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

Clinical Trial Report synopsis – ICH E3 Section 2

NAME OF SPONSOR
Novo Nordisk A/S, Novo Allé 1, DK-2880 Bagsvaerd, Denmark

NAME OF ACTIVE SUBSTANCE
Semaglutide

Trial ID
NN9535-3744

Trial registration ID-number	**UTN** – U1111-1131-7227
NCT01720446	**IND number** – 79,754
	EudraCT number – 2012-002839-28

TITLE OF TRIAL
SUSTAIN 6 – Long-term Outcomes
A long-term, randomised, double-blind, placebo-controlled, multinational, multi-centre trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes.

INVESTIGATORS
One principal investigator was appointed at each of the 229 trial sites in the trial. The following investigators were designated signatory investigators for the trial, and were responsible for reviewing and approving the clinical trial report:

- [redacted], MD, [redacted]
- [redacted], MD, [redacted].

TRIAL SITES
The trial was conducted at 229 sites in 20 countries, as follows: Algeria: 4 sites, Argentina: 7 sites, Australia: 8 sites, Brazil: 8 sites, Bulgaria: 5 sites, Canada: 13 sites, Denmark: 5 sites, Germany: 7 sites, Israel: 6 sites, Italy: 6 sites, Malaysia: 6 sites, Mexico: 9 sites, Poland: 5 sites, Russia: 11 sites, Spain: 6 sites, Taiwan: 4 sites, Thailand: 5 sites, Turkey: 10 sites, United Kingdom: 8 sites and United States: 96 sites.

PUBLICATION
Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016.

TRIAL PERIOD	**DEVELOPMENT PHASE**
Initiation date (first subject first visit): 21 February 2013 Completion date (last subject last visit): 15 March 2016	Phase 3a

DATA CUT-OFF DATES
The results presented reflect the data available in the clinical database as of 22 June 2016, and the safety database as of 22 March 2016.

DATE OF THE REPORT
24 October 2016

OBJECTIVES
Primary objective:

- To confirm that treatment with semaglutide does not result in an unacceptable increase in cardiovascular risk as compared to placebo in adults with type 2 diabetes (T2D). This is done by demonstrating that the upper limit of the two-sided 95% confidence interval (CI) of the hazard ratio for semaglutide versus placebo is less than 1.8 when comparing time to first occurrence of a major adverse cardiovascular event (MACE).

Secondary objectives:

- To assess the long-term safety and efficacy of semaglutide 0.5 mg and 1.0 mg once weekly compared to placebo, both added on to standard-of-care, in adults with T2D at high risk of cardiovascular events.

METHODOLOGY

This trial was a long-term, multi-centre, multi-national, randomised, double-blind, parallel-group, controlled trial performed to establish the cardiovascular (CV) safety and long term outcomes of semaglutide compared to placebo, when added to standard-of-care, in men and women with T2D at high risk of CV events.

An external, independent event adjudication committee (EAC) was constituted for this trial to perform ongoing adjudication and assessment of selected events, e.g. potential major adverse cardiovascular events (MACE), deaths and predefined medical events of special interest (MESI), in a blinded manner.

An independent, external Data Monitoring Committee (DMC) was constituted for the trial to perform ongoing safety surveillance of the trial. The DMC had access to unblinded data.

The trial consisted of a screening period of up to 2 weeks, a randomisation visit (visit 2) where subjects were randomly assigned (1:1:1:1) to either semaglutide 0.5 mg, semaglutide 1.0 mg or volume-matched placebo once-weekly, a treatment period of 104 weeks and a post-treatment follow-up period of 5 weeks. The trial duration was partly event-driven and was to be terminated when the projected number of subjects with 3-component EAC-confirmed MACE was at least 122, and at the earliest 104 weeks after the last subject had been randomised. Due to a higher actual accrual rate of EAC-confirmed MACE than anticipated, the projected number of MACE was reached earlier than predicted. Therefore, each subject was treated for 104 weeks with a post-treatment follow-up period of 5 weeks, resulting in a planned trial duration of 109 weeks per subject.

Subjects followed a fixed dose-escalation regimen to reach the maintenance dose of either 0.5 mg or 1.0 mg. All randomised subjects started with doses of 0.25 mg. After 4 weeks of treatment, the dose was escalated (doubled). Hence, the target dose of 0.5 mg was achieved after 4 weeks of treatment and the target dose of 1.0 mg was achieved after 8 weeks of treatment.

Subjects were scheduled to attend the trial site once every month during the first 6 months and every 3 months during the rest of the trial, and to have monthly phone contacts with the investigator between the site visits.

Diligent efforts were made to collect outcome data on all randomised subjects. Subjects were followed for the complete duration of the trial irrespective of their adherence to allocated trial treatment or adherence to the protocol in general, unless consent was withdrawn. A subject was considered lost to follow-up if the subject did not complete the trial and did not withdraw consent. Attempts to obtain vital status for these subjects were done up until database lock. Subjects, for which vital status could not be obtained in this way, were considered lost to follow-up for vital status.

Investigators were encouraged to treat-to-target (current guideline targets) to reach glycaemic control; hence, additional glucose-lowering medications (except drugs affecting the incretin pathway such as other GLP-1 receptor agonists, DPP-4 inhibitors or pramlintide) were allowed to be added to the trial treatment regimen to maintain target glycaemic control at the discretion of the investigator.

Randomisation was stratified to ensure even distribution within strata according to the following 3 stratification variables: evidence of CV disease at baseline (clinical or subclinical), insulin treatment at baseline (none, basal insulin or pre-mixed insulin), renal impairment with GFR value <30 mL/min/1.73 m2 at baseline (presence or absence).

By trial design, subjects with severe renal impairment always fall into the “clinical evidence of CV disease” stratum. This resulted in a total of 9 strata.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

A total of 3260 subjects were planned for randomisation; 4346 were screened and 3297 were randomised. A total of 98.0% of subjects completed the trial and vital status was obtained for 99.6% of all randomised subjects.

Subject disposition - summary - all randomised subjects

	Sema N (%)	Placebo N (%)	Total N (%)
Screened			4346
Screening failures			1049
Full analysis set (all randomised subjects)	1648(100.0%)	1649(100.0%)	3297(100.0%)
Safety analysis set (all exposed subjects)	1642 (99.6%)	1644 (99.7%)	3286 (99.7%)
Treatment completers [1]	1297 (78.7%)	1339 (81.2%)	2636 (80.0%)

	Sema N	(%)	Placebo N	(%)	Total N	(%)
Trial completers	1623	(98.5%)	1609	(97.6%)	3232	(98.0%)
Subjects who died during the trial	62	(3.8%)	60	(3.6%)	122	(3.7%)
Subjects who attended visit 26	1561	(94.7%)	1549	(93.9%)	3110	(94.3%)
Premature treatment discontinuers [2]	350	(21.2%)	310	(18.8%)	660	(20.0%)
Gastrointestinal tolerability	124	(7.5%)	18	(1.1%)	142	(4.3%)
Withdrawal of informed consent	2	(0.1%)	2	(0.1%)	4	(0.1%)
Adverse event other than related to gastrointestinal tolerability	92	(5.6%)	93	(5.6%)	185	(5.6%)
Introduction of disallowed medication	6	(0.4%)	16	(1.0%)	22	(0.7%)
Suspicion of placebo (without introduction of disallowed medication)	6	(0.4%)	25	(1.5%)	31	(0.9%)
Randomised in error	25	(1.5%)	22	(1.3%)	47	(1.4%)
Resistance to injections	2	(0.1%)	2	(0.1%)	4	(0.1%)
Trial fatigue	10	(0.6%)	26	(1.6%)	36	(1.1%)
Other	83	(5.0%)	106	(6.4%)	189	(5.7%)
Withdrawals in relation to or after treatment discontinuation [3]	7	(0.4%)	8	(0.5%)	15	(0.5%)
Last known vital status for subjects not completing the trial	25	(1.5%)	40	(2.4%)	65	(2.0%)
Subjects lost to follow-up [4]	18	(1.1%)	32	(1.9%)	50	(1.5%)
Alive	14	(0.8%)	26	(1.6%)	40	(1.2%)
Dead	1	(0.1%)	2	(0.1%)	3	(0.1%)
Unknown	3	(0.2%)	4	(0.2%)	7	(0.2%)
Withdrawals	7	(0.4%)	8	(0.5%)	15	(0.5%)
Alive	3	(0.2%)	4	(0.2%)	7	(0.2%)
Dead	1	(0.1%)	1	(0.1%)	2	(0.1%)
Unknown	3	(0.2%)	3	(0.2%)	6	(0.2%)

Sema: semaglutide, N: Number of subjects, %: Percentages are based on randomised subjects, Visit 26: Follow-up visit.
[1]: Subjects, who were exposed, did not discontinue treatment prematurely, who did not withdraw from trial and who were not lost to follow-up before the last treatment visit. [2]: Subjects who are not exposed, but have given a reason for premature treatment discontinuation are also included. [3]: All cases were withdrawal of informed consent. [4]: Subjects who did not complete the trial and did not withdraw from trial.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Main inclusion criteria: Men and women with T2D, age ≥50 years at screening and clinical evidence of CV disease or age ≥60 years at screening and subclinical evidence of CV disease, anti-diabetic drug naïve, or treated with one or two oral antidiabetic drug (OADs), or treated with human Neutral Protamin Hagedorn (NPH) insulin or long-acting insulin analogue or pre-mixed insulin, both types of insulin either alone or in combination with one or two OADs, HbA_{1c} ≥7.0% at screening.

Main exclusion criteria: Type 1 diabetes mellitus, use of glucagon-like peptide-1 (GLP-1) receptor agonist (exenatide, liraglutide, or other) or pramlintide within 90 days prior to screening, use of any dipeptidyl peptidase 4 (DPP-IV) inhibitor within 30 days prior to screening, treatment with insulin other than basal and pre-mixed insulin within 90 days prior to screening - except for short-term use in connection with intercurrent illness, acute decompensation of glycaemic control requiring immediate intensification of treatment to prevent acute complications of diabetes (e.g. diabetes ketoacidosis) within 90 days prior to screening, history of chronic pancreatitis or idiopathic acute pancreatitis, acute coronary or cerebrovascular event within 90 days prior to randomisation, currently planned coronary, carotid or peripheral artery revascularisation, chronic heart failure New York Heart Association (NYHA) class IV, personal or family history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma, personal history of non-familial medullary thyroid carcinoma, calcitonin ≥50 ng/L at screening.

Main withdrawal criteria: Subjects were to be withdrawn from the trial if informed consent was withdrawn and in case of pregnancy.

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 as subcutaneous (s.c.) injections either in the thigh, abdomen or upper arm, at any time of day irrespective of meals. Batch numbers (expiry date): BV40330 (26 March 2014), BV40398 (26 March 2014),

BV40439 (04 July 2014), CV40054 (04 October 2014), CV40076 (04 October 2014), BV40434 (01 April 2015), BV40329 (26 June 2015), CV40317 (10 October 2015), CV40344 (10 October 2015), DV40225 (07 May 2017).

DURATION OF TREATMENT
104 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):
BV40314 (23 March 2014), BV40320 (23 March 2014), BV40377 (23 March 2014), CV40023 (01 April 2015), CV40075 (01 October 2014), CV40023 (01 April 2015), BV40438 (01 April 2015), CV40139 (29 July 2015), DV40039 (13 February 2016), DV40231 (05 May 2017).

CRITERIA FOR EVALUATION – TIME TO EVENT ANALYSES
The following variables were assessed: CV death, non-fatal myocardial infarction (MI), non-fatal stroke, revascularization (coronary and peripheral), unstable angina requiring hospitalisation, hospitalisation for heart failure, all-cause death, microvascular events (nephropathy and diabetic retinopathy complications).

CRITERIA FOR EVALUATION – EFFICACY
The following efficacy variables were assessed: Glycosylated haemoglobin (HbA_{1c}), body weight, fasting plasma glucose (FPG), blood pressure (systolic and diastolic), lipid profile (total cholesterol, high density lipoprotein [HDL]-cholesterol, low density lipoprotein [LDL]-cholesterol, triglycerides and free fatty acids), proportion of subjects requiring addition of glucose-lowering medication, and patient-reported outcome (PRO) questionnaire (SF-36v2™) scores.

CRITERIA FOR EVALUATION – SAFETY
The following safety variables were assessed: Treatment-emergent adverse events (AEs, incl. predefined MESI adjudicated by an independent external adjudication committee), hypoglycaemic episodes, pulse rate and laboratory safety variables.

STATISTICAL METHODS
Sample size calculations were based on an assumed annual primary-event rate of 1.98% in each group, a dropout rate of less than 10.0%, a mean observation time of 2.1 years and a true hazard ratio of 1.0. Under these assumptions, 3260 randomized patients were needed to achieve 122 patients with primary outcome, giving 90% power to reject a hazard ratio of at least 1.8.

Analysis sets
The following analysis sets were defined in the protocol and clarified in the statistical analysis plan, prior to unblinding, and in accordance with ICH-E9:

- ***Full Analysis Set (FAS)****:* includes all randomised subjects. The statistical evaluation of the FAS follows the intention-to-treat (ITT) principle, and subjects contribute to the evaluation 'as randomised'.
- ***Safety Analysis Set (SAS)****:* includes all subjects exposed to at least 1 dose of trial product. Subjects in the SAS will contribute to the evaluation based on the trial product received for the majority of the period where they were on treatment. This will be referred to as contributing to the evaluation "as treated".

Observation periods
Two observation periods were defined for this trial:
In-trial observation period: the time-period where subjects were considered trial participants and where data were planned to be collected systematically, starting with the day of randomisation and ending with end-of-trial, defined for trial completers as the subject's planned end-of-trial visit or death, whichever comes first, and defined as the last direct subject-site contact for withdrawals and for subjects lost to follow-up.
On-treatment observation period: a subset of the in-trial observation period representing the time period where subjects were considered exposed to trial product, starting with the timing of first dose of trial product and ending with the subject's end-of-treatment, defined as the end-of-treatment follow-up visit scheduled 5 weeks after date of last dose, date of last dose plus 42* days or end of the subject's in-trial period, whichever comes first. (*For efficacy endpoints

and safety endpoints other than ECGs, adjudicated events, AEs and hypoglycaemic episodes, an ascertainment window of 7 days is used instead of the 42 days).

Primary analysis

The primary endpoint was:

- Time from randomisation to first occurrence of a MACE, defined as CV death, non-fatal MI, or non-fatal stroke.

The primary analysis was based on the FAS using the in-trial observation period. The primary endpoint was analysed using a stratified Cox proportional hazards model with treatment group (semaglutide, placebo) as fixed factor. The model was stratified by all possible combinations of the 3 stratification factors used in the randomisation procedure (in total 9 levels). Subjects not experiencing an event were censored at the end of the in-trial observation period. The analysis was considered confirmatory.

Pre-specified sensitivity analyses of the primary endpoint, using alternative patient selection and censoring strategies for exposure to treatment, were conducted. Exploratory analyses of the primary endpoint were performed in subgroups of demographic- and disease baseline parameters, based on the FAS using the in-trial observation period. For each subgroup analysis the primary endpoint was analysed using an un-stratified Cox proportional hazards model with an interaction between treatment group (semaglutide, placebo) and the relevant subgroup as fixed factor.

Analysis of secondary endpoints

Supportive secondary time to event endpoints addressing the primary objective

The following secondary time to event endpoints were used as supportive endpoints for the primary objective:

- Time from randomisation to first occurrence of an expanded composite CV outcome, defined as either MACE, revascularization (coronary and peripheral), unstable angina requiring hospitalisation or hospitalisation for heart failure.
- Time from randomisation to each individual component of the expanded composite CV outcome.
- Time from randomisation to first occurrence of all-cause death, non-fatal MI, or non-fatal stroke.

All of the above outcomes except peripheral revascularisation were EAC-confirmed events. A list of preferred terms constituting peripheral revascularization was specified *post hoc*. The above time to event endpoints were analysed in the same way as the primary endpoint.

Confirmatory efficacy endpoints addressing the secondary objective

The following secondary efficacy endpoints were considered confirmatory:

- Change from baseline to week 104 in body weight (kg).
- Change from baseline to week 30 in HbA_{1c} for subjects on premix insulin at baseline.
- Change from baseline to week 30 in HbA_{1c} for subjects on sulphonylurea (SU) monotherapy at baseline.

For each of these 3 endpoints, 2 hypotheses were evaluated:

- Superiority for semaglutide 1.0 mg versus placebo.
- Superiority for semaglutide 0.5 mg versus placebo.

Superiority for either change in HbA_{1c} or change in body weight was considered established if the upper limit of the 2-sided 95% CI for the associated estimated treatment difference was below 0% or 0 kg, respectively.

The analyses were based on the FAS and in-trial observation period. The endpoints were analysed using a mixed model for repeated measurement (MMRM); all post-baseline measurements obtained at scheduled visits were included as dependent variables. Treatment group (3 levels: semaglutide 0.5 mg, semaglutide 1.0 mg, placebo) and stratification (9 levels) were included as fixed factors and baseline value as covariate, all nested within visit. For $HbA_{1c,}$ the model included interaction between treatment group and the relevant subgroup (2 levels for SU monotherapy subgroup analysis, 3 levels for insulin subgroup analysis). An unstructured covariance matrix was assumed for measurements within the same subject.

A range of sensitivity analyses investigating the robustness of the confirmatory efficacy analyses were conducted.

Supportive secondary endpoints addressing the secondary objective

Continuous efficacy endpoints:

- Change from baseline to last assessment during the treatment period in:
  - body weight

- HbA_{1c} and FPG
- lipid profile, including total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and free fatty acids.
- systolic and diastolic blood pressure.

- Change from baseline to last assessment during the treatment period in SF-36v2™ patient reported outcome (PRO) scores.

The analyses of continuous efficacy endpoints were based on the FAS using the in-trial observation period and were analysed by a MMRM. The model included treatment group (4 levels: semaglutide 0.5 mg, semaglutide 1.0 mg, placebo 0.5 mg, placebo 1.0 mg) and stratification (9 levels) as fixed factors and the corresponding baseline value as a covariate, all nested within visit. An unstructured covariance matrix was assumed for measurements within the same subject. ANCOVA models of last available assessment for both in-trial and on-treatment were specified as sensitivity analyses.

Categorical efficacy endpoints:

- Requirement of additional glucose-lowering medication (Yes or No).

The endpoint was analysed using a logistic regression model with treatment (4 levels: semaglutide 0.5 mg, semaglutide 1.0 mg, placebo 0.5 mg and placebo 1.0 mg) and stratification (9 levels) as fixed factors and baseline HbA_{1c} as a covariate. The analysis was based on the FAS using the in-trial observation period.

Time to event safety endpoints (microvascular events):

- Time from randomisation to first occurrence of diabetic retinopathy complication, defined as either a need for retinal photocoagulation, or treatment with intravitreal agents, or vitreous haemorrhage, or diabetes-related blindness (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of less than 20 degrees, in the better eye with best correction possible).
- Time from randomisation to first occurrence of new or worsening nephropathy, defined as new onset of persistent macroalbuminuria (>300 mg/g), or persistent doubling of serum creatinine level and creatinine clearance per modification of diet in renal disease (MDRD) ≤45 mL/min/1.73m^2, or the need for continuous renal-replacement therapy (in the absence of an acute reversible cause), or death due to renal disease).

These time-to-event endpoints were analysed in the same way as the primary endpoint.

Post hoc exploratory analyses of the time to first diabetic retinopathy complication were performed in subgroups of demographic- and disease baseline parameters, based on the FAS using the in-trial observation period. The applied statistical model was similar to the one applied for subgroup analysis of the primary endpoint.

In addition, a *post hoc* mediator analysis of the effect of rapid change in blood glucose on time to first diabetic retinopathy complication was conducted. This analysis applied an unstratified Cox proportional hazards model which in addition to treatment (semaglutide, placebo) as a fixed factor also included "change in HbA_{1c} (%-points) at week 16" as a covariate as well as factors considered to be both predictive for a reduction in HbA_{1c} as well as being risk factors for diabetic retinopathy. These factors were: "HbA_{1c} at baseline", "retinopathy at baseline" (yes, no, unknown/missing) and "baseline duration of diabetes". Change in HbA_{1c} at week 16 was chosen as the mediator as a proxy for rapid change in blood glucose.

Other secondary safety endpoints:

Safety endpoints were generally summarised using the SAS with on-treatment data as well as the FAS with in-trial data. Pre-defined Medical Dictionary for Regulatory Activities (MedDRA) groups consisting of pre-specified preferred terms defined by Novo Nordisk A/S Global Safety were evaluated based on MedDRA version 18.0. Episodes of hypoglycaemia were classified according to the Novo Nordisk A/S and the ADA classification of hypoglycaemia. Pulse rate, amylase, lipase and urinary albumin to creatinine ratio (UACR) were analysed separately with the same MMRM method as for continuous efficacy endpoints with the corresponding baseline value as a covariate. All laboratory assessments were summarised and evaluated by descriptive statistics. Anti-semaglutide antibodies were summarised descriptively by treatment group, based on the FAS and the in-trial observation period.

Time to event analyses of EAC-confirmed neoplasms

Post hoc Cox proportional hazards models similar to the one applied to the primary endpoints were used to investigate time to first neoplasm. Separate analyses were conducted for any neoplasm, neoplasms by malignancy, and malignant neoplasm by organ of origin.

DEMOGRAPHY OF TRIAL POPULATION

Subjects allocated to the 4 treatment arms (semaglutide 0.5 mg, semaglutide 1.0 mg, placebo 0.5 mg and placebo 1.0 mg) were well-matched with respect to demographics and baseline characteristics and are presented for semaglutide and placebo below:

Demographics and baseline characteristics for categorical variables – summary - FAS

	Sema N	(%)	Placebo N	(%)	Total N	(%)
Number of subjects	1648		1649		3297	
Sex						
Female	635	(38.5)	660	(40.0)	1295	(39.3)
Male	1013	(61.5)	989	(60.0)	2002	(60.7)
Race						
White	1384	(84.0)	1352	(82.0)	2736	(83.0)
Black or African American	108	(6.6)	113	(6.9)	221	(6.7)
Asian	121	(7.3)	152	(9.2)	273	(8.3)
American Indian or Alaska Native	3	(0.2)	7	(0.4)	10	(0.3)
Native Hawaiian or Other Pacific Islander	3	(0.2)	0	(0.0)	3	(0.1)
Other	29	(1.8)	25	(1.5)	54	(1.6)
Ethnicity						
Hispanic or Latino	256	(15.5)	254	(15.4)	510	(15.5)
Not Hispanic or Latino	1392	(84.5)	1395	(84.6)	2787	(84.5)
Smoker status						
Current smoker	204	(12.4)	202	(12.2)	406	(12.3)
Never smoked	754	(45.8)	739	(44.8)	1493	(45.3)
Previous smoker	690	(41.9)	707	(42.9)	1397	(42.4)
Unknown			1	(0.1)	1	(0.0)
Renal impairment						
Normal	493	(29.9)	497	(30.1)	990	(30.0)
Mild	686	(41.6)	682	(41.4)	1368	(41.5)
Moderate	423	(25.7)	409	(24.8)	832	(25.2)
Severe	41	(2.5)	54	(3.3)	95	(2.9)
End stage	5	(0.3)	7	(0.4)	12	(0.4)
Insulin treatment						
None	692	(42.0)	692	(42.0)	1384	(42.0)
Basal insulin	515	(31.3)	531	(32.2)	1046	(31.7)
Premix insulin	441	(26.8)	426	(25.8)	867	(26.3)
SU monotherapy						
No	1589	(96.4)	1585	(96.1)	3174	(96.3)
Yes	59	(3.6)	64	(3.9)	123	(3.7)
Clinical evidence of CV disease						
No	295	(17.9)	267	(16.2)	562	(17.0)
Yes	1353	(82.1)	1382	(83.8)	2735	(83.0)

Sema: semaglutide, N: Number of subjects, %: Percentage of subjects, BMI: Body mass index, MDRD: Modification of diet in renal disease, eGFR: estimated glomerular filtration rate. Baseline information is defined as the measurement at the latest assessment before dosing. The renal function categories are based on the MDRD eGFR.

Demographics and baseline characteristics for continuous variables - summary - FAS

	Sema Mean	(SD)	Placebo Mean	(SD)	Total Mean	(SD)
Age (years)	64.7	(7.2)	64.6	(7.5)	64.6	(7.4)
Body weight (kg)	92.33	(20.66)	91.86	(20.55)	92.09	(20.60)
Height (m)	1.675	(0.100)	1.671	(0.101)	1.673	(0.101)
Body mass index (kg/m2)	32.80	(6.23)	32.80	(6.16)	32.80	(6.20)
Waist circumference (cm)	110.1	(14.67)	110.3	(14.86)	110.2	(14.76)
HbA1c (%)	8.70	(1.45)	8.70	(1.47)	8.70	(1.46)
HbA1c (mmol/mol)	71.59	(15.90)	71.55	(16.11)	71.57	(16.01)
Fasting plasma glucose (mmol/L)	10.22	(3.72)	10.28	(3.65)	10.25	(3.68)
Fasting plasma glucose (mg/dL)	184.1	(67.06)	185.2	(65.68)	184.7	(66.37)
Duration of diabetes (years)	14.17	(8.20)	13.60	(8.02)	13.89	(8.11)

	Sema Mean	(SD)	Placebo Mean	(SD)	Total Mean	(SD)
Diastolic BP (mmHg)	76.99	(10.00)	77.10	(10.04)	77.05	(10.02)
Systolic BP (mmHg)	136.0	(17.47)	135.3	(16.82)	135.6	(17.15)
Pulse rate (beats/min)	72.11	(11.05)	71.98	(10.77)	72.05	(10.91)
LDL-cholesterol, calculated (mmol/L)	2.32	(0.95)	2.33	(0.99)	2.33	(0.97)
LDL-cholesterol, calculated (mg/dL)	89.67	(36.84)	90.08	(38.13)	89.87	(37.49)
HDL-cholesterol (mmol/L)	1.18	(0.33)	1.17	(0.33)	1.17	(0.33)
HDL-cholesterol (mg/dL)	45.45	(12.72)	45.21	(12.61)	45.33	(12.66)
MDRD GFR 'estimated' (mL/min/1.73 m2)	75.88	(25.88)	76.39	(27.19)	76.13	(26.54)

Sema: semaglutide, SD: Standard deviation, MDRD: Modification of diet in renal disease, GFR: glomerular filtration rate. The baseline value is defined as the latest pre-dosing value. Body mass index is calculated based on baseline measurement of body weight and height.

TIME TO EVENT ANALYSIS RESULTS

MACE

- EAC-confirmed MACE occurred in 108 of 1648 subjects (6.6%) in the semaglutide group and in 146 of 1649 subjects (8.9%) in the placebo group. The total number of first MACE events of 254 was more than twice as large as originally planned.
- For the primary endpoint of time to first EAC-confirmed MACE, the primary hypothesis that semaglutide would be non-inferior to placebo was confirmed, with the upper bound of the 95% CI being below 1.8 with associated p-value <0.0001. Semaglutide-treated subjects had a significantly lower risk of the primary MACE outcome/endpoint than did those receiving placebo. The hazard ratio (HR) was 0.74 $[0.58; 0.95]_{95\%CI}$ (p=0.0167), corresponding to a 26% risk reduction. Similar risk reductions were observed for the individual dose levels of semaglutide (0.5 mg and 1.0 mg).
- For the MACE components, the results for non-fatal MI (HR: 0.74 $[0.51; 1.08]_{95\%CI}$, p=0.1194) and non-fatal stroke (HR: 0.61 $[0.38; 0.99]_{95\%CI}$, p=0.0438) contributed to the favourable overall treatment effect of semaglutide on MACE. The occurrence of CV death was similar with semaglutide and placebo (HR: 0.98 $[0.65; 1.48]_{95\%CI}$, p=0.9181).
- All sensitivity analyses supported the primary analysis results.
- No differential effect on MACE was apparent for any subgroups.

Other composite CV endpoints

- Semaglutide significantly reduced the risk for the composite CV endpoint of all-cause death, non-fatal MI, non-fatal stroke by 23% versus placebo (HR 0.77 $[0.61; 0.97]_{95\%CI}$).
- Semaglutide significantly reduced the risk for the expanded composite CV endpoint of MACE, revascularisation, unstable angina requiring hospitalisation and hospitalisation for heart failure by 26% versus placebo **(**HR 0.74 $[0.62; 0.89]_{95\%CI}$).

Individual components of CV endpoints

- The estimated HRs (with 95% CIs) for the individual components of the composite CV endpoints were as follows: CV death: 0.98 $[0.65; 1.48]_{95\%CI}$; Non-fatal MI: 0.74 $[0.51; 1.08]_{95\%CI}$; Non-fatal stroke: 0.61 $[0.38; 0.99]_{95\%CI}$; All-cause death: 1.05 $[0.74; 1.50]_{95\%CI}$; Revascularisation: 0.65 $[0.50; 0.86]_{95\%CI}$; Unstable angina requiring hospitalisation: 0.82 $[0.47; 1.44]_{95\%CI}$; Hospitalisation for heart failure: 1.11 $[0.77; 1.61]_{95\%CI}$.

Microvascular endpoints

- A significant increased risk of EAC-confirmed events of diabetic retinopathy complications was observed with semaglutide (3.0%) as compared with placebo (1.8%) (HR: 1.76 $[1.11; 2.78]_{95\%CI}$). The treatment difference appeared early and continued throughout the trial. There was no increased risk seen in subjects without a history of diabetic retinopathy. The majority of subjects with EAC-confirmed events of diabetic retinopathy complications during the trial had a prior history of diabetic retinopathy, long duration of diabetes at baseline, high baseline HbA_{1c}, and insulin use. The increased risk of diabetic retinopathy complications appeared to be mediated through the larger initial rapid reduction in HbA_{1c} observed for semaglutide than for placebo.
- The risk of new or worsening nephropathy was significantly lower with semaglutide than with placebo (HR of 0.64 $[0.46; 0.88]_{95\%CI}$). The reduction in risk of events of nephropathy events was mainly driven by the component

'new onset of persistent macroalbuminuria'.
- Time to composite of diabetic retinopathy complication or new or worsening nephropathy was a secondary endpoint. The estimated HR was 0.86 $[0.66; 1.12]_{95\%CI}$.

SUMMARY CONCLUSIONS

EFFICACY RESULTS

Confirmatory secondary endpoint – change in body weight at week 104

- Superiority of semaglutide 0.5 mg and 1.0 mg in reducing body weight from baseline to week 104 was demonstrated compared with pooled placebo with estimated treatment differences of -2.95 kg $[-3.47; -2.44]_{95\%CI}$ and -4.27 kg $[-4.78; -3.75]_{95\%CI}$ with semaglutide 0.5 mg and 1.0 mg, respectively. From a mean baseline of 92.09 kg, larger reductions in body weight were seen at week 104 with semaglutide 0.5 mg (3.57 kg) and 1.0 mg (4.88 kg) compared with pooled placebo (0.62 kg).
- The robustness of the results was supported by three sensitivity analyses that produced significant estimated treatment differences that were comparable to the results of the primary analysis.

Confirmatory secondary endpoint – change in HbA_{1c} at week 30

- Superiority of semaglutide 0.5 mg and 1.0 mg in reducing HbA_{1c} from baseline to week 30 in subgroups of baseline use of SU monotherapy or premix insulin was demonstrated compared with pooled placebo.
  - For subjects on SU monotherapy at baseline, the estimated treatment differences were -1.74 %-points $[-2.28; -1.19]_{95\%CI}$ and -1.64 %-points $[-2.16; -1.12]_{95\%CI}$ with semaglutide 0.5 mg and 1.0 mg, respectively, compared with pooled placebo.
  - For subjects on premix insulin at baseline, the estimated treatment differences were -0.86 %-point $[-1.06; -0.66]_{95\%CI}$ and -1.37 %-points $[-1.57; -1.17]_{95\%CI}$ with semaglutide 0.5 mg and 1.0 mg, respectively, compared with pooled placebo.
  - The robustness of the results for each of the subgroups for the confirmatory secondary endpoint was supported by five different sensitivity analyses that produced significant estimated treatment differences that were comparable to the results of the primary analysis.

Supportive secondary efficacy endpoints

HbA_{1c} at week 104:

- At week 104, larger reductions in HbA_{1c} was seen with semaglutide 0.5 mg (-1.09 %-point) and 1.0 mg (-1.41 %-point) compared with placebo 0.5 mg (-0.44 %-point) and placebo 1.0 mg (-0.36 %-point). Semaglutide 0.5 mg and 1.0 mg significantly reduced HbA_{1c} compared with their respective placebo groups with estimated treatment differences of -0.66 %-point $[-0.80; -0.52]_{95\%CI}$ and -1.05 %-point $[-1.19; -0.91]_{95\%CI}$.

Requirement of additional glucose-lowering medication:

- At week 104, fewer subjects with semaglutide 0.5 mg and 1.0 mg (21% and 19%) had required additional glucose-lowering medication during the trial compared with placebo 0.5 mg and 1.0 mg (42% and 39%) in an attempt to achieve target glycaemic control. The estimated odds were 0.33 $[0.27; 0.42]_{95\%CI}$ and 0.35 $[0.27; 0.44]_{95\%CI}$ with semaglutide 0.5 mg and 1.0 mg, respectively, vs the respective placebo group.
- At week 30, addition of glucose-lowering medication did not favour the semaglutide treatment effect in the subgroups of premix insulin or SU monotherapy
  - The proportion of subjects with addition of glucose-lowering medication for subjects on premix insulin at baseline was low for all three treatment groups and was not significantly different with semaglutide 0.5 mg (6.3%) or semaglutide 1.0 mg (3.7%) compared with pooled placebo (4.7%).
  - The proportion of subjects with addition of glucose-lowering medication for subjects on SU monotherapy at baseline was significantly lower with semaglutide 0.5 mg (3.6%) and appeared lower with semaglutide 1.0 mg (12.9%) compared with pooled placebo (31.3%).

Glucose metabolism:

- FPG decreased significantly more from baseline to week 104 with semaglutide 0.5 mg and 1.0 mg compared with the respective placebo group with estimated treatment differences of -0.72 mmol/L $[-1.06; -0.38]_{95\%CI}$ and -1.22 mmol/L $[-1.56; -0.88]_{95\%CI}$, respectively (-13.05 mg/dL $[-19.17; -6.94]_{95\%CI}$ and -22.03 mg/dL $[-28.15; -15.91]_{95\%CI}$).

Lipids:

- Overall, circulating lipids improved with semaglutide 1.0 mg treatment compared with placebo 1.0 mg, albeit the changes were modest.
  - With semaglutide 1.0 mg, levels of free fatty acids, HDL-cholesterol and triglycerides significantly improved at

week 104 compared with placebo 1.0 mg, with estimated treatment ratios of 0.92 [0.88; 0.96]$_{95\%CI}$, 1.04 [1.02; 1.06]$_{95\%CI}$ and 0.93 [0.89; 0.97]$_{95\%CI}$, respectively, while there were no significant differences for total cholesterol and LDL-cholesterol.

– With semaglutide 0.5 mg, levels of total cholesterol, and LDL-cholesterol significantly improved at week 104 compared with placebo 0.5 mg, with estimated treatment ratios of 0.97 [0.95; 1.00]$_{95\%CI}$ and 0.96 [0.93; 0.99]$_{95\%CI}$, respectively, while there were no significant differences for free fatty acids, HDL-cholesterol and triglycerides.

Blood pressure:

- Systolic blood pressure was significantly reduced at week 104 with semaglutide 1.0 mg compared with placebo 1.0 mg with an estimated treatment difference of -2.59 mmHg [-4.09; -1.08]$_{95\%CI}$, while there was no significant difference with semaglutide 0.5 mg compared with placebo 0.5 mg.
- Diastolic blood pressure was not significantly changed with semaglutide treatment compared with placebo.

PROs:

- The SF-36v2^{TM} mental and physical summary component scores both significantly improved with semaglutide 1.0 mg vs placebo 1.0 mg, whereas there was no significant difference with semaglutide 0.5 mg vs placebo 0.5 mg.

SAFETY RESULTS

During the 104 weeks of treatment, semaglutide was generally safe and well-tolerated, and overall, the safety and tolerability was consistent with other GLP-1RAs.

Overall AE safety profile

- A total of 132 subjects died during the trial (from randomisation to database lock). Of these, 122 subjects (3.7%) died during the 2-year in-trial period as determined by the EAC, with the 10 remaining deaths (5 with semaglutide and 5 with placebo) occurring after the in-trial period and before database lock. Of the 122 deaths during the in-trial period, 90 deaths were categorised as CV deaths (comprising confirmed CV deaths and deaths due to undetermined causes), corresponding to mortality rates of 1.2, 1.4 and 1.4 deaths per 100 patient years of observation with semaglutide 0.5 mg, 1.0 mg and placebo, respectively. The remaining 32 deaths during the in-trial period were adjudicated as non-CV deaths, corresponding to mortality rates of 0.5, 0.5 and 0.4 deaths per 100 patient years of observation with semaglutide 0.5 mg, 1.0 mg and placebo, respectively. The types of AEs with fatal outcome were similar with semaglutide and placebo.
- The proportion of subjects reporting AEs was similar with semaglutide and placebo (0.5 mg: 88.9%; 1.0 mg: 88.2%; placebo: 88.4%), whereas the corresponding rate was higher with semaglutide than with placebo (0.5 mg: 334.7 events per 100 patient years of exposure (PYE); 1.0 mg: 350.2 events per 100 PYE; placebo: 313.2 events per 100 PYE). The difference was mainly driven by more gastrointestinal (GI) AEs reported with semaglutide than with placebo.
- The majority of AEs were of mild or moderate severity and for most of the AEs, the subjects had recovered or were recovering at the end of trial.
- The most frequently reported AEs in subjects treated with semaglutide were within the system organ class (SOC) of GI disorders (nausea, vomiting and diarrhoea) whereas the most frequently reported AEs in subjects treated with placebo were within the SOC of infections and infestations.
- The proportion of subjects reporting serious adverse events (SAEs) was lower with semaglutide than with placebo (0.5 mg: 32.1%; 1.0 mg: 29.3%; placebo: 34.9%). Only the proportion of serious GIAE was higher with semaglutide than with placebo. There was no other consistent pattern in reported SAEs across treatment groups or preferred terms. As expected in the population enrolled in this cardiovascular outcomes trial, SAEs were most frequently reported in the SOC cardiac disorders across all treatment groups.
- The proportion of subjects with AEs leading to premature treatment discontinuation was higher with semaglutide (0.5 mg: 11.5%; 1.0 mg: 14.5%) than with placebo (6.7%). This treatment difference was primarily due to GI AEs with onset during the first 20 weeks. After 30 to 35 weeks, the frequency of AEs leading to premature treatment discontinuation was similar for all treatment groups.
- Despite the increased number of GI AEs with semaglutide 1.0mg, the overall AE safety profile remained unchanged in subjects receiving the high maintenance dose.

Hypoglycaemia

- Across all treatment groups, approximately 20% of the subjects reported one or more ‘severe or blood glucose (BG) confirmed symptomatic’ episodes.
- There were no statistically significant differences between semaglutide and placebo with respect to number of

episodes or subjects experiencing severe or BG confirmed symptomatic hypoglycaemic episodes, including nocturnal episodes.

- Only few episodes of severe hypoglycaemia were reported (68 in total) and they were evenly distributed across treatment groups. All subjects recovered from the severe episodes.
- Generally, for all groups, SU and/or insulin was the background medication at the time of episode for most of the severe or BG confirmed symptomatic hypoglycaemic episodes.

Safety areas of interest

Gastrointestinal disorders:

- The rates of GI AEs were higher with semaglutide 0.5 mg and 1.0 mg than with placebo (81.2, 94.9 and 40.5 events per 100 PYE respectively). The most frequently (≥5% of the subjects) reported AEs were 'nausea', 'diarrhoea', 'vomiting', 'constipation', 'dyspepsia', 'abdominal pain upper' and 'abdominal pain', the majority of which were non-serious and of mild or moderate severity.
- The majority of the events occurred within the initial 3 to 4 months of treatment and the median durations of the GI AEs 'nausea', 'diarrhoea' and 'vomiting' were between 2 and 7 days with all 3 treatment groups (semaglutide 0.5 mg and 1.0 mg and placebo).

Cardiovascular disorders:

- Results on all EAC-confirmed CV events and CV AEs identified by MedDRA search confirmed the conclusions based on time-to-first event analyses of EAC-confirmed first CV events
- 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 2.75 bpm $[1.75; 3.75]_{95\%CI}$ and 3.20 bpm $[2.20; 4.21]_{95\%CI}$, respectively.

Pancreatitis:

- EAC-confirmed events of pancreatitis were balanced with semaglutide and placebo (semaglutide 0.5 mg: 5 events; semaglutide 1.0 mg: 3 events; placebo: 10 events).
- Estimated treatment ratios for lipase and amylase from baseline to end of treatment (week 104) were significantly higher with both semaglutide doses compared to placebo doses (0.5 mg: 1.26 $[1.20; 1.32]_{95\%CI}$ and 1.11 $[1.08; 1.14]_{95\%CI}$, respectively; 1.0 mg: 1.32 $[1.26; 1.39]_{95\%CI}$ and 1.17 $[1.13; 1.20]_{95\%CI}$, respectively). The clinical relevance of these findings is currently unknown.
- Very few subjects with lipase and/or amylase levels >3xupper limit of normal (ULN) experienced EAC-confirmed pancreatitis. The evidence does not support that the elevation of pancreatic enzymes seen with semaglutide predicts the development of pancreatitis, although the well-known relationship between a confirmed diagnosis of pancreatitis and the confirmatory elevation of lipase and/or amylase was maintained.

Hepatobiliary disorders:

- The proportions of subjects with gallbladder-related AEs (3.5%, 3.2% and 3.4%) and SAEs (1.3%, 0.5% and 1.2%) were similar across the semaglutide 0.5 and 1.0 mg and placebo groups, respectively. With semaglutide, the most frequent gallbladder-related AE was cholelithiasis, of which few events were serious or severe; the proportion of subjects with such events was similar with semaglutide and placebo.
- The number of subjects with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels > 3x or >5xULN was low and balanced between semaglutide (0.5 and 1.0 mg) and placebo groups. Six (6) subjects with concurrent ALT/AST >3xULN levels and total bilirubin >2xULN levels (1 with semaglutide 0.5 mg; 2 with semaglutide 1.0 mg and 3 with placebo) all had plausible alternative aetiologies that explained the changes in liver parameters, and in accordance with the FDA guidance these changes were not consistent with drug induced liver injury.

Neoplasms:

- The proportion of subjects with EAC-confirmed neoplasms overall was 9.4% in the semaglutide vs 8.4% in the placebo group. The corresponding proportions were 5.7% vs 4.2% for EAC-confirmed benign neoplasms, and 4.0% vs 4.2% for EAC-confirmed malignant neoplasms with semaglutide and placebo, respectively. Applied *post hoc* statistical analyses indicated no apparent differences between semaglutide and placebo groups across the groups of EAC-confirmed neoplasms.
- Slightly more subjects had EAC-confirmed neoplasms with semaglutide 1.0 mg than with semaglutide 0.5 mg and placebo. This finding was consistent with neoplasms identified by the MedDRA search.
- The higher proportion of subjects with benign neoplasms and rate of events with semaglutide 1.0 mg was primarily driven by colorectal and skin neoplasms.

- The most frequent malignant neoplasms were skin, male reproductive, lung/bronchus and colorectal with an overall distribution of EAC-confirmed malignant neoplasms across several organ/tissue sites of origin and with no observed pattern of clustering within specific organ sites
- No C-cell cancers were reported in the trial.
- There were no clinically relevant changes in calcitonin values throughout the treatment period within or between treatment groups.
- The proportion of subjects with thyroid, pancreas and malignant colorectal neoplasms as well as event rates were similar with semaglutide and placebo.
- The higher proportion of subjects with malignant neoplasms observed with semaglutide 1.0 mg was primarily driven by skin, although numbers were small and they should be interpreted with caution.
- Applied *post hoc* statistical analyses indicated no apparent treatment differences in any of the specific types EAC-confirmed malignant neoplasms.

Renal disorders:

- The proportion of subjects with AEs and SAEs of acute renal failure (broad MedDRA search) were similar between semaglutide 0.5 mg (8.0% and 2.1%) and placebo (7.7% and 2.1%); compared with those two groups, the frequency was lower with semaglutide 1.0 mg (4.9% and 1.1%). The most common SAE was acute kidney injury, which was less frequent with semaglutide 1.0 mg than with semaglutide 0.5 mg and placebo
- Semaglutide treatment was associated with an initial decrease in the estimated glomerular filtration rate (eGFR), particular in subjects with normal renal function or mild renal impairment at baseline. With placebo, the eGFR decreased at a more constant and higher rate than with semaglutide throughout the trial. At week 104, the eGFR did not differ significantly between the groups.

Anti-semaglutide antibodies:

- Anti-semaglutide antibody formation was low; 30 subjects (1.9%) were tested positive for anti-semaglutide antibodies at any time point post-baseline; 11 subjects (1.4%) in the semaglutide 0.5 mg treatment group and 19 subjects (2.3%) in the semaglutide 1.0 mg treatment group. Of the subjects developing anti-semaglutide antibodies, 19 subjects (63.3%) had anti-semaglutide antibodies cross-reacting to endogenous GLP-1. The level of anti-semaglutide antibodies in subjects that tested positive for anti-semaglutide antibodies was low; individual levels ranged up to 12.97 %-bound radioactivity/total radioactivity. At follow-up, 4 subjects (0.3%) were tested positive for anti-semaglutide antibodies and no subjects had anti-semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect. There did not appear to be any influence of the presence of anti-semaglutide antibodies on the efficacy of semaglutide, as seen from HbA_{1c} levels over time in subjects that tested positive for anti-semaglutide antibodies.

CONCLUSIONS

This trial with known vital status for 99.6% of subjects, achieved its primary objective of showing non-inferiority of semaglutide vs placebo in terms of MACE by ruling out an 80% increased risk.

- Semaglutide significantly reduced the risk for MACE by 26% vs placebo.
  - The MACE risk reduction was driven by risk reductions for non-fatal stroke and non-fatal myocardial infarction.
- Semaglutide significantly improved glycaemic control and was superior in reducing body weight compared to placebo after 2 years in the trial.
  - Semaglutide 0.5 mg and 1.0 mg was superior to placebo in reducing HbA_{1c} at week 30 in subgroups on SU monotherapy or premix insulin at baseline.
  - Significantly fewer subjects with semaglutide compared with placebo required additional glucose-lowering medication to achieve target glycaemic control.
- For microvascular complications, an increased risk of EAC-confirmed events of diabetic retinopathy complications during the trial was observed with semaglutide relative to placebo. The treatment difference appeared early and continued throughout the trial. There was no increased risk seen in subjects without a history of diabetic retinopathy. The majority of subjects with EAC-confirmed events of diabetic retinopathy complications during the trial had a prior history of diabetic retinopathy, long duration of diabetes at baseline, high baseline HbA_{1c}, and insulin use. The increased risk of diabetic retinopathy complications appeared to be mediated through the larger initial rapid reduction in HbA_{1c} observed for semaglutide than for placebo. In contrast, semaglutide significantly reduced the risk of nephropathy events.
- Semaglutide was generally well-tolerated. Except for an observed increase in risk of diabetic retinopathy

complications, the overall safety profile of semaglutide was in accordance with the known GLP-1 receptor agonist class effects, with the notable exception of a reduced risk of MACE with semaglutide relative to placebo when added to standard-of-care in the investigated high CV risk population.

The trial was conducted in accordance with the Declaration of Helsinki (2013) and ICH Good Clinical Practice (1996) and EN ISO 14155 Part 1 and 2 and 21 CFR 312.120.

CTR Synopsis Addendum − Germany

PROTOCOL AMENDMENT(S)
As of 24-Oct-2016, the following protocol amendments have been made to the original protocol, version 1.0, dated 22-Aug-2012.

Amendment number	Issue date	Countries affected	Key changes
1	23-Sep-2012	Israel	All relevant sections regarding collection of blood sample for genetic testing in the protocol were deleted, due to long approval process for genetic testing in Israel.
2	17-Sep-2012	Argentina	To reflect requirements from health authority (HA), it was specified that for Argentina, all diabetic treatments throughout the trial were covered by Novo Nordisk Pharma Argentina S.A.
3	13-Nov-2012	United Kingdom	Following request from the MHRA it was specified that for women of childbearing potential two effective forms of contraception were to be used with their partners.
4	07-May-2013	Global	To accommodate a request from FDA and changes in FDA requirements the primary objective, the statistical section and other relevant sections were updated accordingly. Additional minor updates were made.
5	06-Mar-2013	Denmark	Change in principal investigator (PI) at 1 site.
6	13-Mar-2013	Argentina	Information that trial product should be discontinued in case of occurrence of a serious adverse event (SAE) suspected to be related to the trial product was added as requested by HA.
7	01-Apr-2013	Turkey	Change in PI at 2 sites, addition of 2 new sites.
8	NA	NA	Not in use, cancelled
9	NA	NA	Not in use, cancelled
10	13-May-2013	Bulgaria	Addition of 1 new site.
11	07-Oct-2013	Israel	Dietary counselling was added as part of the retention strategy in Israel.
12	04-Nov-2013	Brazil	To reflect requirements from HA, changes in protocol Section 8.4 Laboratory Assessments and Section 8.7.6 Thyroidectomy, tissue sample and genetic testing were made.
13	13-May-2014	Global	The definition of hypoglycaemia was updated incl. related endpoints, associated statistical analysis and how to report. Additional minor updates for clarification.
14	18-Feb-2014	Bulgaria	New content in patient chronicle to be submitted to HA/ethics committee (EC) locally
15	04-Nov-2014	Bulgaria	New content in patient chronicle to be submitted to HA/EC locally.
16	29-Jan-2015	Bulgaria	New content in patient chronicle to be submitted to HA/EC locally.
17	04-Aug-2015	Bulgaria	New edition of patient chronicle, thank you letter and leaflet on maintaining good health to be submitted to HA/EC locally
18	14-Oct-2015	Bulgaria	New content in patient chronicle to be submitted to HA/EC locally.

TRIAL SITES – additional information
The following trial sites randomised/assigned subjects to treatment in the trial.

Site no.	Address	Country
[redacted]	Internal medicine department -EHU 01 Novembre 1954-Oran-Algeria	Algeria
[redacted]	Internal Medicine department Lamali Ahmed - Tizi Ouzou- Algeria	Algeria
[redacted]	Internal medicine department - Saadna Mohamed hospital – Sétif-Algeria	Algeria
[redacted]	Endocrinology department - IBN SINA Hospital-Annaba-Algeria	Algeria
[redacted]	Fundación Sanatorio Güemes - Francisco Acuña de Figueroa 1240 - CABA (C1180AAX)	Argentina
[redacted]	Hospital Sirio Libanés - Fernández de Enciso 4620 - CABA (C1419AHN) -	Argentina
[redacted]	Centro Diabetológico Dr. Waitman - Av. Velez Sarfield 576 6°"A" Cordoba (5003)	Argentina
[redacted]	CIAD Moron – Belgrano 244 – Moron - (B1708IFF)	Argentina
[redacted]	CENUDIAB – Av. Juan B. Alberdi 5275 depto. 4 – CABA - (C1440AAD)	Argentina
[redacted]	Hospital Universitario Fundación Favaloro - Av. Belgrano 1746 - CABA (C1093AAS)	Argentina
[redacted]	Instituto de Investigaciones Clínicas Mar del Plata – Av. Colon 3364 – Mar del Plata (B7600FZN)	Argentina
[redacted]	Repatriation General Hospital Southern Adelaide Diabetes & Endocrine Services Daws Road DAW PARK SA 5041	Australia
[redacted]	Box Hill Diabetes and Endocrine Services Suite [redacted] Nelson Road BOX HILL VIC 3128	Australia
[redacted]	Blacktown Clinical School Blacktown Hospital. Marcel Cres BLACKTOWN NSW 2148	Australia
[redacted]	St Vincent's Hospital Department of Endocrinology [redacted] Daly Wing, 35 Victoria Pde	Australia

Site no.	Address	Country
	FITZROY VIC 3065	
[redacted]	South Australian Endocrine Research Pty Ltd 8a Hampton Road Keswick SA 5035	Australia
[redacted]	Royal North Shore Hospital Endocrine Department Level [redacted], Acute Services Building Pacific Highway ST LEONARDS NSW 2065	Australia
[redacted]	School of Medicine and Pharmacology Level [redacted] T Block Alma Street Fremantle Hospital FREMANTLE WA 6160	Australia
[redacted]	Ipswich Hospital Health Plaza 21 Bell St, IPSWICH QLD 4305	Australia
[redacted]	Centro de Pesquisa Clínica em Diabetes e Obesidade do Hospital do Rim e Hipertensão, Fundação Oswaldo Ramos – UNIFESP Fundação Oswaldo Ramos – UNIFESP R. Borges Lagoa, 971 –5º andar- salas 51 e 52- São Paulo SP – CEP: 04038-002	Brazil
[redacted]	CPCLIN - Centro de Pesquisas Clínicas R. Goiás, 193 Higienópolis- São Paulo , SP 01244-030	Brazil
[redacted]	Disciplina de Endocrinologia - HC FMUSP Av. Dr. Enéas de Carvalho Aguiar, 155. 4º andar - Bloco 15- São Paulo, SP 05403-900	Brazil
[redacted]	PUCCAMP - Hospital e Maternidade Celso Pierro Disciplina de Cardiologia - Divisão de Pesquisa Clínica Av. John Boyd Dunlop, s/n Jardim Itaussurama- Campinas, SP 13059-740	Brazil
[redacted]	Hospital de Clínicas da Universidade Federal do Paraná Av. Agostinho Leão Júnior, 285 - Alto da Glória- Curitiba, Paraná 80030-110	Brazil
[redacted]	Centro de Pesquisas em Diabetes Ltda. Rua Gonçalo de Carvalho, 412 Bairro Floresta- Porto Alegre, RS 90035-170	Brazil
[redacted]	Hospital Universitário João de Barros Barreto - UFPA Rua dos Mundurucus, 4487, Térreo Setor de Pesquisa Clínica- Belém , Para	Brazil

Site no.	Address	Country
	66073-000	
[redacted]	Current site: CPQuali Pesquisa Clínica Ltda Avenida Angélica, 916 - Conjunto 506 Santa Cecília-São Paulo, SP 01228-000 Former site: Endoclínica Avenida 9 de Julho, 3858, Jardins, São Paulo, São Paulo, 01406-100, Brazil	Brazil
[redacted]	MMA MHAT, Clinic of Endocrinology and Metabolic Diseases 3 “Sv. Georgi Sofijski” Str., 1606 Sofia Bulgaria	Bulgaria
[redacted]	MHAT ”Sveta Marina”, Clinic of Endocrinology and Metabolic Diseases 1 “Hr. Smirnenski” str. 9010 Varna Bulgaria	Bulgaria
[redacted]	UMHAT “Dr. Georgi Stranski” , Department of Endocrinology and Metabolic Diseases 91 “Gen. Vladimir Vazov” str. 5800 Pleven Bulgaria	Bulgaria
[redacted]	CCB SAI Ministry of interior, Department of Endocrinology 79 “Skobelev” Blvd. 1606 Sofia Bulgaria Note: The site name changed to: Medical Institute of Ministry of interior, MHAT - Central Clinical Base in Sofia, Department of Endocrinology and Metabolic Diseases 79 “Skobelev” Blvd. 1606 Sofia Bulgaria	Bulgaria
[redacted]	DCC XII-Sofia EOOD, Endocrinology Consulting room 17 “Korenyak” str., 1324 Sofia Bulgaria	Bulgaria
[redacted]	St. Michael’s Health Centre 61 Queen Street East, Room [redacted] Toronto, ON M5C 2T2	Canada
[redacted]	Applied Medical Informatics Research 100-4427 Sherbrooke Street West, Westmount, QC H3Z 1E5	Canada

Site no.	Address	Country
[redacted]	Winnipeg Regional Health Authority Health Sciences Centre Winnipeg Diabetes Research Group 838-715 McDermot Ave Winnipeg, MB R3E 3P4	Canada
[redacted]	601-73 Water Street North Cambridge, ON N1R 7L6	Canada
[redacted]	University of Alberta Alberta Diabetes Institute 2-004 Li Ka Shing Centre for Health Research Innovation 87 Avenue - 112 Street Edmonton, AB T6G 2E1	Canada
[redacted]	Canadian Centre For Research On Diabetes 218 Percy Street Smiths Falls, ON K7A 4W8	Canada
[redacted]	Institut universitaire de cardiologie et de pneumologie de Quebec Recherche en medecine interne 2725, chemin Sainte-Foy Quebec, QC G1V 4G5	Canada
[redacted]	St. Joseph's Health Care 268 Grosvenor Street, Room [redacted] London, ON N6A 4V2	Canada
[redacted]	Medexa Recherche 7-39 rue Laurier Est Victoriaville, QC G6P 6P6	Canada
[redacted]	C-endo Diabetes and Endocrinology Clinic Suite [redacted], 1016-68th Ave SW Calgary, AB T2V 4J2	Canada
[redacted]	Scisco Clinical Research 820 McConnell Avenue, Suite# [redacted] Cornwall, ON K6H 4M4	Canada
[redacted]	Rhodin Recherche Clinique 110 St-Jean, Suite [redacted] Drummondville, QC J2B 7T1	Canada
[redacted]	Sameh Fikry Medicine Professional Corporation 149 Union Street East Waterloo, ON N2J 1C4	Canada
[redacted]	Gentofte Hospital Kildegårdsvej 28	Denmark

Site no.	Address	Country
	Opgang 7, 3. sal Center for Diabetesforskning 2900 Hellerup Denmark	
[redacted]	Steno Diabetes Center Den Kliniske Forskningsenhed Niels Steensensvej 2 Bygning NSH, 4.sal 2820 Gentofte Denmark	Denmark
[redacted]	Hvidovre Hospital Med. endokrinologisk amb. 541 Kettegårds alle 30 2650 Hvidovre Denmark	Denmark
[redacted]	Odense Universitetshospital Endokrinologisk afdeling M Kløvervænget 6, 3. sal 5000 Odense Denmark	Denmark
[redacted]	Aarhus Universitetshospital THG Klinisk Ernæringsforskning Indgang 4A Tage Hansensgade 2 8000 Århus C Denmark	Denmark
[redacted]	Dr. med. Andreas Hagenow Zentrum für KlinischeStudien Südbrandenburg GmbH Lange Str. 13 04910 Elsterwerda	Germany
[redacted]	Dr. med. Jörg Lüdemann Poststr. 46 + 48-50 14612 Falkensee	Germany
[redacted]	Dr. med, Ludger Rose Institut für Diabetesforschung GmbHHohenzollernring 70 48145 Münster	Germany
[redacted]	Dr. med. Thomas Schaum Sana Kliniken Ostholstein GmbH Klinik Oldenburg Mühlenkamp 5 23758 Oldenburg Since 3-Jul-2014 new Site name: RED-Institut für medizinische Studien und Fortbildung GmbH	Germany
[redacted]	Prof. Dr. med. Jochen Seufert Universitätsklinikum Freiburg Klinik für Innere Medizin II Hugstetter Str. 55 79106 Freiburg	Germany
[redacted]	Dr. med. Michael Esser Hauptstr. 54 45219 Essen	Germany
[redacted]	Dr. med. Andreas Klinge	Germany

Site no.	Address	Country
	Gemeinschatfspraxis für innere Medizin Beseler Str. 2a 22607 Hamburg	
[redacted]	Endrocrinolgy Clinic Sheba Medical Center, Tel-Hashomer 1 Emek Ha'ela street Ramat-Gan, 52621 Israel	Israel
[redacted]	Institute of Endocrinology, Metabolism and Diabetes Rabin Medical Center Beilinson Campus 39 Zabotinsky street Petach-Tikva, 49100 Israel	Israel
[redacted]	Diabetes Unit Hadassah Ein Karem MC Kiryat Hadassah street Jerusalem, 91120 Israel	Israel
[redacted]	Institute of Endocrinology, metabolism and hypertension, Sourasky Medical Center, 6 Weizmann Street Tel-Aviv, 64239 Israel	Israel
[redacted]	Diabetes Clinic Wolfson Medical Center , 62 Halochamim street, Holon, 58100 Israel	Israel
[redacted]	Diabetes, Endocrinology and Metabolism Institute Western Galilee Hospital, 89 Road, P.O.B 21 Nahariya, , 22100 Israel	Israel
[redacted]	Azienda Ospedaliera di Padova U.O. Clinica Medica 3 c/o 9° piano monoblocco via Giustiniani, 2 35128 - Padova	Italy
[redacted]	Ospedale Maggiore "C. A. Pizzardi" Largo Nigrisoli, 2 40133 - Bologna	Italy
[redacted]	Ospedale San Giovanni di Dio via Canova 07026 - Olbia	Italy
[redacted]	Fondazione Università degli studi "G. D'Annunzio" - CESI Centro di Ricerca Clinica Via Colle dell'Ara 66013 – Chieti Scalo	Italy
[redacted]	A.O. Papa Giovanni XXIII Day Hospital Diabetologia - Torre n°2	Italy

Site no.	Address	Country
	piano Piazza OMS - Organizzazione Mondiale della Sanità, 1 24127 - Bergamo	
[redacted]	Azienda Ospedaliera Universitaria Senese U.O. Diabetologia 3 lotto piano 5S Viale Mario Bracci, 16 53100 - Siena	Italy
[redacted]	Sarawak General Hospital Medical Clinic, (Pintu K), [redacted] Specialist Block, Hospital Umum Sarawak, Jalan Tun Ahmad Zaidi Adruce, 93586 Kuching, Malaysia.	Malaysia
[redacted]	Sarawak General Hospital Heart Centre Jalan Lingkaran Luar Kuching, CRC, Sawarak General Hospital Heart Centre, 94300 Kota Samarahan, Sarawak, Malaysia.	Malaysia
[redacted]	Hospital Melaka CRC, Hospital Melaka Jalan Mufti Haji Khalil 75400, Melaka, Malaysia.	Malaysia
[redacted]	Columbia Asia Medical Centre Internal Medicine Suite, Columbia Asia Medical Centre, Jalan Haruan 2,Oakland Commercial Center 70300 Seremban, Negeri Sembilan, Malaysia	Malaysia
[redacted]	Pusat Perubatan Universiti Malaya, Clinical Investigational Centre, Main Tower, [redacted] Pusat Perubatan University Malaya, Lembah Pantai, Kuala Lumpur 59100, Malaysia.	Malaysia
[redacted]	Hospital Serdang, Cardiology Clinic, Level [redacted] Hospital Serdang, Jalan Puchong,43000 Serdang,Selangor, Malaysia	Malaysia
[redacted]	Cardioarritmias e Investigación Magallanes # 255, Col. Burócratas del Estado, San Luis Potosí, San Luis Potosí, Mexico, CP 78200	Mexico
[redacted]	Instituto de Diabetes obesidad y	Mexico

Site no.	Address	Country
	Nutrición S.C. 5 de Mayo No 400 Col. El empleado, Cuernavaca, Morelos, Mexico, CP 62250	
[redacted]	CICEJ Centro de Investigación Clínica Endocrinológica de Jalisco S.C. Tarascos #3469 INT. 505-503 y 503-A, Col. Fraccionamiento Monraz, Guadalajara, Jal. Mexico, C.P. 44670.	Mexico
[redacted]	Clínicos Asociados BOCM, S.C. Victor Hugo 191-bis altos, Col. Portales Sur, Delegación Benito Juárez, México DF, CP 03300, México	Mexico
[redacted]	Centro de Estudios de Investigación Metabólicos y Cardiovasculares S.C. Altamira No. 104 Oriente, zona centro, CP 89000 Tampico Tamaulipas, Mexico.	Mexico
[redacted]	Ultimate Medica, S.A. de C.V. Av. Alfredo de Musset No. 44, colonia Polanco, Del. Miguel Hidalgo, CP 11550, México DF, México. (entrada de pacientes por Anatole France No 145 Col. Polanco)	Mexico
[redacted]	Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán" Unidad del paciente ambulatorio, 5to piso, Clínica de obesidad Vasco de Quiroga 15, Col. Sección XVI , Del. Tlalpan, México, D. F., CP14000	Mexico
[redacted]	República del Perú No. 202. Fraccionamiento Las Americas C.P.20230, Aguascalientes, Ags.	Mexico
[redacted]	Centro de Investigación Médico Biológica y Terapia Avanzada, S.C. Severo Diaz No.27, Col. Arcos Vallarta, CP. 44130, Guadalajara, Jalisco	Mexico
[redacted]	SPSK nr 1 im. Prof. Stanisława Szyszko ŚUM w Katowicach Poradnia Chorób Metabolicznych i Diabetologii ul. 3-go Maja 13/15, Budynek nr 4, 41-800 Zabrze, Poland (Until 30.09.2014) Poradnia Diabetologiczna, SPSK Nr 1 im. Prof. Stanisława Szyszko Śląskiego Uniwerystetu Medycznego w Katowicach, ul. 3 Maja 13-15, 41-800 Zabrze. (from 1.10.2014)	Poland
[redacted]	NSZOZ Ośrodek Diabetologiczny, Popula S.C. Al. Piłsudskiego 4a lok. 1 15-445 Białystok, Poland	Poland

Site no.	Address	Country
[redacted]	Niepubliczny Zakład Opieki Zdrowotnej (NZOZ) Gdańska Poradnia Cukrzycowa Sp. z o.o. ul. Wałowa 27, 80-858 Gdańsk, Poland	Poland
[redacted]	Synexus Polska Sp. z o.o. Oddział w Warszawie ul. Leszno 12 01-192 Warszawa, Poland	Poland
[redacted]	„CenterMed Lublin" Sp. z o.o. Ul. Weteranów 46 20-044 Lublin	Poland
[redacted]	The State Budgetary Educational Institution of Higher Professional Learning " the First Moscow State Medical University n.a. I.M. Sechenov" of the Ministry of Health Care and Social Development, endocrinology department 119991, Russia, Moscow, 8, Trubetskaya street, bld.2, on the base of University clinic #2, 119435, Pogodinskaya street, 1, b.1	Russia
[redacted]	The State Healthcare Institution of Additional Professional Learning "Penza Medical Refresher Institute" of Federal Agency for Public Health and Social Development 28, Lermontova, str., 440026, Penza	Russia
[redacted]	The State Healthcare Institution "Regional Clinical Hospital", endocrinology department 410053, Russia, Saratov, 1, Smirnovskoye ushelje	Russia
[redacted]	Municipal Healthcare Institution "Municipal Hospital № 5" 75, Zmeinogorsky tract, 656045, Barnaul	Russia
[redacted]	The State Budgetary Educational Institution of Higher Professional Learning "Novosibirsk State Medical University" of the Ministry of Health Care and Social Development, 630091, Russia, Novosibirsk, 52, Krasniy avenue, on the base of the Municipal Healthcare Institution "Municipal Clinical Hospital № 1", 630047, Russia, Novosibirsk, 6, Zalesskogo street	Russia
[redacted]	The State Budgetary Healthcare Institution of Arkhangelsk Region "the First Municipal Clinical Emergency Hospital n.a. E.E. Volosevich" 1, Suvorova str., 163045, Arkhangelsk	Russia
[redacted]	The State Healthcare Institution of Yaroslavl Region "Regional Clinical Hospital" 7, Yakovlevskaya str., 150062, Yaroslavl	Russia
[redacted]	The State Budgetary Educational Institution of Higher Professional Learning "Smolensk State Medical University" of the Ministry of Health Care and Social Development, 214019, Russia, Smolensk, 28, Krupskoy street, on the base of Centre for clinical studies of diagnostic tools and drugs, 214019, Russia, Smolensk, 46-a, Kirova street	Russia

Site no.	Address	Country
[redacted]	The State Budgetary Educational Institution of Higher Professional Learning "Kazan State Medical University", 420012, Russia, Tatarstan Republic, Kazan. 49, Butlerova street, on the base of Republican Clinical Hospital, 420064, Tatarstan Republic, Kazan, 11, Mushtari	Russia
[redacted]	Municipal Healthcare Institution "City Clinical Hospital #9" 410012, Saratov, Bolshaya Gornaya str., 43	Russia
[redacted]	Policlinic #1 at Russian Scientific Academy 199034, Saint Petersburg, Universitetskaya nab., 5	Russia
[redacted]	Hospital Quirón Consulta de Endocrinología, 3ª Planta C/ Diego de Velázquez, 1 28223 Pozuelo de Alarcón (Madrid)	Spain
[redacted]	Clínica San Pedro Plaza de San Pedro, 5; 1-3 Servicio de Endocrinología 04001 Almería	Spain
[redacted]	Hospital Comarcal de Antequera Avda. Poeta Muñoz Rojas, s/n Servicio de Medicina Interna Secretaría - Planta 4ª - Area Hospitalización 29200 Antequera (Málaga)	Spain
[redacted]	Hospital Infanta Luisa Consultas Externas - Servicio de Endocrinología Unidad de Diabetes San Jacinto, 87 41010 Sevilla	Spain
[redacted]	CAP El Remei Passatge Pla del Remei, 10-12 Unidad de Ensayos Clínicos Equipo de Atención Primaria de Vic 08500 Vic (Barcelona)	Spain
[redacted]	Hospital Virgen del Camino Servicio de Medicina Interna Carretera Chipiona, km. 0,6 11540 Sanlúcar de Barrameda (Cádiz)	Spain
[redacted]	Chung Gung Medical Foundation- Linkou Branch 5, Fushing St., Gueishan, Taoyuan, 333, Taiwan	Taiwan
[redacted]	Tri-Service General Hospital No 325, Sec.2, Chen-Kung Rd., Neihu 11490, Taipei, Taiwan	Taiwan
[redacted]	Ditmanson Medical Foundation Chia-Yi Christian Hospital No. 539, Zhongxiao Rd, East District, Chiayi City, 600, Taiwan	Taiwan

Site no.	Address	Country
[redacted]	Chi-Mei Medical Center No.901, Zhonghua Rd., Yongkang Dist., Tainan City 710, Taiwan	Taiwan
[redacted]	Rajavithi hospital, Diabetes & Endocrinology unit, Department of Medicine Bangkok 10400, Thailand	Thailand
[redacted]	Division of Cardiology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University Bangkok 10400, Thailand	Thailand
[redacted]	Division of Cardiology, Department of Medicine Faculty of Medicine, Siriraj Hospital, Mahidol University Bangkok 10700, Thailand	Thailand
[redacted]	Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Chulalongkorn Hospital Bangkok 10330, Thailand	Thailand
[redacted]	Endocrine unit, Department of Medicine, Phramongkutklao Hospital Bangkok 10400, Thailand	Thailand
[redacted]	Kocaeli University Medical Faculty, 41380, Kocaeli	Turkey
[redacted]	Dokuz Eylul University Medical Faculty Internal Diseases Department Endocrinology and Metabolism Unit, Mithatpasa cad. no 1606 Inciralti Yerleskesi, 35340 Balcova, Izmir	Turkey
[redacted]	Medeniyet University Goztepe Training and Research Hospital, Ressam Salih Ermez Caddesi Merdivenkoy, 34722 Kadikoy Istanbul	Turkey
[redacted]	Ankara Numune Training and Research Hospital, Hacettepe Mahallesi Talatpasa Bulvari No:44, 06100 Altindag Ankara	Turkey
[redacted]	Dıskapi Yildirim Beyazit Training and Research Hospital, Irfan Bastug Caddesi F Blok 3 Kat, 06110 Diskapi Ankara	Turkey
[redacted]	Haseki Training and Research Hospital, Millet Caddesi 3. Blok 2. Kat Dahiliye Klinigi Aksaray, 34130 Fatih Istanbul	Turkey
[redacted]	Akdeniz University Medical Faculty, Dumlupinar Bulvari, 07058 Kampus Antalya	Turkey
[redacted]	Canakkale 18 Mart University Medical Faculty, Cumhuriyet Mahallesi Sahil Yolu Caddesi No:5, 17000 Kepez Canakkale	Turkey
[redacted]	Pamukkale University Medical Faculty, 20070, Kinikli Kampusu Denizli	Turkey
[redacted]	Kartal Dr. Lutfi Kirdar Training and	Turkey

Site no.	Address	Country
	Research Hospital, Semsi Denizer Caddesi E-5 Karayolu, 34990 Cevizli Mevkii Istanbul	
[redacted]	Clinical Research Unit Morriston Hospital Swansea SA6 6NL	United Kingdom
[redacted]	Heart of England NHS Foundation Trust MIDRU Birmingham Heartlands Hospital Bordesley Green East Birmingham B9 5SS	United Kingdom
[redacted]	Leodis Research Moorfield House Surgery 11 Wakefield Road Garforth Leeds LS25 1AN	United Kingdom
[redacted]	Diabetes Research Department Clinical Trials Unit Horizon Centre Torbay Hospital Lawes Bridge Torquay TQ2 7AA	United Kingdom
[redacted]	Department of Obesity and Endocrinology Clinical Sciences Centre University Hospital Aintree Lower Lane Liverpool L9 7AL	United Kingdom
[redacted]	Medinova South London Clinical Studies Centre Block A, Level [redacted] Queen Mary's Hospital Frognal Avenue Sidcup Kent DA14 6LT	United Kingdom
[redacted]	Health Sciences Building University of Aberdeen Foresterhill Aberdeen AB25 2ZD	United Kingdom
[redacted]	Medinova North London Clinical Studies Centre Batchworth House Mount Vernon Hospital Rickmansworth Road	United Kingdom

Site no.	Address	Country
	Northwood Middlesex HA6 2RN	
[redacted]	L-MARC Research Center 3288 Illinois Avenue Louisville, KY 40213	United States
[redacted]	Marin Endocrine Care & Research, Inc. 900 South Eliseo Drive, Suite [redacted] Greenbrae, CA 94904	United States
[redacted]	Albany Medical College Division of Community Endocrinology 1365 Washington Avenue, Suite [redacted] Albany, NY 12206 formerly The Endocrine Group 1365 Washington Avenue, Suite [redacted] Albany, NY 12206	United States
[redacted]	Meridien Research 5700 State Road 64 East Bradenton, FL 34208	United States
[redacted]	Valley Clinical Trials 18433 Roscoe Blvd., Suite [redacted] Northridge, CA 91325 formerly Valley Clinical Trials, Inc. 18433 Roscoe Blvd., Suite [redacted] Northridge, CA 91325	United States
[redacted]	Advanced Medical Research 6450 Wheatstone Ct Maumee, OH 43537	United States
[redacted]	University Of Tennessee Health Science Center 920 Madison Avenue Suite [redacted] Memphis, TN 38163 formerly University Of Tennessee Health Science Center Division of Endocrinology Diabetes and Metabolism 920 Madison Avenue Suite [redacted] Memphis, TN 38163	United States
[redacted]	Rochester Clinical Research, Inc. 500 Helendale Road L20 Rochester, NY 14609	United States
[redacted]	Anaheim Clinical Trials, LLC 1085 N. Harbor Blvd Anaheim, CA 92801	United States
[redacted]	Carolina Health Specialists 945 82nd Parkway, Suite [redacted] Myrtle Beach, SC 29572	United States
[redacted]	Diabetes And Endocrinology Specialists Inc. 222 S. Woods Mill Road, Suite [redacted] Chesterfield, MO 63017	United States

Site no.	Address	Country
[redacted]	Renstar Medical Research 104 SE 1st Avenue, Suite [redacted] Ocala, FL 34471	United States
[redacted]	Primary Care Research South, Inc. 114 Gallery Drive McMurray, PA 15317 formerly Primary Care Research South, Inc. 2581 Washington Road, Suite [redacted] Upper St. Clair, PA 15241	United States
[redacted]	University of Vermont Medical Center Diabetes Research Center 62 Tilley Drive South Burlington, VT 05403-7205 formerly Fletcher Allen Health Care Diabetes Research Center 62 Tilley Drive South Burlington, VT 05403-7205	United States
[redacted]	Jacksonville Center For Clinical Research 4085 University Blvd. South, Suite [redacted] Jacksonville, FL 32216	United States
[redacted]	American Institute of Research 1127 Wilshire Blvd, Suite [redacted] Los Angeles, CA 90017-4006 formerly American Institute of Research 1127 Wilshire Blvd, Suite [redacted] Los Angeles, CA 90017-4006	United States
[redacted]	Wake Research Associates 3100 Duraleigh Road Suite [redacted] Raleigh, NC 27612	United States
[redacted]	University Hospitals Case Medical Center 11100 Euclid Avenue, Mail Stop 5030 Cleveland, OH 44106	United States
[redacted]	Heritage Valley Medical Group, Inc. 500 Sharon Rd Beaver, PA 15009-1957	United States
[redacted]	Panacea Clinical Research 4151 Callaghan Rd Suite [redacted] and [redacted] San Antonio, TX 78228-3419	United States
[redacted]	Optimal Research 5920 Friars Road, Suite [redacted] San Diego, CA 92108 formerly Accelovance, Inc.	United States

Site no.	Address	Country
	5920 Friars Road, Suite [redacted] San Diego, CA 92108	
[redacted]	University of North Carolina, UNC Diabetes Care Center 300 Meadowmont Village Circle, Suite [redacted] Chapel Hill, NC 27517 formerly UNC Diabetes Care Center 5316 Highgate Drive, Suite [redacted] Durham, NC 27713	United States
[redacted]	Accelovance 3030 Venture Lane, Suite [redacted] Melbourne, FL 32934 formerly Accelovance 1600 West Eau Gallie Blvd Melbourne, FL 32935	United States
[redacted]	Robley Rex VA Medical Center 800 Zorn Avenue Louisville, KY 40206	United States
[redacted]	Univ. of AL Preventive Medicine 1717 11th Ave S Birmingham, AL 35205-4731 formerly Division of Preventive Medicine University of Alabama at Birmingham 1717 11th Avenue South, [redacted] Birmingham, AL 35205	United States
[redacted]	Harold Hamm Diabetes 1000 N. Lincoln Boulevard, HHDC 1000 Oklahoma City, OK 73104 formerly Harold Hamm Diabetes Center 1000 N. Lincoln Blvd., HHDC 1000 Oklahoma City, OK 73104 formerly Harold Hamm Diabetes Center 1000 N. Lincoln Blvd., HHDC 2900 or 1000 Oklahoma City, OK 73104	United States
[redacted]	UT Southwestern Medical Center 5323 Harry Hines Blvd Dallas, TX 75390-9302	United States
[redacted]	Midwest CRC 380 N. Terra Cotta Road, Suite [redacted] Crystal Lake, IL 60012 formerly	United States

Site no.	Address	Country
	Midwest Endocrinology LLC 380 N. Terra Cotta Road, Suite [redacted] Crystal Lake, IL 60012	
[redacted]	Saint Luke's Lipid and Diabetes Research Center 4320 Wornall Road Medical Plaza I Suite [redacted] Kansas City, MO 64111	United States
[redacted]	Vanderbilt Diabetes Center 1211 21st Ave. S, 315 MAB Nashville, TN 37212	United States
[redacted]	Mountain View Clinical Research Inc. 405 Memorial Drive Ext. Greer, SC 29651	United States
[redacted]	University Of Wisconsin-Madison 600 Highland Ave, H6/166 Madison, WI 53792	United States
[redacted]	Alta Pharmaceutical Research Center, Inc. 4553 N. Shallowford Road, Suite [redacted] Dunwoody, GA 30338	United States
[redacted]	Naidu Clinic 605 E 4th Street, Suite [redacted] Odessa, TX 79761	United States
[redacted]	La Porte County Institute For Clinical Research Inc. 8733 West 400 North Michigan City, IN 46360	United States
[redacted]	Physician Research Associates, LLC 758 Old Norcross Road, Suite [redacted] Lawrenceville, GA 30046	United States
[redacted]	Pangtay Research Corporation, MSCI 2021 N MacArthur Blvd, Suite [redacted] Irving, TX 75061-2210	United States
[redacted]	Nature Coast Clinical Research – Crystal River 6122 West Corporate Oaks Drive Crystal River, FL 34429 formerly West Florida Medical Associates 3775 North Lecanto Highway Beverly Hill, FL 34465	United States
[redacted]	IMMC Clinical Trials, LLC 195 Highway US 46, Suite [redacted] Mine Hill, NJ 07803	United States
[redacted]	Arthritis And Diabetes Clinic, Inc. 3402 Magnolia Cove Monroe, LA 71203	United States
[redacted]	Denver VA Medical Center 1055 Clermont Street Denver, CO 80220 formerly	United States

Site no.	Address	Country
	Levinson Eye Clinic 4545 E. 9th Ave., Suite [redacted] Denver, CO 80220	
[redacted]	Radiant Research Inc. 7515 Greenville Avenue, Suite [redacted] Dallas, TX 75231	United States
[redacted]	Dallas Diabetes & Endocrine Center 7777 Forest Lane Suite [redacted] Dallas, TX 75230	United States
[redacted]	University Physicians Group Research Division 1460 Victory Boulevard Staten Island, NY 10301	United States
[redacted]	Health First Medical Group 1223 Gateway Drive Melbourne, FL 32901 formerly Health First Physicians, Inc. 1223 Gateway Drive Melbourne, FL 32901 formerly MIMA Century Research Associates Melbourne Internal Medicine Associates 1223 Gateway Drive Melbourne, FL 32901	United States
[redacted]	St. Johns Center For Clinical Research 141 Hilden Road, Suite [redacted] Ponte Vedra, FL 32081	United States
[redacted]	Southern New Hampshire Diabetes and Endocrinology 29 Northwest Boulevard Nashua, NH 03063 formerly Joslin Diabetes Center Affiliate of SNHMC 29 Northwest Boulevard Nashua, NH 06063	United States
[redacted]	Southgate Medical Group, LLP 1026 Union Road West Seneca, NY 14224	United States
[redacted]	Chase Medical Research LLC 500 Chase Parkway, [redacted] Waterbury, CT 06708	United States
[redacted]	Diabetes and Thyroid Center of Fort Worth 7801 Oakmont Blvd, Suite [redacted] Fort Worth , TX 76132	United States
[redacted]	Tulane University School of Medicine Clinical Translational Unit (CTU) 1440 Canal Street, Suite [redacted] New Orleans, LA 70112 formerly	United States

Site no.	Address	Country
	Tulane University Health Sciences Center Tidewater Building 1440 Canal Street, Suite [redacted] New Orleans , LA 70112	
[redacted]	DCOL Center for Clinical Research 707 Hollybrook Drive, Suite [redacted] Longview , TX 75605	United States
[redacted]	Sterling Research Group, Ltd. 2230 Auburn Avenue, [redacted] Cincinnati, OH 45219	United States
[redacted]	University of Colorado Anchutz Health and Wellness Center 12348 E. Montview Blvd Mailstop C263 Aurora, CO 80045	United States
[redacted]	Dartmouth-Hitchcock Medical Center Endocrinology Section 5C One Medical Center Drive Lebanon, NH 03756	United States
[redacted]	Clinical Investigations Of Texas 1524 Independence Parkway, Suite [redacted] Plano, TX 75075	United States
[redacted]	Monterey Endocrine & Diabetes Institute, Inc. 2 Upper Ragsdale Drive, Suite [redacted] Monterey, CA 93940	United States
[redacted]	Clinical Investigation Specialists Inc. 1800 Nations Drive, Suite [redacted] Gurnee, IL 60031	United States
[redacted]	ActivMed Practice & Research 421 Merrimack Street Suite [redacted] Methuen, MA 01884 formerly ActivMed Practices and Research One Water Street, Suite [redacted] Haverhill, MA 01830	United States
[redacted]	Holston Medical Group 105 West Stone Drive [redacted], Suite [redacted] Kingsport, TN 37660 formerly Holston Medical Group 105 West Stone Drive [redacted], Suite [redacted] Kingsport, TN 37660 formerly Holston Medical Group 105 West Stone Drive [redacted], Suite [redacted] Kingsport, TN 37660	United States

Site no.	Address	Country
	formerly The Regional Eye Center 135 West Ravine Road Kingsport, TN 37660	
[redacted]	Selma Medical Associates 104 Selma Drive Winchester, VA 22601-3834 formerly Valley Health Clinical Research 220 Campus Blvd., Suite [redacted] Winchester, VA 22601	United States
[redacted]	Clinical Study Center Of Asheville LLC 131 McDowell Street, Suite [redacted] Asheville, NC 28801 formerly Clinical Study Center of Asheville, LLC 15 Yorkshire Street, Suite [redacted] Asheville, NC 28803	United States
[redacted]	Asheboro Research Associates 550 White Oak Street Asheboro, NC 27203 formerly White Oak Family Physicians PA/ Asheboro Research Associates 550 White Oak Street Asheboro, NC 27203	United States
[redacted]	Physicians Research Center LLC 601 Route 37 West, Suite [redacted] Toms River, NJ 08755-8050	United States
[redacted]	Mercy Health Research 12680 Olive Boulevard, Suite [redacted] St. Louis, MO 63141	United States
[redacted]	Gotham Cardiovascular Research, PC 275 Seventh Avenue, [redacted] New York , NY 10001 formerly Gotham Cardiovascular Research, PC/In Care of New York Cardiovascular Associates, PLLC 275 Seventh Avenue, [redacted] New York, NY 10001	United States
[redacted]	Albert J Weisbrot 7451 S Mason Montgomery Rd, Suite [redacted] Mason, OH 45040-6815	United States
[redacted]	Optimal Research, LLC 3550 Park Place West, Suite [redacted] Mishawaka, IN 46545 formerly	United States

Site no.	Address	Country
	Accelovance, Inc. 3550 Park Place West, Suite [redacted] Mishawaka, IN 46545	
[redacted]	AM Diabetes And Endocrinology Center 3025 Kate Bond Road Bartlett, TN 38133 formerly AM Diabetes And Endocrinology Center 2996 Kate Bond Road, Suite [redacted] Bartlett, TN 38133	United States
[redacted]	Infinity Medical Research 370 Faunce Corner Road, [redacted] North Dartmouth, MA 02747	United States
[redacted]	St. Louis Medical Center for Clinical Research 10012 Kennerly Rd, Suite [redacted] St. Louis, MO 63128 formerly St. Louis Medical Clinic 3009 N. Ballas Road, Suite [redacted] Building B St. Louis, MO 63131	United States
[redacted]	Whiteville Medical Associates, PA 819 East Jefferson Street Whiteville, NC 28472 formerly Whiteville Medical Associates, PA 823 E. Jefferson Street Whiteville, NC 28472	United States
[redacted]	PMG Research of Wilmington, LLC 1907 Tradd Court Wilmington, NC 28401	United States
[redacted]	Achieve Clinical Research LLC 2017 Canyon Road, Suite [redacted] Birmingham, AL 35216 formerly Endocrinology & Internal Medicine Associates, PC 805 St. Vincent's Drive, Suite [redacted] Birmingham, AL 25205	United States
[redacted]	Radiant Research Inc. - Arizona 2081 W. Frye Road, Suite [redacted] Chandler, AZ 85224	United States
[redacted]	Borgess Research Institute 1521 Gull Road, NP, Suite [redacted] Kalamazoo, MI 49048 formerly	United States

Site no.	Address	Country
	Borgess Research Institute 1717 Schaffer St., Suite [redacted] Kalamazoo, MI 99048 formerly Borgess Diabetes and Endocrine Center 1722 Schaffer Street, Suite [redacted] Kalamazoo, MI 99048	
[redacted]	East Coast Institute for Research, LLC/ Northeast Florida Endocrine and Diabetes Associates 3550 University Blvd. S., Suite [redacted] Jacksonville, FL 32216 formerly East Coast Institute for Research, LLC/ Jacksonville, FL 32216 Northeast Florida Endocrine and Diabetes Associates 3550 University Blvd. S., Suite [redacted] Jacksonville, FL 32216 formerly East Coast Institute for Research, LLC/ Northeast Florida Endocrine and Diabetes Associates 3550 University Blvd. S., Suite [redacted]	United States
[redacted]	Diabetes Center 984120 Nebraska Medical Center Omaha, NE 68198 formerly University Of Nebraska Medical Center UNMC Diabetes Center 983020 Nebraska Medical Center Omaha, NE 68198-3020	United States
[redacted]	Founders Research Corporation 7901 Bustleton Ave., Suite [redacted] Philadelphia, PA 19152	United States
[redacted]	Coastal Metabolic Research Center 3454 Loma Vista Road Ventura, CA 93003 formerly Coastal Metabolic Research Center 64 N. Brent Street, #B Ventura, CA 93003 formerly Ronald H. Chochinov, MD, Inc. 168 North Brent Street, Suite [redacted] Ventura, CA 93003	United States
[redacted]	Stanley F. Stockhammer, Jr. D.O. P.A.	United States

Site no.	Address	Country
	2370 E. International Speedway Boulevard Deland , FL 32724 formerly Central Florida Medical Associates 2575 S. Volusia Avenue, Suite #[redacted] Orange City, FL 32763 formerly Central Florida Medical Associates 927 N. Spring Garden Avenue Deland, FL 32720	
[redacted]	Dominion Medical Associates 304 East Leigh Street Richmond, VA 23219	United States
[redacted]	Family Physicians P.A. 9119 South Gessner Drive, Suite [redacted] Houston, TX 77074	United States
[redacted]	Physician's East Endocrinology 1006 WH Smith Blvd Greenville, NC 27834 formerly Physicians's East PA 1850 West Arlington Blvd. Greenville, NC 27834	United States
[redacted]	First Valley Medical Group 44725 N. 10th Street West, Suite [redacted] Lancaster, CA 93534	United States
[redacted]	Wasatch Clinical Research 4001 South 700 East, Suite [redacted] Salt Lake City, UT 84107 formerly Holiday Family Practice (IP and Clinic Location) 999 Murray Holiday Road, Suite [redacted] Salt Lake City, UT 84117	United States
[redacted]	Heartland Research Associates LLC 3730 N. Ridge Rd., Suite [redacted] Wichita, KS 67205	United States
[redacted]	Carl R. Meisner Medical Clinic, PLLC 2225 Williams Trace Blvd, #110 Sugar Land, TX 77478	United States
[redacted]	Cedar-Crosse Research Center 800 S. Wells Street, Suite [redacted] Chicago, IL 60607	United States
[redacted]	Meridien Research 16176 Cortez Boulevard Brooksville, FL 34601 formerly	United States

Site no.	Address	Country
	Hernando Eye Institute 14543 Cortez Boulevard Brooksville, FL 34613	
[redacted]	Prestige Clinical Research 333 Conover Drive, Suite [redacted] Franklin, OH 45005	United States
[redacted]	Amherst Family Practice 1867 Amherst St. Winchester, VA 22601	United States
[redacted]	Wenatchee Valley Hospital and Clinics 820 N. Chelan Ave Wenatchee, WA 98801-2028	United States
[redacted]	Facey Medical Foundation 11333 N. Sepulveda Blvd. Mission Hills, CA 91345	United States
[redacted]	Briggs Clinical Research, LLC 98 Briggs, Suite [redacted] San Antonio, TX 78224	United States
[redacted]	NorCal Endocrinology and Internal Medicine 111 Deerwood Road, Suite [redacted] San Ramon, CA 94583	United States