)	56.4 (10.5)	54.8 (9.2)	54.3 (10.1)	55.0 (9.8)
HbA_{1c} (%)	8.1 (0.8)	8.2 (0.9)	8.2 (0.9)	8.1 (0.9)	8.2 (0.9)	8.0 (0.8)	8.0 (0.7)	8.0 (0.8)	8.1 (0.7)	8.1 (0.8)
FPG (mmol/L)	8.9 (1.5)	9.8 (2.7)	9.4 (2.5)	9.3 (2.1)	9.5 (2.4)	9.6 (2.1)	9.1 (1.9)	9.0 (2.3)	9.4 (2.0)	9.3 (2.2)
Weight (kg)	90.5 (13.0)	89.5 (14.2)	86.3 (15.1)	87.0 (14.0)	85.9 (15.1)	85.7 (12.6)	84.5 (14.0)	90.5 (13.5)	87.2 (13.1)	87.5 (13.8)
BMI (kg/m2)	31.7 (3.8)	31.5 (4.6)	30.4 (3.9)	29.7 (4.5)	30.7 (4.5)	31.2 (4.2)	30.9 (4.7)	31.0 (4.6)	30.9 (4.6)	30.9 (4.4)

Mean (SD). *: Race and Ethnicity not known for French subjects

Efficacy Results

Primary Endpoint HbA_{1c}

HbA_{1c} – Semaglutide versus Placebo

- A dose-dependent decrease in the estimated mean HbA_{1c} change from baseline (FAS, LOCF) was observed across the five semaglutide dose levels (six treatment arms):

Estimated Adjusted Means (%)	N	Estimate
Sema 1.6 mg T	41	-1.69
Sema 0.8 mg T	42	-1.44
Sema 0.8 mg	40	-1.46
Sema 0.4 mg	45	-1.10
Sema 0.2 mg	40	-0.90
Sema 0.1 mg	47	-0.58
Placebo	46	-0.50
Lira 1.8 mg	47	-1.34
Lira 1.2 mg	44	-1.18

- The reduction in HbA_{1c} at end of treatment (12 weeks, FAS, LOCF) was shown to be statistically significantly greater for all but the lowest semaglutide dose level (semaglutide 0.1 mg) compared to placebo:

Estimated Treatment Differences (%)	Estimate	95% CI	P-value	Superiority
Sema 1.6 mg T - Placebo	-1.19	[-1.58 ; -0.80]	<.0001	Yes
Sema 0.8 mg T - Placebo	-0.95	[-1.33 ; -0.57]	<.0001	Yes
Sema 0.8 mg - Placebo	-0.97	[-1.35 ; -0.59]	<.0001	Yes
Sema 0.4 mg - Placebo	-0.61	[-0.98 ; -0.23]	0.0002	Yes
Sema 0.2 mg - Placebo	-0.41	[-0.79 ; -0.02]	0.0324	Yes
Sema 0.1 mg - Placebo	-0.09	[-0.46 ; 0.28]	0.9772	No

HbA_{1c} – Semaglutide versus Liraglutide

- Treatment with 1.6 mg T semaglutide was superior to treatment with 1.2 mg and 1.8 mg liraglutide (estimates and CIs not corrected for multiple testing: -0.51 [-0.80;-0.22] and -0.35 [-0.64;-0.06], FAS), respectively:

Estimated Treatment Differences (%)	Estimate	95% CI
Sema 1.6 mg T - Lira 1.8 mg	-0.35	[-0.64 ; -0.06]
Sema 0.8 mg T - Lira 1.8 mg	-0.11	[-0.39 ; 0.18]
Sema 0.8 mg - Lira 1.8 mg	-0.13	[-0.42 ; 0.16]
Sema 0.4 mg - Lira 1.8 mg	0.24	[-0.05 ; 0.52]
Sema 0.2 mg - Lira 1.8 mg	0.44	[0.15 ; 0.73]
Sema 0.1 mg - Lira 1.8 mg	0.75	[0.48 ; 1.03]
Lira 1.8 mg - Placebo	-0.84	[-1.12 ; -0.56]
Sema 1.6 mg T - Lira 1.2 mg	-0.51	[-0.80 ; -0.22]
Sema 0.8 mg T - Lira 1.2 mg	-0.27	[-0.56 ; 0.02]
Sema 0.8 mg - Lira 1.2 mg	-0.29	[-0.58 ; 0.01]
Sema 0.4 mg - Lira 1.2 mg	0.08	[-0.22 ; 0.37]
Sema 0.2 mg - Lira 1.2 mg	0.28	[-0.02 ; 0.57]
Sema 0.1 mg - Lira 1.2 mg	0.59	[0.31 ; 0.88]
Lira 1.2 mg - Placebo	-0.68	[-0.97 ; -0.40]

Likelihood of Achieving HbA_{1c} Targets

- The proportion of subjects achieving ADA (< 7%) and AACE (≤ 6.5%) targets for HbA_{1c} increased with increasing semaglutide dose (Week 12, FAS, LOCF):

	Placebo	Semaglutide						Liraglutide	
		0.1 mg	0.2 mg	0.4 mg	0.8 mg	0.8 mg T	1.6 mg T	1.2 mg	1.8 mg
Mean baseline HbA_{1c} (%)	8.1	8.2	8.2	8.1	8.2	8.1	8.0	8.0	8.1
HbA_{1c} < 7% LOCF	7 (15.2)	13 (27.7)	18 (45.0)	25 (55.6)	29 (72.5)	29 (69.0)	33 (80.5)	26 (59.1)	27 (57.4)
HbA_{1c} ≤ 6.5% LOCF	2 (4.3)	6 (12.8)	11 (27.5)	9 (20.0)	20 (50.0)	19 (45.2)	26 (63.4)	15 (34.1)	17 (36.2)

N (%)

- The odds ratio for a subject to reach the ADA HbA_{1c} target of < 7% (FAS, LOCF) was statistically significantly higher for the semaglutide 0.2–1.6 mg T treatment groups compared to placebo (odds ratio, range: 6.21–43.02) but not semaglutide 0.1 mg compared to placebo (odds ratio: 2.4).
- The odds ratio for a subject to reach AACE target of ≤6.5% (FAS, LOCF) was statistically significantly higher for the semaglutide 0.8, 0.8 T and 1.6 T treatment groups as compared to placebo (odds ratios: 35.62, 25.86 and 73.26, respectively), but not semaglutide 0.1, 0.2 and 0.4 mg versus placebo (odds ratios: 3.34, 10.44 and 6.11).

Dose-response Model

- The glucose lowering effect of semaglutide (as assessed by reduction in HbA_{1c} from baseline. FAS, LOCF) increased with increasing dose; the maximal effect (E_{max}) was estimated to 1.25% from baseline (semaglutide 0.8–1.6 mg doses) while the semaglutide dose resulting in half of the maximal effect (ED50) was estimated to 0.41 mg.

Secondary Endpoint – Additional Glycaemic Control Parameters

Fasting Plasma Glucose

- A dose-dependent decrease in mean FPG (adjusted) at 12 week (FAS, LOCF) was observed across the five semaglutide dose levels (6 treatment arms):

Estimated Least Square Means (mmol/L)	N	Estimate
Sema 1.6 mg T	43	-2.56
Sema 0.8 mg T	42	-2.43
Sema 0.8 mg	38	-2.40
Sema 0.4 mg	48	-1.63
Sema 0.2 mg	42	-1.08
Sema 0.1 mg	47	-0.51
Placebo	46	-0.44
Lira 1.8 mg	49	-2.23
Lira 1.2 mg	45	-1.65

- The change in FPG at end of treatment (12 weeks, FAS, LOCF) was shown to be statistically significantly lower for the 0.4 mg to 1.6 mg T semaglutide dose levels (4 treatment arms) compared to placebo:

Estimated Treatment Diff. (mmol/L)	Estimate	95% CI	P-value	Superiority
Sema 1.6 mg T - Placebo	-2.12	[-3.03 ; -1.21]	<.0001	Yes
Sema 0.8 mg T - Placebo	-1.99	[-2.89 ; -1.09]	<.0001	Yes
Sema 0.8 mg - Placebo	-1.96	[-2.88 ; -1.04]	<.0001	Yes
Sema 0.4 mg - Placebo	-1.18	[-2.05 ; -0.31]	0.0025	Yes
Sema 0.2 mg - Placebo	-0.64	[-1.53 ; 0.26]	0.2639	No
Sema 0.1 mg - Placebo	-0.07	[-0.95 ; 0.81]	0.9998	No

- The proportion of subjects achieving ADA FPG target (5.0–7.2 mmol/L) increased with increasing semaglutide dose (Week 12, FAS, LOCF):

	Placebo	Semaglutide						Liraglutide	
		0.1 mg	0.2 mg	0.4 mg	0.8 mg	0.8 mg T	1.6 mg T	1.2 mg	1.8 mg
Baseline FPG: N (%)	6 (13.0)	9 (19.1)	8 (18.6)	7 (14.6)	4 (9.1)	4 (9.3)	5 (11.4)	7 (15.6)	7 (14.3)
Week 12 FPG: N (%) LOCF	8 (17.4)	12 (25.5)	11 (26.2)	21 (43.8)	25 (65.8)	30 (71.4)	32 (72.7)	26 (57.8)	27 (54.0)

Fasting Insulin

- Fasting insulin level at Week 12 (LOCF) was statistically significantly higher for the 0.2 mg, 0.4 mg, 0.8 mg T and 1.6 mg T semaglutide treatment groups compared to placebo:

Estimated Treatment Diff. (pmol/L)	Estimate	95% CI	P-value	Superiority
Sema 1.6 mg T - Placebo	32.68	[4.78 ; 60.58]	0.0154	Yes
Sema 0.8 mg T - Placebo	33.10	[5.79 ; 60.40]	0.0110	Yes
Sema 0.8 mg - Placebo	10.46	[-16.54 ; 37.46]	0.8260	No
Sema 0.4 mg - Placebo	31.76	[5.88 ; 57.65]	0.0090	Yes
Sema 0.2 mg - Placebo	32.36	[5.73 ; 58.98]	0.0108	Yes
Sema 0.1 mg - Placebo	19.31	[-6.46 ; 45.07]	0.2232	No

Fasting C-peptide

- Fasting C-peptide level at Week 12 (LOCF) was statistically significantly higher for the 0.8 mg T semaglutide treatment group compared to placebo:

Estimated Treatment Differences (nmol/L)	Estimate	95% CI	P-value	Superiority
Sema 1.6 mg T - Placebo	0.10	[-0.10 ; 0.30]	0.6462	No
Sema 0.8 mg T - Placebo	0.23	[0.03 ; 0.42]	0.0152	Yes
Sema 0.8 mg - Placebo	0.07	[-0.12 ; 0.26]	0.8588	No
Sema 0.4 mg - Placebo	0.14	[-0.05 ; 0.33]	0.2269	No
Sema 0.2 mg - Placebo	0.14	[-0.05 ; 0.33]	0.2182	No
Sema 0.1 mg - Placebo	0.01	[-0.18 ; 0.19]	1.0000	No

Fasting Glucagon

- Fasting glucagon at Week 12 (FAS, LOCF) was statistically significantly lower for the 1.6 mg T semaglutide treatment group compared to placebo:

Estimated Treatment Differences (ng/L)	Estimate	95% CI	P-value	Superiority
Sema 1.6 mg T - Placebo	-16.39	[-32.73 ; -0.05]	0.0488	Yes
Sema 0.8 mg T - Placebo	-14.14	[-30.12 ; 1.84]	0.1023	No
Sema 0.8 mg - Placebo	-13.41	[-29.63 ; 2.81]	0.1441	No
Sema 0.4 mg - Placebo	-8.01	[-23.85 ; 7.83]	0.6153	No
Sema 0.2 mg - Placebo	-3.63	[-19.85 ; 12.60]	0.9856	No
Sema 0.1 mg - Placebo	-3.28	[-18.80 ; 12.24]	0.9892	No

Homeostasis Model Assessment – HOMA-B and HOMA-IR

- The HOMA index of beta-cell function at Week 12 (LOCF) was statistically significantly higher for the 0.4 mg to 1.6 mg T semaglutide treatment groups compared to placebo:

Estimated Treatment Differences (%)	Estimate	95% CI	P-value	Superiority
Sema 1.6 mg T - Placebo	64.28	[28.47 ; 100.08]	<.0001	Yes
Sema 0.8 mg T - Placebo	54.36	[18.07 ; 90.65]	0.0009	Yes
Sema 0.8 mg - Placebo	53.01	[18.85 ; 87.17]	0.0006	Yes
Sema 0.4 mg - Placebo	42.50	[9.38 ; 75.62]	0.0052	Yes
Sema 0.2 mg - Placebo	27.68	[-5.98 ; 61.34]	0.1497	No
Sema 0.1 mg - Placebo	13.67	[-19.45 ; 46.79]	0.7888	No

- The HOMA index of insulin resistance at Week 12 (LOCF) was not statistically significantly different for any of the semaglutide treatment groups compared to placebo:

Estimated Treatment Differences (%)	Estimate	95% CI	P-value	Superiority
Sema 1.6 mg T - Placebo	0.02	[-1.61 ; 1.65]	1.0000	No
Sema 0.8 mg T - Placebo	0.52	[-1.14 ; 2.17]	0.9219	No
Sema 0.8 mg - Placebo	-0.57	[-2.13 ; 0.99]	0.8557	No
Sema 0.4 mg - Placebo	0.53	[-0.97 ; 2.04]	0.8705	No
Sema 0.2 mg - Placebo	1.13	[-0.40 ; 2.67]	0.2309	No
Sema 0.1 mg - Placebo	0.68	[-0.83 ; 2.20]	0.7111	No

Insulin/Pro-insulin Ratio

- Fasting insulin to pro-insulin ratio at Week 12 (FAS, LOCF) was statistically significantly higher for the 1.6 mg T semaglutide treatment group compared to placebo:

Estimated Treatment Differences (%)	Estimate	95% CI	P-value	Superiority
Sema 1.6 mg T - Placebo	8.50	[4.57 ; 12.43]	<.0001	Yes
Sema 0.8 mg T - Placebo	3.77	[-0.11 ; 7.64]	0.0594	No
Sema 0.8 mg - Placebo	2.74	[-0.92 ; 6.40]	0.2326	No
Sema 0.4 mg - Placebo	2.03	[-1.47 ; 5.52]	0.4919	No
Sema 0.2 mg - Placebo	1.96	[-1.61 ; 5.52]	0.5510	No
Sema 0.1 mg - Placebo	2.09	[-1.50 ; 5.68]	0.4876	No

Secondary Endpoints – Body Weight, Waist and Hip Circumference

- A dose-dependent decrease in the estimated mean body weight from baseline to end of treatment was observed across the five semaglutide dose levels (12 weeks, FAS, LOCF):

Estimated Least Square Means (kg)	N	Estimate
Sema 1.6 mg T	45	-4.82
Sema 0.8 mg T	43	-3.59
Sema 0.8 mg	41	-3.37
Sema 0.4 mg	48	-2.02
Sema 0.2 mg	43	-1.04
Sema 0.1 mg	47	-0.79
Placebo	46	-1.18
Lira 1.8 mg	50	-2.59
Lira 1.2 mg	45	-1.85

- The estimated mean reduction in body weight at end of treatment (12 weeks, FAS, LOCF) was statistically significant for the 0.8 and 1.6 mg T semaglutide dose levels (3 treatment arms) compared to placebo:

Estimated Treatment Differences (kg)	Estimate	95% CI	P-value	Superiority
Sema 1.6 mg T - Placebo	-3.64	[-4.97 ; -2.31]	<.0001	Yes
Sema 0.8 mg T - Placebo	-2.41	[-3.74 ; -1.08]	<.0001	Yes
Sema 0.8 mg - Placebo	-2.19	[-3.53 ; -0.85]	0.0002	Yes
Sema 0.4 mg - Placebo	-0.84	[-2.13 ; 0.45]	0.3443	No
Sema 0.2 mg - Placebo	0.14	[-1.18 ; 1.46]	0.9998	No
Sema 0.1 mg - Placebo	0.38	[-0.91 ; 1.68]	0.9380	No

- Hip circumference, from baseline to end of treatment at Week 12, was reduced by 1–4 cm across all 9 treatment groups.
- Waist circumference after 12 weeks of treatment was reduced by 2, 2, 2, 3, 4 and 4 cm respectively, from baseline to end of treatment in the semaglutide 0.1–1.6 mg T groups. In the liraglutide 1.2 and 1.8 mg groups, a reduction by 3 and 2 cm was observed while the reduction in the placebo group was 1 cm.

Secondary Endpoints – Fasting Lipids

- Mean baseline fasting lipid levels were close to recommended levels according to the ADA targets 2009: TC (4.93–5.27 mmol/L), HDL-C (1.03–1.23 mmol/L), LDL-C (2.61–3.04 mmol/L), TG (1.88–2.89 mmol/L), VLDL-C (0.82–1.17 mmol/L). Approximately 30% of all subjects received lipid-lowering medication at baseline.

- A dose-dependent decrease in the levels of TC and LDL-C from baseline to end of treatment (Week 12) was observed in the semaglutide 0.2–1.6 mg T treatment groups (TC: -0.17 mmol/L to -0.60 mmol/L and LDL-C:-0.18 to -0.49 mmol/L, FAS, no imputation).
- No clinically meaningful changes (FAS, no imputation) in HDL-C, VLDL-C and TG from baseline to end of treatment were seen in any of the 9 treatment groups.

Secondary Endpoints – Postprandial Glucose, Insulin, C-peptide, Gastric Emptying and Sensations of Appetite, Thirst, Well-being and Nausea

- Although identical meals were served at baseline and at end of treatment (approximately 520 g, or 2000 KJ, of which the majority was carbohydrate), there was a decrease in food consumption in the semaglutide and liraglutide groups at end of trial compared to baseline (FAS: up to 39.8 g less, corresponding to 203.5 kJ). This may confound interpretation of treatment effects on postprandial responses (glucose, insulin and C-peptide, gastric emptying and appetite sensations, thirst, well-being and nausea).

Postprandial Glucose

- Treatment with semaglutide (all treatment groups but the lowest 0.1 mg) was associated with a statistically significant and dose-dependent reduction of glucose $AUC_{0\text{-}240min}$ compared to placebo (FAS):

Estimated Treatment Ratio	Estimate	95% CI	P-value	Superiority
Sema 1.6 mg T / Placebo	0.65	[0.56 ; 0.74]	<.0001	Yes
Sema 0.8 mg T / Placebo	0.71	[0.63 ; 0.81]	<.0001	Yes
Sema 0.8 mg / Placebo	0.73	[0.65 ; 0.83]	<.0001	Yes
Sema 0.4 mg / Placebo	0.78	[0.69 ; 0.88]	<.0001	Yes
Sema 0.2 mg / Placebo	0.87	[0.77 ; 0.99]	0.0251	Yes
Sema 0.1 mg / Placebo	0.93	[0.83 ; 1.05]	0.4775	No

- A statistically significant reduction in C_{max} for postprandial glucose was found for all but the two lowest semaglutide doses compared to placebo (FAS):

Estimated Treatment Ratio	Estimate	95% CI	P-value	Superiority
Sema 1.6 mg T / Placebo	0.70	[0.62 ; 0.80]	<.0001	Yes
Sema 0.8 mg T / Placebo	0.76	[0.67 ; 0.86]	<.0001	Yes
Sema 0.8 mg / Placebo	0.78	[0.69 ; 0.88]	<.0001	Yes
Sema 0.4 mg / Placebo	0.84	[0.75 ; 0.94]	0.0010	Yes
Sema 0.2 mg / Placebo	0.91	[0.80 ; 1.02]	0.1510	No
Sema 0.1 mg / Placebo	0.96	[0.85 ; 1.07]	0.8167	No

- A statistically significant reduction in postprandial glucose $iAUC_{0\text{-}240min}$ was found for all but the two lowest semaglutide doses compared to placebo (FAS):

Estimated Treatment Differences (mmol/L*h)	Estimate	95% CI	P-value	Superiority
Sema 1.6 mg T - Placebo	-8.38	[-11.98 ; -4.77]	<.0001	Yes
Sema 0.8 mg T - Placebo	-5.92	[-9.27 ; -2.57]	<.0001	Yes
Sema 0.8 mg - Placebo	-5.55	[-8.84 ; -2.26]	0.0002	Yes
Sema 0.4 mg - Placebo	-4.66	[-7.86 ; -1.46]	0.0017	Yes
Sema 0.2 mg - Placebo	-3.10	[-6.39 ; 0.20]	0.0743	No
Sema 0.1 mg - Placebo	-2.65	[-5.70 ; 0.40]	0.1179	No

Postprandial Insulin

- Overall, there were no statistically significant difference in postprandial insulin $AUC_{0\text{-}240min}$ and C_{max} between semaglutide and placebo. A statistically significant increase in postprandial insulin $AUC_{0\text{-}240min}$ and C_{max} was found for semaglutide 0.8 mg T compared to placebo.

Postprandial C-peptide

- Overall, no statistically significant differences in postprandial C-peptide $AUC_{0\text{-}240min}$ and C_{max} were found between semaglutide doses and placebo. A statistically significantly increase in postprandial C-peptide $AUC_{0\text{-}240min}$ was

found for 0.8 mg T semaglutide compared to placebo and statistically significantly increases in postprandial C-peptide C_{max} were found for semaglutide 0.8 mg and 0.8 mg T compared to placebo.

Gastric Emptying as Assessed by Postprandial Paracetamol Concentrations

- Semaglutide (all doses) delayed the early (i.e. within the first hour) postprandial rate of gastric emptying compared to placebo ($AUC_{0\text{-}60min,\ paracetamol}$, $C_{max,\ paracetamol}$), but no overall effect (i.e., within the 4-hour duration of the meal) on gastric emptying was observed ($AUC_{0\text{-}240min,\ paracetamol}$).
- Compared to the liraglutide groups the effect on overall gastric emptying was not more pronounced with semaglutide ($AUC_{0\text{-}240min,\ paracetamol}$ $C_{max,\ paracetamol}$).

Sensation of Appetite, Thirst, Well-being and Nausea

- Overall, no statistically significant differences were shown for appetite sensations (hunger, fullness, satiety and prospective food consumption), thirst, well-being or nausea prior to or following a standard meal.

Safety Results

- Adverse Events (AEs)
  - A total of 74 subjects of 415 randomised subjects withdrew from the trial (17.8%) of which 45 withdrew due to TEAEs (61%). The proportion of AE withdrawals was 0.0% in the placebo group, 4.4% and 10.0% in the liraglutide 1.2 mg and 1.8 mg groups. The proportion of AE withdrawals increased dose-dependently up to 29.8% in the semaglutide treatment groups. Across all treatment groups, the majority of the AE withdrawals were caused by gastrointestinal disorders such as diarrhoea, nausea, vomiting (39 of 45 AE withdrawals [86.7%]). The majority of these GIAEs were of moderate/severe severity and assessed by the investigator to be possibly/probably related to trial product. The proportion of subjects withdrawing due to GIAEs increased with increasing semaglutide dose (range: 0.0–27.7%) and was 2.2% and 10.0% in liraglutide 1.2 and 1.8 mg groups.
  - A total of 10 TESAEs and 2 non-TESAEs were reported by 10 subjects, 8 of which were treated with semaglutide, one subject treated with liraglutide, and by one subject receiving placebo treatment. The reported TESAEs spanned several system organ classes. The most frequently reported events belonged to the system organ classes of cardiac disorders (4 events reported by 3 subjects) and vascular disorders (2 events reported by 2 subjects). No apparent dose- or time dependency was observed. All TESAEs in semaglutide treated subjects were judged by the investigator as being unlikely related to the trial product. There were no reports of pancreatitis or thyroid-related events in semaglutide treated subjects.
  - The proportion of subjects reporting TEAEs increased with increasing semaglutide dose group (range: 55.8–93.6%) and increasing liraglutide dose (55.6% and 62.0%). The proportion of subjects reporting TEAEs in the placebo group was 43.5%.
  - The most frequently reported TEAEs in the semaglutide and liraglutide groups were gastrointestinal disorders (nausea, vomiting, diarrhoea, dyspepsia and constipation). The frequency of gastrointestinal disorders increased with increasing semaglutide dose (range: 20.9–78.6%) as compared to liraglutide 1.2 mg and 1.8 mg groups (range: 30.0–33.3%) and placebo (10.9%). Most GIAEs occurred within the first two weeks after dosing and incidences of nausea and vomiting were transient in nature, both for semaglutide and liraglutide treatment groups.
  - The majority of TEAEs were mild or moderate in severity. The proportion of subjects with TEAEs assessed by the investigator to be possibly or probably related to trial products increased dose-dependently from 20.9–85.1% in the semaglutide 0.2–1.6 mg T treatment groups (29.8% in the semaglutide 0.1 mg group) and was 38% in the liraglutide treatment groups and 15.2% in the placebo group. The majority of these TEAEs were gastrointestinal disorders.
  - The proportion of subjects reporting severe TEAEs increased dose-dependently in the semaglutide groups

(range: 2.1%–17%) compared to the liraglutide 1.2 mg and 1.8 mg groups (2.2% and 4.0%) and placebo (0.0%). The most commonly reported severe TEAEs were gastrointestinal disorders, reported by 0.0%–12.8% across the semaglutide groups (dose-dependent increase), compared to 2.0–2.2% in the liraglutide groups.
  - Few cases of injection site and allergic reactions were observed, with no obvious differences between treatment groups.
  - Five (5) MESIs were reported by 5 subjects. One moderate MESI was considered to be probably related to trial product (accidental overdose).
- Titration
  - Compared to no titration, inclusion of a one-week treatment step with 0.4 mg semaglutide prior to escalating to 0.8 mg, markedly reduced the proportion of subjects reporting nausea and vomiting (nausea 59.5% versus 39.5%; vomiting 40.5% versus 30.2%).
  - Although the one-week titration step reduced the proportion of subjects reporting GIAE, no apparent effect on total or AE withdrawal was observed compared to the semaglutide 0.8 mg without titration (AE withdrawal in semaglutide 0.8 mg T group (20.9%, 9 subjects) compared to the semaglutide 0.8 mg without titration (14.3%, 6 subjects)).
- Laboratory Analyses
  - No clinically relevant differences from baseline to Week 12 or between the 9 treatment groups were observed for standard safety laboratory parameters.
  - Specifically, there were no differences between treatment groups (including placebo) with regard to calcitonin concentrations. Irrespective of treatment group, the vast majority (75.0–88.6%) of subjects remained within their baseline calcitonin concentration category (Category 1: 'below LLOQ', Category 2: 'between LLOQ and UNR', Category 3: 'between UNR and 2 times UNR' and Category 4: 'above 2 times UNR') and the proportion of subjects exhibiting an upward shift was similar between treatment groups and not different from placebo. No subject shifted from 'below UNR' to 'above 2 tiomes UNR'.
  - Lower limit of quantification of the calcitonin assay in this trial was 0.7 ng/L. Median baseline calcitonin concentration across treatment groups was 0.55 ng/L and the estimated means ranged from 0.58–0.82 ng/L at Week 12. Using repeated measures analysis to assess potential treatment related effects of semaglutide treatment on calcitonin concentrations compared to placebo or liraglutide no treatment-related effects were found.
- Vital signs and physical findings
  - Modest reduction (up to 6.22 mmHg, estimated mean) of systolic bood pressure from baseline to Week 12 was observed for all treatment groups including placebo (excluding 0.1 mg semaglutide) with no statistically significant differences between treatment groups. No consistent change in diastolic blood pressure was observed. A slight increase in pulse was observed for all treatment groups (up to 4.83 beats per minutes, estimated mean) including placebo. The increase was not statistically significantly different from placebo or between semaglutide and liraglutide treatment groups.
- Hypoglycaemic episodes
  - No major hypoglycaemic episodes were reported and only few subjects experienced a minor hypoglycaemic episode (confirmed plasma glucose < 3.1 mmol/L). The frequency of minor hypoglycaemia was comparable between treatment groups and no dose-dependent trends were observed (range across all 9 treatment arms: 0.0–4.4% corresponding to 0–0.205 episodes per subject year).
- Antibodies
  - A single subject in the semaglutide 1.6 mg T treatment group developed low titre anti-semaglutide antibodies, which did not cross-react with native GLP-1 and had no neutralising effect *in vitro*.
- Pregnancies
  - None

Conclusions

- The pharmacodynamic effects of semaglutide appear to be consistent with those of other GLP-1 receptor agonists.
- Once-weekly administration of semaglutide (0.2–1.6 mg) for 12 weeks, as add-on to stable regimens of either metformin monotherapy or diet and exercise alone, provides clinically meaningful improvement of glycaemic control (reduction in HbA_{1c}) and weight.
- Although not formally designed and powered for comparison with liraglutide, clinical efficacy of 0.4 mg of semaglutide in terms of glycaemic control and weight loss appears to be comparable to liraglutide 1.2 mg, whereas semaglutide doses of 0.8 and above brought more patients to HbA_{1c} target and provided greater weight loss than liraglutide 1.8 mg.
- No safety concerns associated with semaglutide treatment have been raised by this trial. However, a dose-dependent increase in nausea, vomiting and withdrawal due to GIAE was observed – which for doses of comparable efficacy appeared more pronounced for semaglutide than with liraglutide.
- Based on reduction of the number of subjects reporting GIAE in the 0.8 mg T compared to the 0.8 mg dose arm without the one week treatment step with semaglutide 0.4 mg, it may be anticipated that an even slower dose escalation regimen will lead to further improvement in GI tolerability of semaglutide.

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 29 by the WMA General Assembly, Washington 2002 and 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 01-Dec-2009.