

**Publication of the results of clinical trials
according to § 42b(1) AMG**

Name of Sponsor: **Novo Nordisk A/S**

Name of finished product: **Ozempic®**

Name of Active Ingredient: **Semaglutide**

To protect personal data names and other identifying details have been redacted.

CTR synopsis

NAME OF SPONSOR Novo Nordisk A/S, Novo Allé, DK-2880 Bagsvaerd, Denmark	
NAME OF ACTIVE SUBSTANCE Semaglutide	
Trial registration ID-number NCT02054897	UTN – U1111-1139-3090 IND number – 79,754 EudraCT number – 2013-000632-94 Japanese registration number – JapicCTI-142442
TITLE OF TRIAL SUSTAIN 1: Efficacy and safety of semaglutide once-weekly versus placebo in drug-naïve subjects with type 2 diabetes	
INVESTIGATORS One principal investigator was appointed at each of the 72 trial sites in the trial. The following investigator was designated signatory investigator for the trial, and was responsible for reviewing and approving the clinical trial report: [REDACTED], MD, Billings Clinic Research Ctr, 1045 North 30 th , Billings, Montana 59101, United States	
TRIAL SITE There were 72 sites in 8 countries that randomised subjects: Canada: 7 sites; Italy: 6 sites; Japan: 5 sites; Mexico: 2 sites; Russian Federation: 8 sites; South Africa: 8 sites; United Kingdom: 4 sites; United States: 32 sites.	
PUBLICATIONS No publications were available at the time of this clinical trial report synopsis.	
TRIAL PERIOD Initiation date: 03 February 2014 Completion date: 08 May 2015	DEVELOPMENT PHASE Phase 3a
DATA CUT-OFF DATE The results presented reflect the data available in the clinical database as of 22 June 2015.	
DATES OF THE REPORT CTR version 1.0: 22 February 2016 CTR version 2.0: 28 June 2016 CTR version 3.0: 05 July 2016	
OBJECTIVES Primary objective: To demonstrate superiority of once-weekly dosing of two dose levels of semaglutide versus placebo on glycaemic control after 30 weeks of treatment in drug-naïve subjects with T2D. Secondary objective: To compare the effects of once-weekly dosing of two dose levels of semaglutide versus placebo after 30 weeks of treatment on: – Inducing and maintaining weight loss – Other parameters of efficacy, safety and tolerability.	
METHODOLOGY This was a randomised, double-blind, parallel-group, placebo-controlled, multinational, multicentre, four-armed trial to evaluate the efficacy and safety of once-weekly semaglutide as monotherapy in adult subjects with T2D. Subjects were adult males and females diagnosed with T2D and treated with diet and exercise for at least 30 days before screening. The trial consisted of a 2-week screening period, a 30-week randomised treatment period and a 5-week follow-up period. After the screening visit, eligible subjects attended the randomisation visit and were randomised 2:2:1:1 to treatment with either 0.5 mg semaglutide, 1.0 mg semaglutide, 0.5 mg semaglutide placebo or 1.0 mg semaglutide placebo (hereafter referred to as placebo) once weekly for 30 weeks. After randomisation, subjects followed a fixed	

dose-escalation. The maintenance dose of 0.5 mg was reached after 4 doses (4 weeks) of 0.25 mg. The maintenance dose of 1.0 mg was reached after 4 doses (4 weeks) of 0.25 mg, followed by 4 doses (4 weeks) of 0.5 mg. After the maintenance dose was reached, the dose was not to be changed during the remaining period of the trial. If necessary for safety reasons suspected to be due to trial product, treatment could be discontinued and in such cases treatment should not be re-initiated, except in cases where suspicion of acute pancreatitis was ruled out. Treatment continued until visit 10 at the end of week 30. A follow-up visit taking place five weeks after the actual date of the last treatment visit was the last scheduled visit for each subject.

Novo Nordisk constituted an internal semaglutide safety committee performing ongoing safety surveillance on blinded safety data. The semaglutide safety committee was responsible for the overall safety surveillance of the trial. An external Data Monitoring Committee (DMC), established to independently review and evaluate un-blinded accumulating safety data from the ongoing semaglutide CV outcome trial (NN9535-3744), evaluated all major adverse cardiovascular events (MACEs) in the present trial. An independent external event adjudication committee (EAC) was constituted to perform ongoing adjudication, standardisation and assessment of selected events. The purpose of the adjudication was to consistently confirm events by independent external medical experts according to standardised criteria.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

A total of 650 subjects were planned for screening with 390 planned to be randomised. In total, 652 and 388 subjects were actually screened and randomised, respectively:

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Placebo N (%)	Total N (%)
Screened				652
Screening failures				264 (40)
Randomised	129 (100)	130 (100)	129 (100)	388 (100)
Exposed/FAS/SAS	128 (99)	130 (100)	129 (100)	387 (100)
Treatment completers[1]	111 (86)	114 (88)	115 (89)	340 (88)
Trial completers[2]	119 (92)	123 (95)	117 (91)	359 (93)
Premature treatment discontinuers	17 (13)	16 (12)	14 (11)	47 (12)
Other	5 (4)	7 (5)	9 (7)	21 (5)
Pregnancy			1 (1)	1 (0)
Protocol violation	4 (4)	2 (2)	1 (1)	7 (2)
Due to adverse event	8 (6)	7 (5)	3 (2)	18 (5)

Notes: [1] Subjects who completed treatment according to end-of-trial eCRF form. [2] Subjects with a follow-up visit.

Abbreviations: Sema: semaglutide, N: Number of subjects, %: Percentages of randomised subjects, FAS: Full Analysis Set, SAS: Safety Analysis Set.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Main inclusion criteria: Diagnosis of T2D and treatment with diet and exercise ≥ 30 days before screening, HbA_{1c} 7.0–10.0 % (53–86 mmol/mol) (both inclusive), for Japan only: male or female, age ≥ 20 years at the time of signing informed consent.

Main exclusion criteria: Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive method throughout the trial including the 5 week follow-up period, any chronic disorder or severe disease which, in the opinion of the investigator, might jeopardise subject's safety or compliance with the protocol, treatment with any glucose lowering agent(s) in a period of 90 days prior to screening (except short-term treatment with insulin in connection with inter-current illness), history of chronic or idiopathic acute pancreatitis, screening calcitonin ≥ 50 ng/L (pg/mL), personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, impaired renal function defined as estimated glomerular filtration rate < 30 mL/min/1.73 m², acute coronary or cerebrovascular event within 90 days before randomisation, heart failure (New York Heart Association class IV).

United Kingdom: Adequate contraceptive measures are defined as established use of oral, injected or implanted hormonal methods of contraception, placement of an intrauterine device or intrauterine system, barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository), male sterilisation (where partner is sole partner of subject), or true abstinence (when in line with preferred and usual lifestyle).

Main treatment discontinuation criteria: Safety concerns suspected to be related to the trial products or unacceptable intolerance to the treatment.

Withdrawal criterion: Subjects could electively withdraw from the trial at any time by withdrawal of informed

consent.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Semaglutide solution for injection, 1.34 mg/mL in a 1.5 mL pre-filled PDS290 pen-injector was administered in doses of 0.5 mg or 1.0 mg once-weekly by sub-cutaneous (s.c.) injections either in the thigh, abdomen or upper arm, at any time of day irrespective of meals. Semaglutide batch numbers (expiry date): CV40206 (19 August 2015) and DV40009 (10 April 2016).

DURATION OF TREATMENT

30 weeks.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Semaglutide placebo was supplied in a 1.5 mL pre-filled PDS290 pen-injector and administered by s.c. injection as semaglutide in doses of 0.5 mg or 1.0 mg. The composition of the placebo corresponded to that of semaglutide drug product but with absence of the active pharmaceutical ingredient. Placebo batch numbers (expiry date): CV40231 (29 July 2015) and DV40008 (13 February 2016).

CRITERIA FOR EVALUATION – EFFICACY

HbA_{1c}, body weight, fasting plasma glucose and systolic and diastolic blood pressure.

CRITERIA FOR EVALUATION – SAFETY

Treatment-emergent adverse events (AEs, incl. predefined medical events of special interest adjudicated by an independent external adjudication committee), hypoglycaemic episodes, pulse and laboratory safety variables.

STATISTICAL METHODS

Power calculation

The sample size calculation was based on the primary endpoint and the confirmatory secondary endpoint. It was pre-specified that the placebo groups were to be pooled, thereby assuming that there was no correlation between the change in outcome parameters after 30 weeks and the administered volume of placebo. Using a one-sided CI with a confidence level of 97.5% and assuming a true difference of 0.5% and a SD of 1.1% in change in HbA_{1c} after 30 weeks of treatment, a total of 103 subjects per group would give 90% power to conclude superiority for the primary endpoint when comparing two treatments. The same number of subjects and an assumed SD of 4 kg would give more than 99% power to detect a true difference of 2.5 kg in change in body weight at 30 weeks. To account for the expected rates of discontinuations from trial product or initiations of rescue medication, 129 subjects were to be randomised in each group. Thus, a total of 390 subjects were planned to be randomised accounting for the 2:2:1:1 randomisation and a total of 650 subjects were to be screened.

Definition of analysis sets

Both the Full Analysis Set (FAS) and the Safety Analysis Set (SAS) included all randomised subjects who had received at least one dose of randomised semaglutide or placebo but subjects in the FAS and SAS contributed to the evaluation based on their randomised and actual treatment, respectively.

Observation periods

In-trial: The time period after randomisation in which a subject was considered a trial participant and where data were collected systematically. This period was used for supportive analyses of both efficacy and safety.

On-treatment: The observation period where the subject was expected to be treated and exposed to trial product. This period was the primary observation period for examination of safety endpoints including adjudicated events, ECGs, and AEs including hypoglycaemic episodes.

On-treatment without rescue medication: Information that was collected after initiation of anti-diabetic rescue therapies was excluded from this observation period. Specifically, it included observations recorded at or after the date of first dose of trial product and not recorded after occurrence of the end-date of the on-treatment observation period or initiation of rescue medication. This period was the primary observation period for examination of efficacy endpoints.

Statistical analysis

Superiority for either change in HbA_{1c} or change in body weight was claimed if the upper limit of the 2-sided 95% CI for the estimated difference was below 0% or 0 kg, respectively. To preserve the overall type 1 error, the conclusion of superiority with treatment of each semaglutide dose versus placebo was evaluated hierarchically for the primary and

confirmatory secondary endpoints, testing the highest semaglutide dose first.

Primary endpoint

Change from baseline to week 30 in HbA_{1c}: The analysis was based on the FAS. The primary endpoint was analysed using a standard mixed model for repeated measurement (MMRM); all post-baseline HbA_{1c} measurements obtained at all planned visits before discontinuation from randomised treatment or before the initiation of rescue treatment were included as dependent variables. Treatment and country were included as fixed factors and baseline HbA_{1c} as covariate, all nested within visit. Furthermore, interaction in terms of visit by treatment, visit by country and visit by baseline HbA_{1c} were included. An unstructured covariance matrix for HbA_{1c} measurements within the same subject was employed. Missing data were treated with a missing at random (MAR) assumption.

To evaluate the robustness of the conclusions of the primary analyses and thus the potential impact of missing data, 4 pre-specified sensitivity analyses were performed for the primary endpoint and the confirmatory secondary endpoint using the FAS data set: An MMRM on complete cases, an LOCF analysis to benchmark against previous clinical trials in diabetes. For the approach based on the pattern mixture model (PMM), the effect of semaglutide was gradually removed by imputing missing data in the semaglutide groups, assuming that their response trajectories followed that of the placebo group. This analysis tested MAR assumption deviations that tend to disfavour semaglutide. Finally, an 'in-trial' MMRM analysis was used for all data collected post-randomisation regardless of whether subjects were on or off treatment or received rescue medication and was included to compare the estimated outcome of the primary estimand (de-jure effect) defined in this trial with an effectiveness (de-facto) outcome.

Confirmatory secondary endpoint

Change from baseline to week 30 in body weight: This endpoint was analysed in the same type of model as the primary endpoint but with baseline body weight as covariate.

Key supportive secondary efficacy endpoints

Change from baseline to week 30 in:

Fasting plasma glucose

Systolic and diastolic blood pressure

These endpoints were analysed using the same type of model as described for the primary endpoint but with the associated baseline value as a covariate.

Subjects who after 30 weeks treatment achieve (yes/no):

HbA_{1c} <7.0% (53 mmol/mol) American Diabetes Association target*

HbA_{1c} ≤6.5% (48 mmol/mol) American Association of Clinical Endocrinologists target*

These endpoints were analysed separately but in the same logistic regression model presenting odds ratio and 95% CI. The model included treatment and country as fixed factors and baseline HbA_{1c} as covariate. Missing response data at 30 weeks were imputed from the MMRM used for the primary analysis of HbA_{1c}.

Supportive secondary safety endpoints

All safety endpoints were summarised and analysed using the SAS.

Treatment-emergent AEs were summarised descriptively. Pre-defined groups of AEs of special interest were evaluated based on MedDRA searches (version 18.0). These groups were defined by Novo Nordisk A/S Global Safety and consisted of pre-specified preferred terms.

Episodes of hypoglycaemia episodes were classified according to the Novo Nordisk A/S and the ADA classification of hypoglycaemia. Treatment emergent episodes of hypoglycaemia were summarised descriptively and presented as the episode rate per 100 years of observation.

Pulse rate was analysed separately with the same type of methods as for the primary endpoint but with the pulse rate value at baseline as a covariate.

All laboratory assessments were summarised and evaluated by descriptive statistics using the SAS.

Importantly, for data presentation of all endpoints, the word significant is only used if supported by a statistical analysis.

DEMOGRAPHY OF TRIAL POPULATION

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	128	130	129	387
Sex				
Female	68 (53.1)	50 (38.5)	59 (45.7)	177 (45.7)
Male	60 (46.9)	80 (61.5)	70 (54.3)	210 (54.3)
Age (years)				
Mean (SD)	54.6 (11.1)	52.7 (11.9)	53.9 (11.0)	53.7 (11.3)
Body weight (kg)				
Mean (SD)	89.81 (22.96)	96.87 (25.59)	89.05 (22.16)	91.93 (23.83)
Body mass index (kg/m ²)				
Mean (SD)	32.46 (7.62)	33.92 (8.43)	32.40 (6.86)	32.93 (7.68)
Race				
White	83 (64.8)	88 (67.7)	78 (60.5)	249 (64.3)
Black or African American	11 (8.6)	11 (8.5)	9 (7.0)	31 (8.0)
Asian	26 (20.3)	25 (19.2)	32 (24.8)	83 (21.4)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.3)
Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	8 (6.3)	6 (4.6)	9 (7.0)	23 (5.9)
Smoker status				
Current smoker	28 (21.9)	28 (21.5)	27 (20.9)	83 (21.4)
Never smoked	71 (55.5)	74 (56.9)	77 (59.7)	222 (57.4)
Previous smoker	29 (22.7)	28 (21.5)	25 (19.4)	82 (21.2)
Renal function				
Normal	69 (53.9)	85 (65.4)	93 (72.1)	247 (63.8)
Mild Renal Impairment	53 (41.4)	39 (30.0)	29 (22.5)	121 (31.3)
Moderate Renal Impairment	6 (4.7)	6 (4.6)	7 (5.4)	19 (4.9)
Severe Renal Impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
End stage Renal Impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HbA _{1c} (%)				
N	128	130	129	387
Mean (SD)	8.09 (0.89)	8.12 (0.81)	7.95 (0.85)	8.05 (0.85)
Fasting plasma glucose (mmol/L)				
N	125	129	127	381
Mean (SD)	9.66 (2.77)	9.90 (2.50)	9.68 (2.77)	9.75 (2.67)
Duration of Diabetes (years)				
N	127	129	129	385
Mean (SD)	4.85 (6.11)	3.65 (4.89)	4.06 (5.48)	4.18 (5.52)
MDRD eGFR (mL/min/1.73 m ²)				
N	128	130	129	387
Mean (SD)	95.91 (26.23)	100.9 (27.74)	100.2 (24.97)	99.02 (26.37)

Abbreviations: N: Number of subjects, %: Percentage of subjects, BMI: Body mass index, MDRD: Modification of diet in renal disease, eGFR: estimated glomerular filtration rate, SD: standard deviation

SUMMARY CONCLUSIONS:

EFFICACY RESULTS

This trial reached its primary objective.

Primary endpoint – Change in HbA_{1c}

- Superiority of semaglutide treatment in reducing HbA_{1c} levels from baseline to week 30 was demonstrated with both doses when compared with placebo with ETDs of -1.43 %-points [-1.71; -1.15]_{95%CI} and -1.53 %-points [-1.81; -1.25]_{95%CI} with semaglutide 0.5 mg and 1.0 mg, respectively. A larger reduction in HbA_{1c} from baseline to week 30 was seen with semaglutide 0.5 mg (-1.45 %-points) and 1.0 mg (-1.55 %-points) when compared with placebo (-0.02 %-points).
- The robustness of the primary MMRM analysis was supported by 4 different sensitivity analyses that all confirmed significantly better glycaemic efficacy with semaglutide compared with placebo. The 4 sensitivity analyses showed similar ETDs ranging from -1.16 %-points [-1.43; -0.88]_{95%CI} to -1.36 %-points [-1.63; -1.09]_{95%CI} with semaglutide 0.5 mg and -1.34 %-points [-1.61; -1.07]_{95%CI} to -1.47 %-points [-1.74; -1.20]_{95%CI} with semaglutide 1.0 mg, supporting superior glycaemic efficacy.

Confirmatory secondary endpoint – Change in body weight

- Superiority of semaglutide treatment in reducing body weight from baseline to week 30 was demonstrated with both doses when compared with placebo with ETDs of -2.75 kg [-3.92; -1.58]_{95%CI} and -3.56 kg [-4.74; -2.38]_{95%CI} with semaglutide 0.5 mg and 1.0 mg, respectively. These numbers represent a weight loss in percent of -3.12 %-points [-4.37; -1.87]_{95%CI} and -3.94 %-points [-5.20; -2.68]_{95%CI} with semaglutide 0.5 mg and 1.0 mg, respectively. A larger reduction in body weight from baseline to week 30 was seen with semaglutide 0.5 mg (3.7 kg, 4.0%) and 1.0 mg (4.5 kg, 4.8%) when compared with placebo (1.0 kg, 0.9%).
- The robustness of the confirmatory MMRM analysis was supported by 4 different sensitivity analyses that all confirmed significantly larger weight loss with semaglutide compared with placebo. The 4 sensitivity analyses showed similar ETDs ranging from -2.48 kg [-3.58; -1.38]_{95%CI} to -2.69 kg [-3.77; -1.61]_{95%CI} with semaglutide 0.5 mg and -2.94 kg [-4.20; -1.68]_{95%CI} to -3.53 kg [-4.61; -2.44]_{95%CI} with semaglutide 1.0 mg, supporting superior weight loss.

Key supportive secondary endpoints

- The HbA_{1c} treatment targets were reached for more subjects with semaglutide 0.5 mg and 1.0 mg compared with placebo, and the odds for reaching all 3 targets were significantly higher with both doses of semaglutide when compared with placebo.
 - An HbA_{1c} level at or below 6.5% was obtained for more subjects with semaglutide 0.5 mg (59%) and 1.0 mg (60%) compared with placebo (13%) with an estimated odds ratio of 16.0 [7.82; 32.68]_{95%CI} and 18.3 [8.96; 37.54]_{95%CI} with semaglutide 0.5 mg and 1.0 mg, respectively.
 - An HbA_{1c} level below 7% was obtained for more subjects with semaglutide 0.5 mg (74%) and 1.0 mg (72%) compared with placebo (25%) with an estimated odds ratio of 16.9 [8.44; 33.89]_{95%CI} and 15.7 [8.00; 30.83]_{95%CI} with semaglutide 0.5 mg and 1.0 mg, respectively.
 - an HbA_{1c} level below 7% without severe or BG-confirmed symptomatic hypoglycaemia and without weight gain was obtained for more subjects with semaglutide 0.5 mg (66%) and 1.0 mg (65%) when compared with placebo (19%) with an estimated odds ratio of 12.7 [6.57; 24.52]_{95%CI} and 12.45 [6.46; 23.99]_{95%CI} with semaglutide 0.5 mg and 1.0 mg, respectively.
- The weight loss targets were reached for more subjects with semaglutide 0.5 mg and 1.0 mg compared with placebo, and the odds for reaching the targets were significantly higher with both doses of semaglutide when compared with placebo.
 - A weight loss of at least 5% was obtained for more subjects with semaglutide 0.5 mg (37%) and 1.0 mg (45%) compared with placebo (7%) with an estimated odds ratio of 7.9 [3.65; 17.04]_{95%CI} and 12.0 [5.53; 26.07]_{95%CI} with semaglutide 0.5 mg and 1.0 mg, respectively.
 - A weight loss of at least 10% was obtained for more subjects with semaglutide 0.5 mg (8%) and 1.0 mg (13%) compared with placebo (2%) with an estimated odds ratio of 3.6 [1.09; 11.95]_{95%CI} and 6.2 [1.98; 19.61]_{95%CI} with semaglutide 0.5 mg and 1.0 mg, respectively.
- FPG was significantly reduced with semaglutide when compared with placebo with ETDs of -1.96 mmol/L [-2.49; -1.43]_{95%CI} and -1.79 mmol/L [-2.31; -1.26]_{95%CI} with semaglutide 0.5 mg and 1.0 mg, respectively. The ETDs in FPG in mg/dL were -35.28 mg/dL [-44.87; -25.70]_{95%CI} and -32.17 mg/dL [-41.71; -22.64]_{95%CI}, with semaglutide 0.5 mg and 1.0 mg, respectively.
- Neither systolic nor diastolic blood pressure was significantly changed at week 30 with semaglutide when compared with placebo.

SAFETY RESULTS

During the 30 weeks of treatment, semaglutide was generally safe and well-tolerated, and overall, the safety and tolerability was consistent with other GLP-1RAs.

Adverse events

- No fatal events were reported
- In the on-treatment observation period, the proportion of subjects reporting any adverse event (AE) during the trial was higher with semaglutide 0.5 mg than with placebo, and the rate of AEs were higher with each semaglutide dose (0.5 mg: 64.1%, 452 events per 100 patient years of exposure [PYE]; 1.0 mg: 56.2%, 328 events per 100 PYE) than

with placebo (53.5%, 275 events per 100 PYE). The difference was mainly driven by more gastrointestinal AEs reported with semaglutide than with placebo.

- In all 3 treatment groups, more than 90% of all AEs were of mild or moderate severity and 72% of the subjects reporting AEs had recovered or were recovering at the end of the trial.
- The most frequently reported AEs in subjects treated with semaglutide were within the system organ class (SOC) ‘gastrointestinal disorders’, whereas the most frequently reported AEs in subjects treated with placebo were within the SOC ‘infections and infestations’
- The proportions of subjects reporting SAEs were low across all 3 treatment groups: 10 SAEs reported by 7 subjects with semaglutide 0.5 mg, 8 SAEs reported by 7 subjects with semaglutide 1.0 mg, and 6 SAEs reported by 5 subjects with placebo. There was no consistent pattern in reported SAEs across treatment groups and PTs.
- The proportion of subjects with AEs leading to premature treatment discontinuation was low and similar for the 2 semaglutide doses, although higher than with placebo (6%, 5% and 2% with semaglutide 0.5 mg, semaglutide 1.0 mg, and placebo, respectively). This treatment difference was primarily due to gastrointestinal AEs with onset during the first ~10–12 weeks, after which the discontinuation rate due to AEs was low for the remainder of the treatment period with no apparent difference between treatment groups.
- Despite the higher maintenance dose of semaglutide 1.0 mg as compared to semaglutide 0.5 mg, the overall AE safety profile did not worsen in subjects receiving the high maintenance dose.

Hypoglycaemia

- No episodes of severe hypoglycaemia were reported. No episodes of ‘severe or BG-confirmed symptomatic hypoglycaemia’ were reported with semaglutide, while 2 subjects with placebo reported 3 episodes.

Safety areas of interest

- **Gastrointestinal disorders**
 - Gastrointestinal disorders were the most frequently reported AEs in this trial. The AEs reported by $\geq 5\%$ of the subjects in either treatment group were ‘nausea’, ‘diarrhoea’, ‘vomiting’, ‘dyspepsia’ and ‘constipation’ in descending order, all of which were reported at a higher rate and by a higher proportion of subjects with each of the semaglutide doses than with placebo. The proportions of subjects reporting the 3 most frequent preferred terms were: ‘nausea’ (20.3%, 23.8% and 7.8% with semaglutide 0.5 mg, semaglutide 1.0 mg and placebo, respectively), ‘diarrhoea’ (12.5%, 10.8% and 2.3% with semaglutide 0.5 mg, semaglutide 1.0 mg and placebo, respectively) and ‘vomiting’ (3.9%, 6.9% and 1.6% with semaglutide 0.5 mg, semaglutide 1.0 mg and placebo, respectively).
 - The AEs were largely mild or moderate in severity, and only 2 subjects reported gastrointestinal SAEs.
 - The majority of the events occurred within the initial 12–14 weeks of treatment and the median duration of the gastrointestinal AEs ‘nausea’, ‘diarrhoea’ and ‘vomiting’ were between 1 and 5 days with all 3 treatment groups.
 - None of the subjects in semaglutide 0.5 mg and 1.0 mg reporting gastrointestinal AEs reported dehydration leading to renal impairment according to the AEs captured by the MedDRA search of ‘acute renal failure’.
- **Cardiovascular disorders**
 - Three (3) cardiovascular events were confirmed by event adjudication; 1 subject had a ‘transient ischaemic attack’ (semaglutide 0.5 mg) and another subject had an acute myocardial infarction followed by a coronary revascularisation (semaglutide 1.0 mg). All 3 events were serious and assessed as unlikely related to trial product. The subjects [REDACTED] and none of the events led to premature discontinuation of trial product.
 - Subjects treated with semaglutide 0.5 mg and 1.0 mg experienced a significant increase in pulse rate from baseline to end of treatment compared to placebo of 2.9 beats per minute (bpm) and 3.0 bpm, respectively.
 - The majority (85–88%) of ECG measurements in both treatment groups were ‘normal’ or ‘abnormal, not clinically significant’ at baseline and week 30. One (1) subject (semaglutide 1.0 mg) had a shift in ECG assessment from ‘normal’ to ‘abnormal, clinically significant’ identified at the end-of-treatment.
- **Pancreatitis**
 - No events of pancreatitis were confirmed by event adjudication, nor were any events identified by the pre-defined MedDRA search.
 - Treatment with semaglutide induced a mean increase in lipase and amylase values that was significantly higher

than with placebo. The vast majority of the subjects had amylase and lipase activities $<2\times\text{ULN}$ throughout the trial, and most of the subjects with lipase or amylase activities $\geq 5\times$ and $\geq 2\times\text{ULN}$, respectively, only had single incidences of activity outliers (100% of those with lipase outliers and 63% of those with amylase outliers). None of the 6 subjects with elevated lipase activity ($\geq 5\times\text{ULN}$) and 1 of the 8 subjects with elevated amylase activity ($\geq 2\times\text{ULN}$) reported concurrent gastrointestinal, hepatobiliary or pancreatitis-related events. The clinical relevance of these findings is currently unknown.

- Hepatobiliary disorders
 - The MedDRA search identified a total of 4 gallbladder-related events reported by 4 subjects; 3 subjects on semaglutide 0.5 mg, 1 on semaglutide 1.0 mg and none on placebo. All 4 events were reported as ‘cholelithiasis’ and 1 was serious; [REDACTED]. None of the events led to premature treatment discontinuation and the 4 events had onset at around week 12. None of the 4 subjects had a noteworthy rapid weight loss at the time of the event. In general, there was a fluctuating pattern in the levels of liver function tests; 3 subjects had alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities $>5\times\text{ULN}$, while no total bilirubin or alkaline phosphatase (ALP) outliers were detected. The mean changes for all 4 parameters from baseline were comparable between semaglutide and placebo.
- Neoplasms
 - A total of 9 events in 9 subjects were confirmed as neoplasms by event adjudication and overall, the proportions of subjects as well as the event rates of event adjudication committee (EAC)-confirmed neoplasms (all and malignant) were low and comparable between the 2 semaglutide doses; no EAC-confirmed events were reported with placebo. The EAC-confirmed neoplasms primarily occurred as single events in single subjects and were equally distributed with regards to type (tissue or organ of origin) and class (5 benign and 4 malignant) across the semaglutide doses. In 5 of the 9 subjects there was relevant pre-existing disease at baseline.
- Thyroid disorders:
 - There were no EAC-confirmed events of thyroid disease requiring thyroidectomy and no findings pertaining to thyroid neoplasms.
 - There were no clinically relevant changes in calcitonin values throughout the treatment period within or between treatment groups.
- Renal disorders:
 - Few AEs related to the MedDRA search on acute renal failure were reported during the trial (0, 1 and 4 AEs with semaglutide 0.5 mg, semaglutide 1.0 mg and placebo, respectively). All of these events were non-serious and none led to premature treatment discontinuation.
 - A 4% decrease in the estimated glomerular filtration rate (eGFR) was observed in subjects treated with semaglutide, primarily in subjects with normal renal function at baseline. The clinical relevance of this change is presently unknown.
 - There were no clinically relevant changes in other renal laboratory parameters over time within and across treatment groups.
- Immunogenicity related AEs and injection site reactions
 - The MedDRA search identified 6 allergic reactions related to skin and upper respiratory disorders reported by 6 subjects (3, 2 and 1 with semaglutide 0.5 mg, semaglutide 1.0 mg and placebo, respectively). None of the events were serious, but 1 event of ‘urticaria’ led to premature treatment discontinuation.
 - A total of 11 subjects tested positive for anti-semaglutide antibodies, and of these, 8 had antibodies that cross-reacted with endogenous GLP-1. Ten (10) of 11 subjects testing positive for anti-semaglutide antibodies had antibody levels of less than 5 % B/T throughout the trial. None of the antibodies had the capacity to neutralise semaglutide or native GLP-1. The presence of anti-semaglutide antibodies did not lead to an increase in HbA1c within these subjects.
 - Eight (8) events of ‘immune complex disease’ in 8 subjects (2, 1 and 5 events with semaglutide 0.5 mg, semaglutide 1.0 mg and placebo) were captured by the pre-defined MedDRA search. There was no apparent pattern in the type or distribution of events. One (1) of the events was serious and none of the events led to permanent premature discontinuation of trial product.
 - Five (5) events of injection site reactions in 2 subjects (4 events with semaglutide 0.5 mg and 1 event with placebo) were captured by the pre-defined MedDRA search. All were non-serious and did not lead to

premature treatment discontinuation.

- No events were reported within the safety areas medication errors, overdose, and suspected transmission of infectious agent via trial product. No relevant clinical findings were reported within the safety area rare events.

Other clinical laboratory evaluations, physical examination and pregnancies

- For biochemistry or haematology laboratory parameters not presented in the safety areas of interest, no clinically relevant changes were observed.
- No clinically relevant treatment differences were observed in physical examination findings.
- One (1) pregnancy was reported in the placebo group; treatment was prematurely discontinued [REDACTED]

CONCLUSIONS

- The efficacy of once-weekly semaglutide at doses of 0.5 mg and 1.0 mg versus placebo was evaluated after 30 weeks of monotherapy in subjects with T2D:
 - Superiority of semaglutide in reducing HbA_{1c} (primary endpoint) and body weight (confirmatory secondary endpoint) from baseline to week 30 was confirmed with both the 0.5 mg and 1.0 mg doses when compared with placebo.
 - Significantly higher odds for reaching the HbA_{1c} treatment targets of $\leq 6.5\%$ or $< 7\%$ and the weight loss responses of $\geq 5\%$ and $\geq 10\%$ were obtained with semaglutide when compared with placebo.
- Improvements in HbA_{1c} and body weight with semaglutide treatment was accompanied by significant and beneficial changes in parameters relating to glycaemia, blood lipids and weight loss, comprising FPG, total cholesterol, LDL, FFAs, BMI and waist circumference.
- While a larger weight loss was observed with the 1.0 mg dose compared with the 0.5 mg dose, there was no apparent difference between the 2 semaglutide doses on improvement in HbA_{1c}.
- Treatment with once-weekly semaglutide 0.5 mg and 1.0 mg was well tolerated as monotherapy in subjects with T2D and no unanticipated safety concerns were identified.

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice.

CTR Synopsis Addendum – Germany

PROTOCOL AMENDMENTS

As of 05-Jul-2016, the following protocol amendments have been made to the original protocol, version 1.0, dated 09-Jul-2013.

Amendment number	Issue date	Countries affected	Key changes
1	08 August 2013	Japan	Updated with local requirements concerning specification of number of Japanese subjects to be included in the trial, examples of contraception methods considered appropriate in Japan and local guidelines for diabetes care.
2	15 November 2013	Russia	Updated with local requirements concerning examples of contraception methods considered appropriate in Russia.
3	04 February 2014	Global	The main objective was to update the definition of hypoglycaemia and to include an additional hypoglycaemic endpoint on severe or BG-confirmed symptomatic hypoglycaemic episodes and associated statistical analysis and minor updates for general clarification.

TRIAL SITES – additional information

The following trial sites randomised/assigned subjects to treatment in the trial.

■	Manna Research Inc. 145-175 ave. Stillview Pointe-Claire H9R 4S3 QC Quebec	Canada
■	C.I.C. Mauricie Inc. 700 Boulevard Thibreau Trois Rivières G8T 7A1 QC Quebec	Canada
■	Manna Research Vancouver 1530 West 7th Room ■ Vancouver V6J 1S3 BC British Columbia	Canada
■	Rivergrove Medical Clinic 2605 Main Street Unit 2 Winnipeg R2V 4W3 MB Manitoba	Canada

■	2320 Main Street London N6P 1A9 ON Ontario	Canada
■	JJ Dig Research Ltd. 3695 Keele Street ■ Toronto M3J 1N2 ON Ontario	Canada
■	Applied Medical Informatics Research 5100 boulevard de Maisonneuve West Suite ■ Montreal H4A 3T2 QC Quebec	Canada
■	A.O.U. Senese Policlinico "Le Scotte" , U.O.C. Diabetologia Dep. Endocrinologia Viale Bracci 1, Siena 53100	Italy
■	Azienda Ospedaliero Universitaria Pisana Ospedale Cisanello U.O. Endocrinologia 1 Via Paradisa 2 PISA 56124	Italy
■	ARNAS Ospedale Garibaldi Azienda Ospedaliera Garibaldi U.O.S. di Diabetologia, Obesità e Dietologia Via Palermo 636 Catania 95122	Italy
■	Az. Osp. "Santa Maria" Diabetologia, Dietologia e nutrizione clinica Via Tristano da Joannuccio, 1 Terni 05100	Italy

■	Fondazione Policlinico Universitario Agostino Gemelli IRCCS DH Patologie dell'Obesità Largo A. Gemelli 8 Rome 00168	Italy
■	Tokyo-Eki Center-building Clinic 3-3-14, Nihombashi Chuo-ku, Tokyo 103 0027	Japan
■	Tokyo Center Clinic 1-5-4 Yaesu, Chuo-ku, Tokyo,103 0028 Name of site has changed on 01-Jan-2014. Medical Corporation Chiseikai Tokyo Center Clinic 1-5-4 Yaesu, Chuo-ku, Tokyo 103-0028	Japan
■	Heishinkai Medical Group Incorporated ToCROM Clinic 6-26-8 Shinjuku, Shinjuku-ku, Tokyo, 160 0022	Japan
■	Kyoto University Hospital 54 Kawaharacho, Shogoin, Sakyo-ku Kyoto-shi, Kyoto 606-8507	Japan
■	Heishinkai Medical Group Incorporated OCROM Clinic 4-12-11, Kasuga Suita-shi, Osaka 565-0853	Japan
■	Centro de Estudios Clínicos y Especialidades Médicas S.C. Canada No. ■ Col. vista Hermosa Monterrey 64620 N.L. Nuevo León	Mexico

■	Centro de Estudios de Investigación Altamira No. ■ Oriente Zona Centro Tampico 89000 TAMPS Tamaulipas	Mexico
■	State Healthcare Institution "Regional Clinical Hospital" 1, Smirnovskoe canyon Saratov 410053	Russian Fed.
■	"Diagnostic Center "Energ" LLC Lit. A, 5, Kievskaya st. Saint-Petersburg, 195257 Saint-Petesburg 195257	Russian Fed.
■	Arkhangelsk Regional Clinical Hospital 292, Prospect Lomonosova Arkhangelsk 163045	Russian Fed.
■	Novosibirsk State Medical University 6/7, Zaleskogo str. Novosibirsk 630047	Russian Fed.
■	State healthcare institution -Kazan Endocrinology Dispensary 3, Sedov street, Kazan 420073	Russian Fed.
■	Regional Endocrinological Dispensary Legal address: 127, Dzerzhinskogo str., 355000, Stavropol, Russia Actual address: 9, Artema str., 355017, Stavropol, Russia	Russian Fed.
■	First City Clinical Hospital of the Emergency Medical Care Suvorova str., 1 Arkhangelsk 163045	Russian Fed.

■	City out-patient department # 117 5/1-A Simonova street Saint-Petersburg 194358	Russian Fed.
■	■ 80 Gembok Avenue Suite ■ Seva Sadan, Lenasia Johannesburg 1827 GAU Gauteng	South Africa
■	Soweto Clinical Trial Centre 1900 Dhlamini, Extension 2, Soweto Johannesburg 1818 GAU Gauteng	South Africa
■	■ Rooms Suite ■ Floor, Mercantile Hospital Korsten Port Elizabeth Port Elizabeth 6014 EC Eastern Cape	South Africa
■	■ 14 Bisset Street Umkomaas Umkomaas 4170 KZN KwaZulu-Natal	South Africa
■	■ Suite ■, 8 Burger Street, Edwill section, Krugersdorp Hospital Krugersdorp 1739 GAU Gauteng	South Africa
■	Medicross: Sophiatown Clinical Research Cnr Millar and Edward Streets, Sophiatown Sophiatown 2129 GAU Gauteng	South Africa

■	1st Med Trial Centre and General Practice 252 Franzina Street,Eloffsdal Pretoria 0084 GAU Gauteng	South Africa
■	■ Rooms 26 Daffodil Street Stanger Manor, Stanger Durban 4450 KZN KwaZulu-Natal	South Africa
■	St. Helens Hospital Diabetes Centre Marshall's Cross Road St Helens WA9 3DA	United Kingdom
■	Joint Clinical Research Facility -Swansea Institute of Life Science 2 Swansea University Swansea SA2 8PP	United Kingdom
■	Ely Bridge Surgery 23 Mill Road Ely Cardiff CF5 4AD	United Kingdom
■	Muirhead Medical Centre Liff Road Muirhead Dundee DD2 5NH	United Kingdom
■	Colorado Springs Health Partners 2405 Research Parkway Colorado Springs 80920 CO Colorado	United States
■	Spartanburg Medical Research 485 Simuel Road Spartanburg 29303 SC South Carolina	United States
■	Pinnacle Research Group LLC 321 East 10th Street Anniston 36207 AL Alabama	United States

■	Langhorne Physician Services Durham Physicians 833 Durham Road Penndel, PA 19047	United States
■	Torrance Clinical Research Institute, Inc. 25043 Narbonne Ave. Lomita 90717 CA California	United States
■	Research Institute of South Florida 9835 SW 72 Street Suite ■ Miami 33173 FL Florida	United States
■	Well Pharma Medical Research Corp 7000 SW 62nd Ave Suite ■ Miami 33143 FL Florida	United States
■	Elite Clinical Research 8080 West Flagler Street Suite ■ Miami 33144 FL Florida	United States
■	Family Clinical Trials 1601 North Palm Ave. Suite ■ Pembroke Pines 33026 FL Florida	United States
■	KRK Medical Research 6750 Hillcrest Plaza Drive Suite ■ Dallas 75230 TX Texas	United States
■	Sealy Urgent Care Center and Medical Clinic 1036 North Circle Drive Sealy 77474 TX Texas	United States

■	San Marcus Research Clinic, Inc 5941 NW 173 Drive, Suite ■ Miami 33015 FL Florida	United States
■	Whiteville Medical Associates, PA 819 E. Jefferson Street Whiteville 28472 NC North Carolina	United States
■	Catalina Research Institute, LLC 14726 Ramona Avenue, Suite ■ Chino, CA 91710	United States
■	CTI Clinical Research Center 334 Thomas More Parkway Suite ■ Crestview Hills 41017-3464 KY Kentucky	United States
■	■ 17510 W. Grand Parkway South Suite ■ Sugar Land 77479 TX Texas	United States
■	School of Clinical Research, USA, LLC. 7309 West Flagler Street Miami 33144 FL Florida	United States
■	Care-Partners-Clinical-Research, LLC 6500 Fort Caroline Road Jacksonville 32277 FL Florida	United States
■	Delaware Research Group, LLC. 6 Lexington Blvd Delaware 43015 OH Ohio	United States

■	OnSite Clinical Solutions, LLC 12311 Copper Way, Suite ■ Charlotte, NC 28277	United States
■	Investigators Research Group, LLC 321 E. Northfield Drive Suite ■ Brownsburg 46112 IN Indiana	United States
■	Albuquerque Clinical Trials, Inc. 801 Encino Place Northeast, Suite ■ Albuquerque, NM 87102	United States
■	American Health Network of IN LLC 1300 W Jefferson Street Suite ■ Franklin 46131 IN Indiana	United States
■	Clinical Research Advantage, Inc./ ■ Family Practice 11020 Prairie Brook Rd. Omaha 68144 NE Nebraska	United States
■	Columbus Clinical Services, LLC 15 SW 107 Avenue Miami 33174 FL Florida	United States
■	American Clinical Trials 12321 E. Carson Blvd. Suite ■ Hawaiian Gardens 90716 CA California	United States
■	Zasa Clinical Research 8188 Jog Road Suite ■ Boynton Beach 33472 FL Florida	United States

■	National Research Institute 2010 Wilshire Blvd. Suite # ■ Los Angeles 90057 CA California	United States
■	■ Medical Clinic, PLLC 2225 Williams Trace Boulevard Suite ■ Sugar Land 77478 TX Texas	United States