Clinical Trial Report Synopsis

Clinical Trial Report synopsis – ICH E3 Section 2

SYNOPSIS

TRIAL TITLE
SELECT − Semaglutide effects on cardiovascular outcomes in people with overweight or obesity

TRIAL NUMBER: EX9536-4388

REGULATORY AGENCY IDENTIFIER NUMBER
clinicaltrials.gov identifier:
NCT03574597

UTN – U1111-1200-5564
IND number – 126360
EudraCT number – 2017-003380-35
Japanese registration number – JapicCTI-194592

TRIAL PHASE
Phase 3b

NAME OF FINISHED PRODUCT
Semaglutide s.c. 2.4. mg once weekly

NAME OF ACTIVE SUBSTANCE
Semaglutide, NNC0113-0217

NAME OF SPONSOR/COMPANY
Novo Nordisk A/S, Novo Allé, DK-2880 Bagsvaerd, Denmark.
Novo Nordisk A/S, Clinical Publishing, Transparency and Archiving (2834); email address: clinicaltrials@novonordisk.com.

NUMBER OF STUDY CENTERS AND COUNTRIES
The trial was conducted at 804 sites in 41 countries, as follows (four investigators each had two site IDs attributed to their site):
Algeria: 3 sites screened/ 3 sites randomised subjects
Argentina: 11 sites screened/ 11 sites randomised subjects
Australia: 13 sites screened/ 13 sites randomised subjects
Austria: 7 sites screened/ 7 sites randomised subjects
Belgium: 6 sites screened/ 6 sites randomised subjects
Brazil: 15 sites screened/ 15 sites randomised subjects
Bulgaria: 15 sites screened/ 15 sites randomised subjects
Canada: 30 sites screened/ 30 sites randomised subjects
Colombia: 6 sites screened/ 6 sites randomised subjects
Croatia: 7 sites screened/ 7 sites randomised subjects
Czech Republic: 11 sites screened/ 11 sites randomised subjects
Denmark: 6 sites screened/ 6 sites randomised subjects
Finland: 7 sites screened/ 7 sites randomised subjects
France: 13 sites screened/ 13 sites randomised subjects
Germany: 26 sites screened/ 26 sites randomised subjects
Greece: 14 sites screened/ 13 sites randomised subjects
Hungary: 7 sites screened/ 6 sites randomised subjects
India: 31 sites screened/ 30 sites randomised subjects
Ireland: 7 sites screened/ 6 sites randomised subjects
Israel: 13 sites screened/ 13 sites randomised subjects

Italy: 21 sites screened/ 21 sites randomised subjects
Japan: 49 sites screened/ 49 sites randomised subjects
Latvia: 8 sites screened/ 8 sites randomised subjects
Malaysia: 11 sites screened/ 11 sites randomised subjects
Mexico: 9 sites screened/ 9 sites randomised subjects
Netherland: 10 sites screened/ 10 sites randomised subjects
Norway: 9 sites screened/ 9 sites randomised subjects
Poland: 22 sites screened/ 22 sites randomised subjects
Portugal: 6 sites screened/ 6 sites randomised subjects
Romania: 25 sites screened/ 25 sites randomised subjects
Russian Federation: 49 sites screened/ 49 sites randomised subjects
Serbia: 8 sites screened/ 8 sites randomised subjects
South Africa: 25 sites screened/ 25 sites randomised subjects
Spain: 11 sites screened/ 11 sites randomised subjects
Sweden: 6 sites screened/ 6 sites randomised subjects
Taiwan: 5 sites screened/ 5 sites randomised subjects
Thailand: 9 sites screened/ 9 sites randomised subjects
Turkey: 20 sites screened/ 20 sites randomised subjects
Ukraine: 17 sites screened/ 17 sites randomised subjects
United Kingdom: 42 sites screened/ 42 sites randomised subjects
United States: 205 sites screened/ 202 sites randomised subjects

PUBLICATIONS

Ryan DH, Lingvay I, Colhoun HM, Deanfield J, Emerson SS, Kahn SE, Kushner RF, Marso S, Plutzky J, Brown-Frandsen K, Gronning MOL, Hovingh GK, Holst AG, Ravn H, Lincoff AM. Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) rationale and design. Am Heart J 2020 Nov;229:61-69. doi: 10.1016/j.ahj.2020.07.008. Epub 2020 Jul 17.PMID: 32916609

Lingvay I, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S, Hovingh GK, Kahn SE, Kushner RF, Lincoff AM, Marso SP, Fries TM, Plutzky J, Ryan DH, SELECT Study Group. Semaglutide for cardiovascular event reduction in people with overweight or obesity: SELECT study baseline characteristics. Obesity (Silver Spring) 2023 Jan;31(1):111-122. doi: 10.1002/oby.23621. Epub 2022 Dec 10.

TRIAL PERIOD

Initiation date: 24 October 2018
Primary completion date: 21 June 2023
Trial completion date: 29 June 2023

DATA CUT-OFF DATES

The results presented reflect the data available in the clinical database as of 18 July 2023, after which the randomisation code was unblinded.

BACKGROUND AND RATIONALE

This trial was a dedicated cardiovascular outcome trial (CVOT) and part of the phase 3 development programme for semaglutide s.c. 2.4 mg once weekly (the STEP programme). It was designed to demonstrate superiority of semaglutide 2.4 mg once weekly versus placebo, both added to cardiovascular (CV) standard of care in subjects with established cardiovascular disease (CVD) and overweight or obesity, but without diabetes, in reducing the risk of major adverse cardiovascular event (MACE) (CV death, nonfatal myocardial infarction (MI) or nonfatal stroke). All subjects were informed of the risks and benefits of the trial and provided informed consent before any trial activities were performed. Subjects were covered by the sponsor's insurance according to local legal requirements.

OBJECTIVES, ENDPOINTS, ESTIMANDS, AND STATISTICAL METHODS

Objectives and endpoints

The primary and secondary objectives of the trial are listed in Table 1 together with the endpoints defined to address these objectives. Exploratory objectives and endpoints are described in the clinical trial report (CTR).

Table 1 Objectives and endpoints

Objectives	Endpoints
Primary objective: To demonstrate that semaglutide s.c. 2.4 mg once weekly lowers the incidence of MACE versus semaglutide placebo, both added to standard of care in subjects with established CV disease and overweight or obesity	**Primary endpoint:** • Time from randomisation to first occurrence of a composite endpoint consisting of CV death, non-fatal MI, or non-fatal stroke **Confirmatory secondary endpoints:** • Time from randomisation to CV death • Time from randomisation to first occurrence of a composite HF endpoint consisting of: HF hospitalisation, urgent HF visit or CV death **Supportive secondary endpoints:** Time from randomisation to first occurrence of: • An expanded composite CV endpoint consisting of: CV death, non-fatal MI, non-fatal stroke, coronary revascularisation or UAP requiring hospitalisation • A composite endpoint consisting of all-cause death, non-fatal MI, or non-fatal stroke • Non-fatal MI • Non-fatal stroke • Coronary revascularisation • UAP requiring hospitalisation • HF hospitalisation or urgent HF visit
Secondary objectives: To compare the effect of semaglutide s.c. 2.4 mg once weekly versus semaglutide placebo both added to standard of care in subjects with established CV disease and overweight or obesity with regards to: • Mortality • CV risk factors • Glucose metabolism • Body weight • Renal function	**Confirmatory secondary endpoint:** • Time from randomisation to all-cause death **Supportive secondary endpoints:** Change from randomisation to year 2/week 104 (visit 14) in: • SBP (mmHg) • DBP (mmHg) • Heart rate (bpm) • hsCRP (mg/L) • Lipids (mg/dL): Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides • Body weight (%) • Waist circumference (cm) • Patient reported outcomes: EuroQol five dimensions five level (EQ-5D-5L) questionnaire (EQ-5D index score (range 0 to 1) and EQ-5D-VAS (range 0 to 100). A higher score indicates better self-reported health status • HbA_{1c} (%, mmol/mol) change from screening (visit 1) to year 2/week 104 (visit 14) Time from randomisation to first occurrence of: • HbA_{1c} ≥48 mmol/mol (6.5%) • A 5-component composite nephropathy endpoint consisting of: onset of persistent macroalbuminuria (UACR >300 mg/g), persistent 50% reduction in eGFR compared with baseline (randomisation), onset of persistent eGFR <15 mL/min/1.73 m^2, initiation of chronic renal replacement therapy (dialysis or transplantation) or renal death For subjects with a screening HbA_{1c} <39 mmol/mol (5.7%): • Time from randomisation to HbA_{1c} ≥39 mmol/mol (5.7%) For subjects with a screening HbA_{1c} ≥39 mmol/mol (5.7%): • Proportion of subjects with HbA_{1c} <39 mmol/mol (5.7%) at each visit where HbA_{1c} is assessed

Abbreviations: CV = cardiovascular; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated haemoglobin, HDL = high-density lipoprotein; HF = heart failure; hsCRP = high-sensitivity c-reactive protein; LDL = low-density lipoprotein, MACE = major adverse cardiovascular event; MI = myocardial infarction; SBP = systolic blood pressure, s.c. = subcutaneously; UACR = urinary albumin-to-creatinine ratio; UAP = unstable angina pectoris.

Estimands

The primary estimand for all objectives is an intention-to-treat estimand, evaluating the effect of the randomised treatment intervention irrespective of adherence to treatment or any changes to background medication. This estimand is addressed using full analysis set (FAS) and the in-trial observation period.

The secondary estimand for selected time-to-event endpoints is described in the clinical trial report (CTR).

Statistical methods

Analysis set

The following analysis set was specified in accordance with ICH E9:

- FAS: All unique randomised subjects were to be analysed according to the treatment to which they were assigned at randomisation.

Observation periods

A trial completer was defined as a subject that either attended the end-of-trial follow-up (FU) visit or who died while active in the trial.

A subject was considered lost to follow-up (LTFU) if the subject did not complete the trial and did not withdraw consent. The date of last contact with subject and status for LTFU were determined by investigator at trial completion.

The in-trial observation period for a subject was defined as the period from date of randomisation to the first of:

- Date of FU visit
- Date when subject withdrew consent
- Date of last contact with subject for subjects who were LTFU
- Date of death

Sample size determination

This trial was designed to have 90% overall power to confirm superiority of the primary endpoint. An assumed true hazard ratio (HR) of 0.83 was based on a conservative assessment of the observed point estimate for the HR in the SUSTAIN 6, which was 0.74 $[0.58; 0.95]_{95\% \text{ CI}}$ for a similar definition of MACE. The in-trial observation period covered the time from randomisation to the last day of the trial, regardless of treatment adherence.

A total of 1,225 first MACEs provide 90% power under the assumed true HR. With a sample size of 17,500 subjects randomised 1:1 to semaglutide 2.4 mg or placebo, the 1,225 events were expected to be accrued at month 59 (~5 years), assuming the overall annualised event rate across the two treatment groups was 2.0%, i.e. 1.8% in the semaglutide group and 2.2% in the placebo group.

The trial was designed with one interim testing for superiority of the primary endpoint when two thirds of the total planned number of primary endpoint events had been accrued. Testing for futility was not included. The Lan-DeMets alpha spending function, approximating the O'Brien-Fleming's stopping boundaries, was used to test superiority at a study-wise one-sided type I error rate of 2.5%.

Statistical analysis

Primary and confirmatory endpoints

The primary endpoint in this trial was time from randomisation to first occurrence of a composite MACE endpoint consisting of CV death, non-fatal MI and non-fatal stroke.

The confirmatory secondary endpoints were analysed under multiplicity control. Given superiority for the primary endpoint, the superiority hypothesis stated below were to be tested for each of the confirmatory secondary endpoints under multiplicity control via a stagewise hierarchical testing scheme using the below order:

1. Time from randomisation to CV death.
2. Time from randomisation to first occurrence of a composite heart failure (HF) outcome consisting of: HF requiring hospitalisation, urgent HF visit or CV death.
3. Time from randomisation to all-cause death.

For the type I error rate to be strongly controlled at the one-sided level of 2.5%, a separate alpha spending function for the confirmatory secondary endpoints was applied. The one-sided alpha spending function is given by

$$g(t) = \min\{\alpha * t^{0.7668}, \alpha\}$$

where t is the proportion of information included in the analysis for the primary endpoint and α is the overall one-sided alpha of 2.5%. The testing procedure was stopped the first time an analysis failed to confirm superiority of the endpoint in question using the nominal significance level derived from the alpha spending function. For the primary analysis, final inference on termination was adjusted for the group sequential design by using likelihood ratio ordering. No adjustments of results for the confirmatory secondary endpoints due to the group sequential design was done.
The primary analysis of the primary endpoint addressed the primary estimand (intention-to-treat). The HR for comparing semaglutide 2.4 mg versus placebo was estimated from a Cox proportional hazards model with treatment group (semaglutide 2.4 mg, placebo) as fixed factor together with the two-sided 95% confidence interval (CI) and one-side fixed design p-value for hypothesis testing. The score test from the Cox model was used for testing. The following superiority hypothesis was tested:

$$H_0: HR \geq 1.0 \text{ against } H_a: HR < 1.0$$

Superiority of semaglutide 2.4 mg versus placebo was considered confirmed if the associated H_0 was rejected using the Lan-DeMets alpha spending function specified above to determine the nominal significance level.

The consistency in the treatment effect for the primary endpoint was explored by subpopulation analyses based on baseline information (sex, age, race, ethnicity, region, glycated haemoglobin (HbA_{1c}), body mass index (BMI), CVD, estimated glomerular filtration rate (eGFR) and chronic HF). The subpopulation analyses were based on Cox proportional hazard models with an interaction between treatment group (semaglutide 2.4 mg, placebo) and the specific baseline variable as factor.

An overview of the statistical methods used for each type of endpoint is available in Table 2.

Table 2 Overview of the statistical methodology applied for each type of endpoint

TTE endpoints
The TTE endpoints were analysed using a Cox proportional hazards model with treatment group (semaglutide, placebo) as fixed factor. The score test from the Cox regression model was used for testing.
Continuous endpoints
The continuous supportive secondary endpoints (change from baseline to 2 years) were analysed using an ANCOVA model with treatment as fixed factor and baseline value as covariate and using multiple imputation for missing values. Where specified, the analysis was done for log-transformed values. The imputation model (linear regression) included baseline value as a covariate and was fitted separately for each treatment arm to subjects having an observed data point (irrespective of adherence to randomised treatment) at the relevant timepoint. The multiple imputed data sets were analysed separately, and the results were combined using Rubin's rule.

Abbreviations: ANCOVA = analysis of covariance; TTE = time-to-event.

METHODOLOGY

This was a randomised, double-blind, parallel group, placebo-controlled trial comparing semaglutide 2.4 mg with semaglutide placebo both administered subcutaneously (s.c.) once weekly in subjects with established CV disease and overweight or obesity and without T2D.
The trial included a 16-week dose escalation period, a maintenance period, and a 5-week follow up period. Treatment pauses were allowed. The trial was event driven with trial closure planned to be performed when the targeted number of primary endpoint events was reached. An independent data monitoring committee (DMC) was to oversee efficacy and subject safety and could recommend stopping the trial early. The trial employed a group sequential design with one interim test for superiority of the primary endpoint evaluated by the DMC.
Subjects were randomised in a 1:1 ratio to receive either semaglutide 2.4 mg or semaglutide placebo as an adjunct to standard of care.
Blinded treatment with semaglutide 2.4 mg or semaglutide placebo offers a robust method for assessment of the effects of semaglutide. A broad spectrum of treatments for co-morbidities and CV risk factors were introduced or adjusted throughout the trial based on standard of care and at investigator's discretion. This is in accordance with a pragmatic approach to compare two treatments: one where semaglutide is available and another where it is not.
Based on the therapeutic experience with GLP-1 RAs and regulatory feedback and requirements, a number of safety focus areas were defined as being of special interest for the safety evaluation; Cardiovascular disorders, Gastrointestinal disorders, Gallbladder-related disorders, Pancreatitis, Kidney disorders, Hepatic disorders, Appendicitis, Malignant neoplasms, Eye disorders, Hypoglycaemia, Allergic reactions, Medication errors, Abuse or misuse, Suicide/self-injury, Rare events, Suspected transmission of an infectious agent via trial product and COVID-19 events.

NUMBER OF SUBJECTS (PLANNED AND ANALYSED)

A total of 17,500 adults with established CV disease and overweight or obesity were planned to be randomised. A total of 21,089 subjects were screened for this trial, of which 3,480 (16.5% of all screened) were screening failures (including those subjects who were eligible for randomisation but did not return for randomisation or who withdrew consent prior to randomisation).

Eligible subjects were randomised to treatment with semaglutide 2.4 mg (8,805 subjects) or placebo (8,804 subjects). Three (3) subjects were randomised twice in the trial and 1 subject was randomised three times; thus, 5 subject identifiers were not included in the FAS as they had been randomised more than once. Thus, the FAS comprised 17,604 subjects (8,803 subjects in the semaglutide 2.4 mg group and 8,801 subjects in the placebo group). A small proportion of randomised subjects in the FAS were not exposed to trial product 9 subjects (0.1%) in the semaglutide 2.4 mg group and 19 subjects (0.2%) in the placebo group, see Table 3.

In total, 96.9% of randomised subjects in the FAS completed the trial (attended the FU visit or died while considered active in the trial). Vital status was available for 99.4% (100%-0.6%) of subjects in the trial. A total of 543 randomised subjects (3.1%) did not complete the trial due to either withdrawal of consent or being LTFU. The number of non-completers was balanced between treatment groups and vital status was obtained for 434 (approximately 80%, (115+6+313)/543) of the non-completers at the end of the trial.

Overall, the proportion of subjects that permanently discontinued trial product was similar with semaglutide 2.4 mg and placebo. Permanent discontinuation of trial product due to an adverse event was more frequent with semaglutide 2.4 mg, primarily driven by GI AEs, whereas discontinuation due to lack of effect was more frequent with placebo.

Table 3 Subject disposition – overview – all subjects

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Screened			21089
Screening failures			3480 (16.5)
All randomised	8805	8804	17609
Randomisations removed due to subject randomised more than once	2	3	5
Full analysis set	8803 (100)	8801 (100)	17604 (100)
Exposed	8794 (99.9)	8782 (99.8)	17576 (99.8)
Not exposed	9 (0.1)	19 (0.2)	28 (0.2)
Trial completers [1]	8544 (97.1)	8517 (96.8)	17061 (96.9)
Attended follow-up visit (P-FU)	8169 (92.8)	8059 (91.6)	16228 (92.2)
Deceased during trial	375 (4.3)	458 (5.2)	833 (4.7)
Non-completers - primary reason and last known vital status	259 (2.9)	284 (3.2)	543 (3.1)
Withdrawal by subject	67 (0.8)	96 (1.1)	163 (0.9)
Alive	50 (0.6)	65 (0.7)	115 (0.7)
Deceased	0	6 (<.1)	6 (<.1)
Unknown	17 (0.2)	25 (0.3)	42 (0.2)
Lost to follow-up	192 (2.2)	188 (2.1)	380 (2.2)
Alive	155 (1.8)	158 (1.8)	313 (1.8)
Unknown	37 (0.4)	30 (0.3)	67 (0.4)
Trial product permanently discontinued - primary reason	2694 (30.6)	2375 (27.0)	5069 (28.8)
Adverse event	1434 (16.3)	696 (7.9)	2130 (12.1)
Lack of effect	64 (0.7)	244 (2.8)	308 (1.7)
Unintentional treatment discontinuation	252 (2.9)	327 (3.7)	579 (3.3)
Currently no contact with the subject	71 (0.8)	101 (1.1)	172 (1.0)
Participation in another clinical trial anytime during the trial	3 (<.1)	4 (<.1)	7 (<.1)
Simultaneous use of prohibited medication	5 (<.1)	29 (0.3)	34 (0.2)
COVID-19 Pandemic	39 (0.4)	43 (0.5)	82 (0.5)
Other	511 (5.8)	647 (7.4)	1158 (6.6)
Missing	306 (3.5)	265 (3.0)	571 (3.2)

[1]: subjects who attended the follow-up visit (P-FU) or who died during the trial.
For screened, screening failures and all randomised, subjects can count more than once.
%: percentage of subjects in full analysis set except for screening failures where it is percentage of screened subjects, N: number of subjects, primary reason: according to the Dose Change form.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION

Key inclusion criteria:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male or female, age ≥45 years at the time of signing informed consent
3. BMI ≥27 kg/m^2
4. Have established CVD as evidenced by at least one of the following:
    a. prior MI
    b. prior stroke (ischemic or hemorrhagic stroke)
    c. symptomatic peripheral artery disease (PAD), as evidenced by intermittent claudication with ankle-brachial index (ABI) <0.85 (at rest), or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease

Key exclusion criteria:

- Any of the following: MI, stroke, hospitalisation for urgent angina pectoris (UAP) or transient ischaemic attack within the past 60 days prior to the day of screening
- Presently classified as being in New York Heart Association (NYHA) Class IV HF
- HbA_{1c} ≥48 mmol/mol (6.5%) as measured by the central laboratory at screening
- History of T1D or T2D (history of gestational diabetes is allowed)

Randomisation criteria:
To be randomised, the randomisation criterion must be answered "yes". The randomisation only occurred after evaluation of the randomisation criteria:

1. None of the following: MI, stroke, hospitalisation for UAP or transient ischaemic attack has occurred, and no revascularisation has been planned between screening and randomisation.

Trial product discontinuation
According to the protocol, the following reasons were to lead to premature trial product discontinuation:

1. Pregnancy
2. Intention of becoming pregnant
3. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product (IMP)
4. If pancreatitis is suspected, trial product must be discontinued; if confirmed, trial product shall not be restarted
5. Calcitonin ≥100 ng/L
6. Treatment with another GLP-1 RA
7. Other safety concerns, at the discretion of the investigator

TRIAL INTERVENTIONS, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBERS

Treatment group	**Semaglutide with PDS290 pen-injector**	**Semaglutide Placebo with PDS290 pen-injector**
Trial product name	Semaglutide B 3.0 mg/mL	Semaglutide placebo
Trial product type	IMP	
Pharmaceutical form	Solution for injection	
Route of administration	Subcutaneous	
Medical device	3 mL PDS290 pre-filled pen-injector	
Trial product strength	3.0 mg/mL	Placebo
Dose and dose frequency	Dosing was once weekly with dose escalation every 4th week until maintenance dose (2.4 mg) was reached. The dose escalations were: 0.24 mg, 0.5 mg, 1.0 mg, 1.7 mg, and the maintenance dose was 2.4 mg.	
Dosing instructions and administration	Injection once weekly at the same day of the week. Injections were to be administered by s.c. injection in the thigh, abdomen or upper arm at any time of day irrespective of meals.	
Sourcing	Manufactured and supplied by Novo Nordisk A/S	
Packaging and labelling	Labelled and packaged by Novo Nordisk A/S Labelled in accordance with Annex 13, local regulations and trial requirements Trial product was provided in 3 mL PDS290 pre-filled pen-injector	
Storage conditions	• Store in refrigerator (2°C–8°C/36°F–46°F) • Do not freeze • Protect from light	

Batch numbers and expiry dates for the IMPs used in this trial are listed in Table 4.

Table 4 Investigational medicinal products – batch numbers and expiry dates

Investigational medicinal product	Dose	Batch number	Expiry date
Semaglutide B 3.0 mg/mL, 3 mL, PDS290 pen-injector	0.24, 0.5, 1.0, 1.7 or 2.4 mg once weekly	HP51338 HP52104 HP53043 HP53045 JP51975 JP53369 KP51914 KP54854 LP58278 MP5A450 MP5C483	2020-04-24 2020-09-13 2020-10-05 2020-12-10 2022-01-14 2022-06-27 2023-01-14 2023-06-30 2024-03-07 2024-11-05 2024-12-09
Semaglutide placebo 0 mg/mL, 3 mL, PDS290 pen-injector	0.24, 0.5, 1.0, 1.7 or 2.4 mg once weekly	HP53676 HP51152 HP53677 JP51682 JP53898 KP52043 KP52563 LP55673 LP58126 MP5A494 MP5B565	2020-03-27 2020-10-30 2021-06-06 2021-11-05 2022-03-27 2023-01-13 2023-01-13 2023-06-29 2024-03-05 2024-11-08 2024-12-10

DURATION OF TRIAL INTERVENTION

The trial was event driven and consequently, the observation time and treatment time varied between subjects depending on when they were recruited into the trial. Average time in-trial was similar across the two treatment groups and average time on-treatment was slightly lower with semaglutide 2.4 mg than with placebo (Table 5). The overall median time in-trial was 41.8 months and overall median on-treatment time was 38.2 months.

Subjects were on treatment in average 85.1% of the planned on-treatment period (Table 5). The median total duration of the no dosing period (i.e., the sum of all days when no dose was administered within 7 days) was 0.2 months (range 0.0 to 53.6 months) corresponding to a mean duration of 6.8 months.

Table 5 Observation time by observation period – FAS

	Sema 2.4 mg	Placebo	Total
Number of subjects	8803	8801	17604
In-trial period (months)			
N	8803	8801	17604
Mean (SD)	39.9 (9.3)	39.7 (9.5)	39.8 (9.4)
Median (Q1, Q3)	41.9 (33.1, 47.1)	41.7 (32.9, 47.0)	41.8 (33.0, 47.0)
Min; Max	0.0 ; 55.2	0.0 ; 55.2	0.0 ; 55.2
Total (Total in years)	351401.6 (29283.5)	349339.8 (29111.6)	700741.4 (58395.1)
On-treatment period (months) [1]			
N	8794	8782	17576
Mean (SD)	33.3 (14.4)	35.1 (13.0)	34.2 (13.7)
Median (Q1, Q3)	37.3 (26.5, 44.6)	38.6 (28.4, 45.3)	38.2 (27.4, 45.1)
Min; Max	0.3 ; 55.0	0.5 ; 55.0	0.3 ; 55.0
Total (Total in years)	293081.9 (24423.5)	308340.6 (25695.0)	601422.5 (50118.5)
Compliance on-treatment period (months) [2]			
N	8794	8782	17576
Mean (SD)	32.2 (14.5)	34.1 (13.0)	33.1 (13.8)
Median (Q1, Q3)	35.9 (25.5, 43.7)	37.5 (27.4, 44.2)	37.0 (26.4, 43.9)
Min; Max	0.2 ; 54.0	0.2 ; 54.0	0.2 ; 54.0
Total (Total in years)	283079.1 (23589.9)	299510.3 (24959.2)	582589.4 (48549.1)
First on-treatment period (months) [3]			
N	8794	8782	17576
Mean (SD)	30.7 (16.0)	33.6 (14.1)	32.2 (15.2)
Median (Q1, Q3)	33.8 (16.8, 44.2)	37.5 (26.4, 44.8)	35.4 (23.6, 44.4)
Min; Max	0.3 ; 55.0	0.5 ; 55.0	0.3 ; 55.0
Total (Total in years)	269948.5 (22495.7)	295253.0 (24604.4)	565201.5 (47100.1)
Planned on-treatment period (months) [4]			
N	8803	8801	17604
Mean (SD)	39.1 (9.2)	38.9 (9.4)	39.0 (9.3)
Median (Q1, Q3)	41.0 (32.3, 46.3)	40.8 (32.0, 46.2)	40.9 (32.2, 46.2)
Min; Max	0.0 ; 55.0	0.0 ; 55.2	0.0 ; 55.2
Total (Total in years)	344195.1 (28682.9)	342100.1 (28508.3)	686295.3 (57191.3)
Compliance on-treatment period /Planned on-treatment period (%)			
N	8794	8782	17576
Mean (SD)	82.5 (30.8)	87.7 (25.2)	85.1 (28.2)
Median (Q1, Q3)	99.4 (82.0, 99.8)	99.5 (94.2, 99.9)	99.5 (89.2, 99.8)
Min; Max	0.4 ; 103	0.4 ; 103	0.4 ; 103
Total no dosing period (months) [5]			
N	7744	7552	15296
Mean (SD)	7.9 (13.3)	5.6 (11.1)	6.8 (12.3)
Median (Q1, Q3)	0.2 (0.1, 9.9)	0.2 (0.1, 4.1)	0.2 (0.1, 6.7)
Min; Max	0.0 ; 53.6	0.0 ; 52.8	0.0 ; 53.6
Total (Total in years)	61119.8 (5093.3)	42594.9 (3549.6)	103714.7 (8642.9)

[1]: On-treatment period: All days from date of first dose to end of the in-trial period where a dose has been administered within 5 weeks (35 days). The period can include non-consecutive time intervals. [2]: Compliance on-treatment period: All days from date of first dose to end of the in-trial period where a dose has been administered within 1 week (7 days). The period can include non-consecutive time intervals. The dose does not have to be the target dose. [3] First on-treatment period: From date of first dose until first time where no dose has been administered within 5 weeks (35 days) or end of the in-trial period, whichever comes first. [4]: Planned on-treatment period: From date of randomisation to end-of-treatment visit plus 6 days or end of the in-trial period, whichever comes first. [5]: Total no dosing period: All days from randomisation to end-of-treatment visit plus 6 days or end of the in-trial period, whichever comes first, where no dose has been administered within 7 days.
N: number of subjects SD: standard deviation Q1: 1st quartile, Q3: 3rd quartile.

The duration of the compliance on-treatment period for individual subjects was up to 54 months with 28.2% of subjects being treated for 24 to 36 months, approximately 80% of subjects with a duration of ≥24 months (Table 6). Most subjects (60.5%) did not have any treatment discontinuation periods. The proportion of subjects with a no dosing period of short duration (below 1 month), was lower with semaglutide than with placebo, whereas the proportion of subjects with a no dosing period of longer duration (remaining categories) was slightly higher with semaglutide than with placebo (Table 6).

Table 6 On-treatment and no dosing periods – FAS

	Sema 2.4 mg N	Sema 2.4 mg (%)	Placebo N	Placebo (%)	Total N	Total (%)
Number of subjects	8803		8801		17604	
Duration of compliance on-treatment period (months) [1]						
0 < to < 4	638	(7.2)	314	(3.6)	952	(5.4)
4 <= to < 8	394	(4.5)	257	(2.9)	651	(3.7)
8 <= to < 12	253	(2.9)	279	(3.2)	532	(3.0)
12 <= to < 24	701	(8.0)	671	(7.6)	1372	(7.8)
24 <= to < 36	2426	(27.6)	2545	(28.9)	4971	(28.2)
36 <= to < 48	3485	(39.6)	3755	(42.7)	7240	(41.1)
48 <= to < 60	897	(10.2)	961	(10.9)	1858	(10.6)
Number of treatment discontinuations [2]						
0	4985	(56.6)	5664	(64.4)	10649	(60.5)
1	2598	(29.5)	2569	(29.2)	5167	(29.4)
2 <= to <= 5	1204	(13.7)	568	(6.5)	1772	(10.1)
6 <= to <= 10	16	(0.2)			16	(<.1)
Duration of total no dosing period (months) [3]						
0 < to < 1	4608	(52.3)	5067	(57.6)	9675	(55.0)
1 <= to < 4	697	(7.9)	590	(6.7)	1287	(7.3)
4 <= to < 8	366	(4.2)	350	(4.0)	716	(4.1)
8 <= to < 12	256	(2.9)	232	(2.6)	488	(2.8)
12 <= to < 24	627	(7.1)	563	(6.4)	1190	(6.8)
24 <= to < 36	589	(6.7)	448	(5.1)	1037	(5.9)
36 <= to < 48	534	(6.1)	273	(3.1)	807	(4.6)
48 <= to < 60	67	(0.8)	29	(0.3)	96	(0.5)

[1]: Compliance on-treatment period: All days from date of first dose to end of the in-trial period where a dose has been administered within 1 week (7 days). The period can include non-consecutive time intervals. The dose does not have to be the target dose. [2]: Planned treatment discontinuation at end of trial does not count. Unexposed subjects are defined to have one treatment discontinuation. [3]: Total no dosing period: All days from randomisation to end-of-treatment visit plus 6 days or end of the in-trial period, whichever comes first, where no dose has been administered within 7 days. The period includes any days between randomisation and first dose of trial product.
%: percentage of subjects in full analysis set, N: number of subjects.

SUMMARY OF RESULTS AND CONCLUSIONS

Demographics and other baseline characteristics

The mean age of the subjects at baseline was 61.6 years. In total, 6,728 (38.2%) subjects were ≥65 years and 1,366 (7.8%) were ≥75 years. In total, 72.3% of subjects were male. Overall, around 10% were of Hispanic or Latino ethnicity. The most prevalent races were White (84.0% of subjects), Asian (8.2% of subjects) and Black or African American (3.8% of subjects). Most subjects were from the European region (38.0%) followed by North America (25.0%, hereof 20.7% recruited from sites in the United States) (Table 7).

Table 7 Baseline characteristics and demographics – FAS

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	8803	8801	17604
Age (years)			
N	8803	8801	17604
Mean (SD)	61.6 (8.9)	61.6 (8.8)	61.6 (8.9)
Median	61	61	61
Min ; Max	45 ; 89	45 ; 93	45 ; 93
Age group (years)			
N	8803 (100)	8801 (100)	17604 (100)
< 55	2057 (23.4)	2094 (23.8)	4151 (23.6)
55 <= to < 65	3387 (38.5)	3338 (37.9)	6725 (38.2)
65 <= to < 75	2656 (30.2)	2706 (30.7)	5362 (30.5)
75 <= to < 85	680 (7.7)	638 (7.2)	1318 (7.5)
85 <=	23 (0.3)	25 (0.3)	48 (0.3)
Sex			
N	8803 (100)	8801 (100)	17604 (100)
Female	2448 (27.8)	2424 (27.5)	4872 (27.7)
Male	6355 (72.2)	6377 (72.5)	12732 (72.3)
Region			
N	8803 (100)	8801 (100)	17604 (100)
Asia	1100 (12.5)	1101 (12.5)	2201 (12.5)
Europe	3326 (37.8)	3366 (38.2)	6692 (38.0)
North America	2200 (25.0)	2201 (25.0)	4401 (25.0)
Other	2177 (24.7)	2133 (24.2)	4310 (24.5)
Race			
N	8803 (100)	8801 (100)	17604 (100)
American Indian or Alaska Native	23 (0.3)	21 (0.2)	44 (0.2)
Asian	720 (8.2)	727 (8.3)	1447 (8.2)
Black or African American	348 (4.0)	323 (3.7)	671 (3.8)
Native Hawaiian or Other Pacific Islander	3 (<.1)	5 (<.1)	8 (<.1)
White	7387 (83.9)	7404 (84.1)	14791 (84.0)
Other	227 (2.6)	247 (2.8)	474 (2.7)
Not Reported	95 (1.1)	74 (0.8)	169 (1.0)
Ethnicity			
N	8803 (100)	8801 (100)	17604 (100)
Hispanic or Latino	914 (10.4)	908 (10.3)	1822 (10.3)
Not Hispanic or Latino	7794 (88.5)	7817 (88.8)	15611 (88.7)
Not Reported	95 (1.1)	76 (0.9)	171 (1.0)

Values are number of subjects (N) and percentage of subjects in full analysis set (%), unless indicated otherwise, SD: standard deviation

Randomised subjects were to have established CV disease in accordance with inclusion criteria #4a-c. For each of the CV inclusion criteria, the distribution of subjects was balanced across treatment groups. The majority (67.6%) of the subjects were enrolled in the trial based on prior MI only, 17.8% were enrolled based on prior stroke only, 4.4% were enrolled based on PAD only and 8.2% fulfilled more than one of these qualifying criteria (Table 8).

Table 8 CV inclusion criteria – FAS

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	8803	8801	17604
CV inclusion criteria			
N	8803 (100)	8801 (100)	17604 (100)
Only MI	5962 (67.7)	5944 (67.5)	11906 (67.6)
Only stroke	1578 (17.9)	1556 (17.7)	3134 (17.8)
Only PAD	376 (4.3)	401 (4.6)	777 (4.4)
MI + stroke	335 (3.8)	348 (4.0)	683 (3.9)
MI + PAD	276 (3.1)	257 (2.9)	533 (3.0)
Stroke + PAD	60 (0.7)	70 (0.8)	130 (0.7)
MI + stroke + PAD	35 (0.4)	32 (0.4)	67 (0.4)
Other	181 (2.1)	193 (2.2)	374 (2.1)

The category "Other" for the CV inclusion criteria includes subjects where it is unknown if the subject fulfilled only one or several criteria and subjects that were randomised in error and did not fulfil any criteria.
%: percentage of subjects in full analysis set, N: number of subjects, MI: Myocardial Infarction, PAD: Peripheral Arterial Disease

Efficacy results

Cardiovascular outcomes

Superiority of semaglutide 2.4 mg vs placebo was confirmed for the primary endpoint of time to first EAC-confirmed MACE, comprising CV death, non-fatal MI and non-fatal stroke.

- The primary analysis of time to first EAC-confirmed MACE resulted in an estimated HR of 0.80 $[0.72; 0.90]_{95\% CI}$ ($p<0.0001$) for semaglutide 2.4 mg relative to placebo. The absolute risk difference between semaglutide 2.4 mg and placebo at week 156 was -0.011 $[-0.019; -0.004]_{95\% CI}$.
- The result of the primary analysis of MACE was supported by all prespecified sensitivity analyses and consistent results were seen across all subpopulations investigated.
- Time to first event analysis of other composite CV endpoints provided results consistent with the primary endpoint, supporting the robustness of the primary analysis.
  - All-cause death, non-fatal MI or non-fatal stroke: Estimated HR 0.80 $[0.72; 0.88]_{95\% CI}$
  - Expanded MACE (3-component MACE, UAP requiring hospitalisation or coronary revascularisation): Estimated HR 0.80 $[0.73; 0.87]_{95\% CI}$

Superiority of semaglutide 2.4 mg vs placebo was not confirmed for the confirmatory secondary endpoint of time to EAC-confirmed CV death:

- The confirmatory analysis of time to EAC-confirmed CV death resulted in an estimated HR 0.85 $[0.71; 1.01]_{95\% CI}$ for semaglutide 2.4 mg relative to placebo.

Superiority of semaglutide 2.4 mg vs placebo for the confirmatory secondary endpoint of time to first EAC-confirmed composite HF outcome endpoint was not tested:

- The confirmatory analysis of time to first EAC-confirmed composite HF outcome endpoint resulted in an estimated HR 0.82 $[0.71; 0.96]_{95\% CI}$ for semaglutide 2.4 mg relative to placebo.

Superiority of semaglutide 2.4 mg vs placebo for the confirmatory secondary endpoint of time to EAC-confirmed all-cause death was not tested:

- The confirmatory analysis of time to EAC-confirmed all-cause death resulted in an estimated HR 0.81 $[0.71; 0.93]_{95\% CI}$ for semaglutide 2.4 mg relative to placebo.

Kidney outcomes

The potential effect of semaglutide 2.4 mg on kidney function in people with overweight and obesity was assessed by time from randomisation to first occurrence of a 5-component composite nephropathy endpoint, as a supportive secondary endpoint. The composite nephropathy endpoint comprised: onset of persistent macroalbuminuria (UACR >300 mg/g), persistent 50% reduction in eGFR compared with baseline (randomisation), onset of persistent eGFR <15 ml/min/1.73 m^2, initiation of chronic renal replacement therapy (dialysis or transplantation) or renal death.

The risk of deterioration in kidney function was lower with semaglutide 2.4 mg than with placebo (HR of 0.78 $[0.63; 0.96]_{95\% CI}$).

Cardiometabolic risk factors

The 2-year treatment effect of semaglutide 2.4 mg vs placebo in subjects with established CV disease and overweight or obesity was evaluated on cardiometabolic risk factors. Beneficial effects in favour of semaglutide 2.4 mg vs placebo were seen for most cardiometabolic risk factors investigated:

- Beneficial effects in favour of semaglutide 2.4 mg vs placebo were seen for body weight:
  - Change from baseline at week 104 in body weight: −9.39% vs −0.88%; ETD −8.51% $[-8.75; -8.27]_{95\% CI}$
- Results for body weight for week 52 supported the results seen for week 104
- Beneficial effects in favour of semaglutide 2.4 mg vs placebo was seen for HbA_{1c}:
  - Change from baseline at week 104 in HbA_{1c}: −0.31% vs 0.01%; ETD −0.32% $[-0.33; -0.31]_{95\% CI}$
- Results for HbA_{1c} for week 52 supported the results seen for week 104
- The risk of having an $HbA_{1c} \geq 6.5\%$ (indicating development of T2D) was lower for the semaglutide 2.4 mg group than for the placebo group.
- Among subjects with an $HbA_{1c} < 5.7\%$ at screening, the risk of having an $HbA_{1c} \geq 5.7\%$ (indicating development of prediabetes) was lower for the semaglutide 2.4 mg group than placebo group.

- Among subjects with an $HbA_{1c} \geq 5.7\%$ at screening, the odds of having an $HbA_{1c} < 5.7\%$ was higher for the semaglutide 2.4 mg group than for the placebo group both at week 52 and week 104, indicating that more subjects in the semaglutide 2.4 mg group vs placebo returned to normoglycemia during the trial.
- Beneficial effects in favour of semaglutide 2.4 mg vs placebo at week 104 were also seen for the other cardiometabolic risk factors investigated, including waist circumference, blood pressure, lipids (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides), and hsCRP.
- Estimated change in heart rate at week 104 was higher with semaglutide 2.4 mg vs placebo: ETD of 3.10% $[2.80; 3.39]_{95\% \text{ CI}}$
- Beneficial effects of semaglutide 2.4 mg vs placebo with respect to the PRO scores for health-related quality of life, EQ-5D-VAS score and EQ-5D-5L index score, at week 104 were seen in this trial.

Safety results

The safety profile of semaglutide 2.4 mg once weekly, added to standard of care, in subjects with established CVD and overweight or obesity was similar to the general population with overweight and obesity as evaluated in the phase 3a development weight management programme (STEP programme). No new safety concerns were identified. A summary of serious adverse events (SAEs) by system organ class (SOC), fatal events and adverse events (AEs) leading to trial product discontinuation is provided in Table 9 and the key safety results are summarised below:

Deaths

- The proportion of subjects with SAEs having a fatal outcome and the corresponding event rate were lower with semaglutide 2.4 mg than with placebo.
- The types of SAEs with a fatal outcome were generally similar with semaglutide 2.4 mg and placebo, whereas lower frequencies were observed with semaglutide 2.4 mg vs placebo for fatal events within the SOCs of Cardiac disorders, Infections and infestations, and General disorders and administration site conditions.

Serious adverse events

- The proportion of subjects reporting SAEs, including events with fatal outcome, were lower with semaglutide 2.4 mg than with placebo.
- Most of the reported SAEs were of severe or moderate severity, had recovered at the end of the trial, and most were assessed by the investigator as unlikely related to trial product, both with semaglutide 2.4 mg and placebo.
- The distribution of SAEs within each SOC was balanced or favouring semaglutide 2.4 mg.

Safety focus areas

- Generally, the evaluation of the safety focus areas showed that the safety profile of semaglutide 2.4 mg was consistent with the known safety profile of semaglutide.
- The proportion of subjects reporting SAEs of Cardiovascular disorders (SOC) was lower with semaglutide 2.4 mg than placebo.
- The proportion of subjects reporting SAEs Gastrointestinal disorders (SOC) was similar with semaglutide 2.4 mg than placebo.
- Similar proportion of subjects in each treatment group reported AEs of acute renal failure (MedDRA search), malignant neoplasms (MedDRA search), pancreatitis (MedDRA search) and COVID-19 (MedDRA search).
- The proportion of subjects reporting AEs of Gallbladder-related disorders (MedDRA search) was higher with semaglutide 2.4 mg than placebo, mainly driven by an imbalance in cholelithiasis (PT).

Clinical laboratory evaluations

- Overall, there were no noteworthy treatment group differences in haematology or biochemistry parameters (not part of a safety focus area).

Safety in special groups and situations

- The safety profile of semaglutide 2.4 mg was not affected to any clinically relevant extent by intrinsic factors (sex, baseline age, race, ethnic origin, baseline BMI, baseline kidney function, baseline HbA_{1c}, baseline chronic HF status and baseline CVD status) or extrinsic factors (region).
- There were no safety concerns for subjects within the semaglutide 2.4 mg group who lost 20% or more of their body weight during the trial, who had post-baseline hypotension, or who had increase in heart rate of >20 bpm during the trial, compared to those who did not.
- Overall, the results from this trial were consistent with observations for the general population with overweight and obesity as evaluated in the phase 3a development weight management programme (STEP programme), in which it was concluded that no dose adjustment is warranted in any selected population.

Table 9 Summary of SAEs by SOC, fatal events and AEs leading to trial product discontinuation – FAS in-trial

	Sema 2.4 mg				Placebo			
System organ class	N	(%)	E	R	N	(%)	E	R
Number of subjects	8803	(100)			8801	(100)		
Observation time (year)	29283				29112			
Serious events	2941	(33.41)	6622	22.61	3204	(36.40)	7507	25.79
Cardiac disorders	1008	(11.45)	1414	4.83	1184	(13.45)	1800	6.18
Infections and infestations	624	(7.09)	805	2.75	738	(8.39)	937	3.22
Nervous system disorders	444	(5.04)	544	1.86	496	(5.64)	623	2.14
Surgical and medical procedures	433	(4.92)	516	1.76	548	(6.23)	676	2.32
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	405	(4.60)	478	1.63	402	(4.57)	462	1.59
Gastrointestinal disorders	342	(3.89)	455	1.55	323	(3.67)	403	1.38
Injury, poisoning and procedural complications	305	(3.46)	414	1.41	313	(3.56)	419	1.44
General disorders and administration site conditions	273	(3.10)	298	1.02	316	(3.59)	354	1.22
Musculoskeletal and connective tissue disorders	236	(2.68)	288	0.98	254	(2.89)	302	1.04
Vascular disorders	231	(2.62)	262	0.89	259	(2.94)	332	1.14
Renal and urinary disorders	192	(2.18)	234	0.80	198	(2.25)	240	0.82
Respiratory, thoracic and mediastinal disorders	180	(2.04)	239	0.82	276	(3.14)	354	1.22
Hepatobiliary disorders	126	(1.43)	153	0.52	105	(1.19)	133	0.46
Blood and lymphatic system disorders	83	(0.94)	94	0.32	62	(0.70)	76	0.26
Metabolism and nutrition disorders	67	(0.76)	87	0.30	76	(0.86)	92	0.32
Reproductive system and breast disorders	65	(0.74)	68	0.23	43	(0.49)	46	0.16
Psychiatric disorders	59	(0.67)	75	0.26	49	(0.56)	59	0.20
Eye disorders	41	(0.47)	49	0.17	41	(0.47)	51	0.18
Investigations	34	(0.39)	41	0.14	41	(0.47)	47	0.16
Ear and labyrinth disorders	27	(0.31)	30	0.10	16	(0.18)	19	0.07
Skin and subcutaneous tissue disorders	19	(0.22)	22	0.08	20	(0.23)	21	0.07
Endocrine disorders	19	(0.22)	19	0.06	20	(0.23)	22	0.08
Congenital, familial and genetic disorders	12	(0.14)	14	0.05	9	(0.10)	9	0.03
Immune system disorders	11	(0.12)	12	0.04	14	(0.16)	14	0.05
Product issues	11	(0.12)	11	0.04	16	(0.18)	16	0.05
Fatal events	371	(4.21)	480	1.64	460	(5.23)	595	2.04
AEs leading to:								
Trial product discontinuation	2669	(30.32)	5360	18.30	1408	(16.00)	2218	7.62
Permanent trial product discontinuation	1461	(16.60)	2073	7.08	718	(8.16)	907	3.12

Note: SAEs by SOC class are sorted in descending order based on the proportion of subjects with at least one event in the semaglutide 2.4 mg group. AEs leading to discontinuation of trial product were events that were reported with action taken 'drug interrupted' or 'drug withdrawn'. AEs leading to permanent discontinuations of trial product were events indicated on the dose change form as being primary reason for treatment discontinuation and where treatment has not been resumed.
%: percentage of subjects in full analysis set, E: number of events, N: number of subjects,
R: events per 100 years of observation

CONCLUSIONS

This trial, including 17,604 subjects, demonstrated superiority of semaglutide 2.4 mg once weekly vs placebo with a clinically relevant reduction of 20% in MACE risk in people with established CV disease and overweight or obesity.

Treatment with semaglutide 2.4 mg resulted in beneficial and consistent effects across all composite endpoints and individual endpoints including all-cause death. Superiority of semaglutide 2.4 mg vs placebo was not confirmed for the confirmatory secondary endpoint of time to EAC-confirmed CV death, and hence superiority of semaglutide 2.4 mg vs placebo was not tested for the confirmatory secondary endpoints of time to first EAC-confirmed composite HF outcome and EAC-confirmed all-cause mortality.

Furthermore, the results from this trial showed that semaglutide 2.4 mg has beneficial effects on CV disease risk markers including body weight, glucose metabolism, blood pressure, lipid profile and hsCRP, and reduced the risk of deterioration in kidney function.

The beneficial and consistent results on individual and composite CV and mortality endpoints as well as CV risk factors support the use of semaglutide 2.4 mg for MACE risk reduction in a broad population of people with established CV disease and overweight or obesity.

The safety profile of semaglutide 2.4 mg in subjects with established CV disease and overweight or obesity is in line with the safety profile previously reported for semaglutide. No new safety concerns were identified for semaglutide 2.4 mg.

Thus, the balance between the benefits and the risks identified for treatment with semaglutide 2.4 mg once weekly in subjects with established CV disease and overweight or obesity is considered favourable.

DATE AND VERSION OF THIS REPORT
Report date: 01 September 2023. Version 1.0.

COMPLIANCE STATEMENT
This trial was conducted in accordance with the principles of the Declaration of Helsinki, ICH Good Clinical Practice, including the archiving of essential documents, and FDA 21 CFR 312.50 and 312.56.