EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2024
EMEA/400658/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Wegovy

International non-proprietary name: Semaglutide

Procedure No. EMEA/H/C/005422/II/0017

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CV	cardiovascular
CVOT	Cardiovascular Outcome Trials in Type 2 Diabetes
DBP	diastolic blood pressure
EAC	event adjudication committee
EMA	European Medicines Agency
ETD	estimated treatment difference
ETR	estimated treatment ratio
FAS	full analysis set
FU	follow up
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
HF	heart failure
LDL	low-density lipoprotein
LTFU	lost to follow-up
MACE	major adverse CV events
MI	myocardial infarction
NNT	number needed to treat
PD	pharmacodynamic(s)
PI	product information
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PYE	patient years exposure
PYO	person-years of observation
RA	receptor agonist
RMP	Risk Management Plan
SAE	serious adverse event

SBP	systolic blood pressure
s.c.	subcutaneous
SmPC	summary of product characteristics
T2D	type 2 diabetes
T2DM	type 2 diabetes melitus
TTE	time-to-event
UAP	unstable angina pectoris

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 10 October 2023 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include risk reduction of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and BMI ≥27 kg/m2 for WEGOVY, based on results from study EX9536-4388 (SELECT); this is a randomised, double-blind, placebo-controlled, trial comparing semaglutide 2.4 mg with placebo both administered s.c. once weekly in subjects with established cardiovascular disease and overweight or obesity. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. As part of the application the MAH is requesting a 1-year extension of the market protection.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0296/2023 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. On 24 June 2024, the applicant withdrew their claim for additional marketing protection.

Scientific advice

The MAH received Scientific Advice from the CHMP on 26 April 2018 (EMEA/H/SA/3657/2/2018/II). The Scientific advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Thalia Marie Estrup Blicher

Timetable	Actual dates
Submission date	10 October 2023
Start of procedure	28 October 2023
CHMP Rapporteur Assessment Report	22 December 2023
CHMP Co-Rapporteur Assessment	4 January 2024
CHMP members comments	15 January 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 January 2024
Request for supplementary information (RSI)	25 January 2024
CHMP Rapporteur Assessment Report	2 April 2024
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	18 April 2024
2nd RSI	25 April 2024
CHMP Rapporteur Assessment Report	12 June 2024
CHMP members comments	17 June 2024
Updated CHMP Rapporteur Assessment Report	21 June 2024
An Oral Explanation took place on	26 June 2024
3rd RSI	27 June 2024
CHMP Rapporteur Assessment Report	11 July 2024
CHMP members comments	15 July 2024
Updated CHMP Rapporteur Assessment Report	18 July 2024
CHMP Opinion	25 July 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The global prevalence of obesity is rising, at present more than 760 million people live with obesity globally and, by 2030 it is predicted that more than 1 billion people will be living with obesity.

Obesity is associated with several health-related complications including an increased risk of CV disease. CV disease is the leading cause of death and morbidity worldwide and currently accounts for more than 17.6 million deaths each year and this number is expected to increase to more than 22.2 million deaths by 2030. Overall, CV disease is more prevalent in individuals living with obesity and the lifetime risk for incident CV disease increases exponentially in both men and women with higher BMI. Moreover, most deaths associated with high BMI are caused by CV disease. Despite improvements in cardiometabolic risk factors, patients with established CV disease and obesity continue to be at considerable increased risk.

State the claimed the therapeutic indication

The MAH initially requested an extension of indication to include risk reduction of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and BMI ≥27 kg/m2.

Following the assessment of all data provided, the CHMP concluded that a separate CV indication is not acceptable. The CHMP does, however, support the addition of relevant data of the SELECT trial in SmPC section 5.1, and a reference to these data in SmPC section 4.1 (see section 'Scientific discussion' below).

Current therapeutic indications

Adults

Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- ≥30 kg/m^2 (obesity), or
- ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.

Adolescents (≥12 years)

Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- obesity* and
- body weight above 60 kg.

Treatment with Wegovy should be discontinued and re-evaluated if adolescent patients have not reduced their BMI by at least 5% after 12 weeks on the 2.4 mg or maximum tolerated dose.

*Obesity (BMI ≥95th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov) (see Table 1).

Table 1 BMI cut-off points for obesity (≥95th percentile) by sex and age for paediatric patients aged 12 and older (CDC criteria)

Age (years)	BMI (kg/m2) at 95th Percentile	
	Males	Females
12	24.2	25.2
12.5	24.7	25.7
13	25.1	26.3
13.5	25.6	26.8
14	26.0	27.2
14.5	26.4	27.7
15	26.8	28.1
15.5	27.2	28.5
16	27.5	28.9
16.5	27.9	29.3
17	28.2	29.6
17.5	28.6	30.0

Management

To date, no dedicated weight management Cardiovascular Outcome Trials (CVOTs) have been able to demonstrate a link between weight loss and CV risk reduction. There is an unmet medical need for weight management drugs targeting the residual CV risk in people with overweight or obesity.

2.1.2. About the product

Semaglutide is a potent GLP-1 analogue with a high degree of homology to human GLP-1. Targeting the GLP-1 receptor with a long-acting GLP-1 RA may reduce CV risk. GLP-1 is also a physiological regulator of appetite and treatment with GLP-1 RAs have been shown to induce weight loss.

Semaglutide (0.5 mg and 1.0 mg) for once weekly s.c. injection is approved worldwide under the tradename Ozempic® for treatment of T2D. Semaglutide 2.4 mg has been approved under the tradename Wegovy® for weight management in several regions and countries worldwide.

In the semaglutide T2D development programme (SUSTAIN), the CV safety of semaglutide s.c. 0.5 mg and 1.0 mg once weekly were assessed in a pre-approval non-inferiority CVOT (SUSTAIN 6) in patients with T2D and high CV risk. The trial indicated a statistically significant 26% risk reduction (HR: 0.74 $[0.58; 0.95]_{95\% CI}$) with semaglutide compared to placebo for the primary endpoint of time to first EAC-confirmed major adverse CV events (MACE), comprising CV death, non-fatal myocardial infarction (MI) and non-fatal stroke. These results are in line with results from other GLP-1 RA CVOTs, where superiority has been demonstrated for albiglutide, dulaglutide, liraglutide, efpeglenatide, and non-inferiority for semaglutide.

Semaglutide 2.4 mg has been approved under the tradename Wegovy® for weight management in several regions and countries worldwide. Trials with semaglutide 2.4 mg also demonstrated a treatment benefit with semaglutide in glucose metabolism and CV disease risk factors (lipids, blood pressure, waist circumference, visceral fat mass, CRP).

Trial 4388 was a phase 3b CVOT that was designed to demonstrate superiority of semaglutide 2.4 mg once weekly vs placebo, both added to standard of care in subjects with established CV disease and overweight or obesity without history of T1D or T2D, in reducing the risk of MACE (CV death, non-fatal MI, or non-fatal stroke). The trial contributed with both efficacy and safety data.

In summary, available data indicate that semaglutide s.c. reduces the risk of MACE in patients with T2D and high CV risk (SUSTAIN 6) and improves cardiometabolic risk factors in patients with obesity and/or T2D (STEP and SUSTAIN phase 3a development programmes). Accordingly, semaglutide s.c. may target the unmet medical need by reducing the residual CV risk in people with overweight or obesity. Trial 4388 was designed as a superiority trial (at the 2.5%, one-sided significance level), investigating semaglutide s.c. 2.4 mg once weekly vs placebo with regards to reduction in risk of adverse CV outcomes, in people with established CV disease and overweight or obesity, but without history of T1D or T2D (see section 'Scientific discussion' below).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The development programme

The global clinical development programme for semaglutide s.c. 2.4 mg for weight management, forming the basis for the initial application, comprised of 8 completed clinical trials:

- clinical pharmacology trials (of which two bioequivalence trials)
- 1 phase 2 dose-finding trial
- 4 phase 3a therapeutic confirmatory trials (referred to as the STEP 1-4 trials)

Compliance with CHMP guidance

Compliance with CHMP guidelines is discussed below; no issues were identified (see section 'Scientific discussion' below).

Scientific advice

The MAH received Scientific advice from the CHMP on 26 April 2018 (EMEA/H/SA/3657/2/2018/II). The Scientific advice pertained to clinical aspects of the dossier. The first discussion point was whether the Trial design and population support an additional indication within the weight management label. The proposed indication was *"to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adult patients with BMI ⩾ 27 kg/m² and established cardiovascular disease".* The CHMP commented that the population can be viewed as a subset of the target weight management population which is treated with the same therapeutic intent of preventing adverse clinical outcomes. Whilst precedent for CHMP decisions in the area of weight management does not exist, the applicant was referred to the fact that the CHMP has previously taken decisions not to accept separate indication wording for effects on different outcome variables within a patient population that is already indicated for treatment with the same therapeutic intent. Hence, additional wording in SmPC Section 4.1 might not be foreseen, unless a distinct target population is treated, or the treatment is justified as having a different therapeutic intent.

2.1.4. General comments on compliance with GCP

The applicant has provided a statement to the effect that clinical trials conducted outside European Union meet the ethical requirements of Directive 2001/20/EC.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

There were no updates to clinical pharmacology with semaglutide 2.4 mg based on SELECT.

GCP

The applicant has provided a statement to the effect that clinical trials conducted outside European Union meet the ethical requirements of Directive 2001/20/EC.

Overview table

Trial ID/Protocol number	All countries involved	Non-EU countries involved
EX9536-4388 (SELECT)	Algeria, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Colombia, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, India, Ireland, Israel, Italy, Japan, Latvia, Malaysia, Mexico, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, United States	Algeria, Argentina, Australia, Brazil, Canada, Colombia, India, Israel, Japan, Malaysia, Mexico, Russia, Serbia, South Africa, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, United States

2.4. Clinical efficacy

2.4.1. Main study

Trial 4388 was a phase 3b CVOT that was designed to demonstrate superiority of semaglutide 2.4 mg once weekly vs placebo, both added to standard of care in subjects with established CV disease and overweight or obesity without history of T1D or T2D, in reducing the risk of MACE (CV death, non-fatal MI, or non-fatal stroke). The trial contributed with both efficacy and safety data.

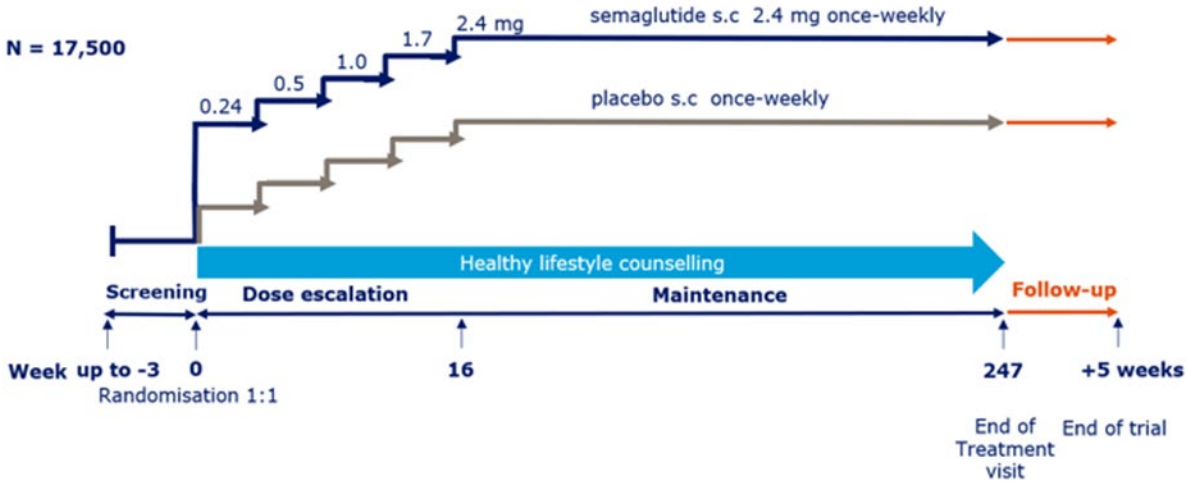
Design

Trial 4388 was a multinational, multicentre, randomised, double-blind, parallel group, placebo-controlled trial. The trial was designed to demonstrate superiority of semaglutide 2.4 mg once weekly vs placebo, both added to CV standard of care in subjects with established CV disease and overweight or obesity, but without history of T1D or T2D, in reducing the risk of MACE (CV death, non-fatal MI or non-fatal stroke).

The trial design is shown schematically in **Figure 1**. The trial included a 16-week dose escalation period, a maintenance period, and a 5-week follow up (FU) period. The trial was event driven with trial closure planned to be performed when the targeted number of primary endpoint events was reached. An independent 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.

A total of 17,500 adults with established CV disease and overweight or obesity were planned to be randomised in a 1:1 ratio to receive either once weekly treatment with semaglutide 2.4 mg or placebo as an adjunct to standard of care.

Figure 1 Trial design of trial 4388



Abbreviations: s.c. = subcutaneously

Study participants

Trial population

Subjects with established CV disease and overweight or obesity and without history of T1D or T2D were enrolled in Trial 4388. People with history of T1D or T2D were not eligible for inclusion in the trial to eliminate any confounding effects that a diabetes diagnosis could have on CV risk.

Inclusion and key exclusion criteria are presented below.

Inclusion criteria

Informed consent obtained before any trial-related activities. Trial-related activities were any procedures that were carried out as part of the trial, including activities to determine suitability for the trial

Male or female, age ≥45 years at the time of signing informed consent

BMI ≥ 27 kg/m^2

Have established CV disease as evidenced by at least one of the following:

a. prior MI

b. prior stroke (ischemic or haemorrhagic stroke)

c. symptomatic PAD, as evidenced by intermittent claudication with 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 unstable angina pectoris (UAP) or transient ischaemic attack within the past 60 days prior to the day of screening
- Presently classified as being in NYHA Class IV HF
- Hemoglobin A1c (HbA_{1c}) ≥ 48 mmol/mol (6.5%) as measured by the central laboratory at screening
- History of T1D or T2D (history of gestational diabetes was allowed)

Objectives, endpoints and estimands

The trial objectives and corresponding endpoints are presented in the table below.

Table 2 Objectives and endpoints

Objectives	Endpoints
Primary objective: To demonstrate that semaglutide s.c. 2.4 mg once weekly lowers the incidence of MACE vs 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 requiring hospitalisation or urgent HF visit
Secondary objectives: To compare the effect of semaglutide s.c. 2.4 mg once weekly vs 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	**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

Objectives	Endpoints
• Renal function	• 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 **Exploratory endpoints:** • Change from randomisation to week 117 in: Glycaemic status (normoglycaemia, pre-diabetes or T2D) • Patient reported outcome: Change from randomisation to year 2/week 104 (visit 14) in: Total score WRSSM
Exploratory objectives: To compare the effect of semaglutide s.c. 2.4 mg once weekly vs placebo as an adjunct to standard of care in subjects with established CV disease and overweight or obesity with regards to: • Smoking status • Hospitalisations	**Exploratory endpoints:** • Being current smoker at year 2/week 104 (visit 14) (yes/no) • Total number of hospitalised days from randomisation to end of trial • Total number of hospitalisations from randomisation to end of trial

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; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio; UAP = unstable angina pectoris; WRSSM = weight related sign and symptom measure.

Estimands

Primary estimand (intention-to-treat)

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.

Secondary estimand for selected time-to-event endpoints

A secondary estimand covers confirmatory endpoints and is evaluating the effect of the randomised treatment intervention in all randomised subjects had they remained on their randomised treatment for the entire trial. This estimand is addressed using FAS and the first on-treatment observation period.

Secondary estimand for body weight

A similar secondary estimand is evaluating the effect of the randomised treatment intervention after 52 weeks on change in body weight, in all randomised subjects had they remained on their randomised treatment for 52 weeks. This estimand is addressed using FAS and the first on-treatment observation period but restricted to the initial 52 weeks.

Evaluation of CV risk reduction

The primary endpoint was time from randomisation to first occurrence of a 3-composite MACE endpoint consisting of CV death, non-fatal MI, and non-fatal stroke (**Table 1**). Fatal MI/stroke was defined as an EAC-confirmed MI/stroke occurring less than 30 days before an EAC-confirmed CV death classified with cause of death being MI/stroke. All other events of MI/stroke were defined as non-fatal. Deaths of undetermined cause (i.e., deaths for which the event adjudication committee (EAC) could not determine the cause) were categorised as CV death. A composite endpoint including all-cause death instead of CV death was defined as a supportive secondary endpoint in this trial (**Table 1**).

Trial 4388 was designed to evaluate CV risk reduction, and reduction in CV death is expected to drive the overall risk reduction of all-cause mortality. However, obesity is associated with increased rates of chronic kidney disease, cancer and diabetes-associated mortality, and thus, the benefits of successful treatment of obesity are expected to influence not only CV mortality risk, but also other components of the overall mortality risk. Based on these considerations, time from randomisation to CV death and all-cause death were confirmatory secondary endpoints in this trial (**Table 1**).

An independent external event adjudication committee (EAC) was established for the trial to perform ongoing blinded adjudication of selected event types, using definitions and guidelines pre specified in the EAC Charter.

As government lockdowns were initiated due to the COVID 19 pandemic (starting date assessed by Novo Nordisk to be 1 February 2020) subjects and investigators participated in the trial while coping with the restrictions of the pandemic.

Statistical methods

A detailed presentation of the statistical analysis methods applied in Trial 4388 is provided in the CTR.

Analysis set and observation periods

Definition of analysis set

The following analysis set was defined in the protocol and the SAP, prior to unblinding, and 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.

Definition of observation periods

A trial completer was defined as a subject that either attended the end-of-trial 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.

In-trial observation period

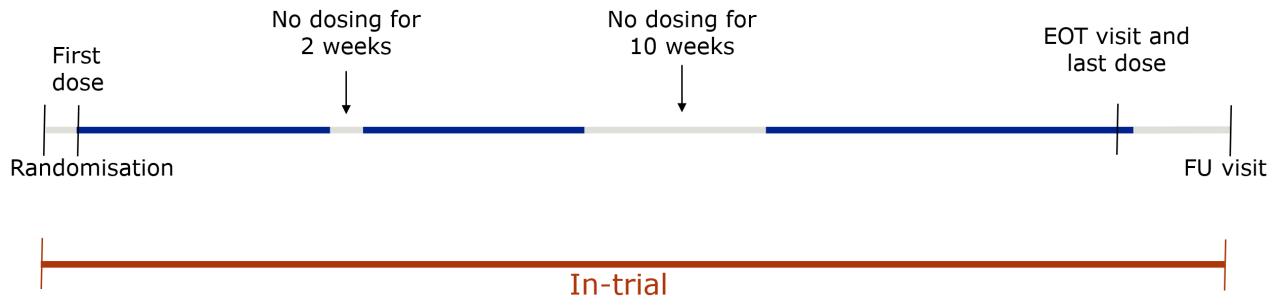
The in-trial observation period for a subject was defined as the period from date of randomisation to the first of:

- Date of FU visit

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

The in-trial observation period covered the time from randomisation to last day in trial, regardless of treatment adherence, as illustrated in the example in **Figure 2**.

Figure 2 Illustration of in-trial observation period for sample subject

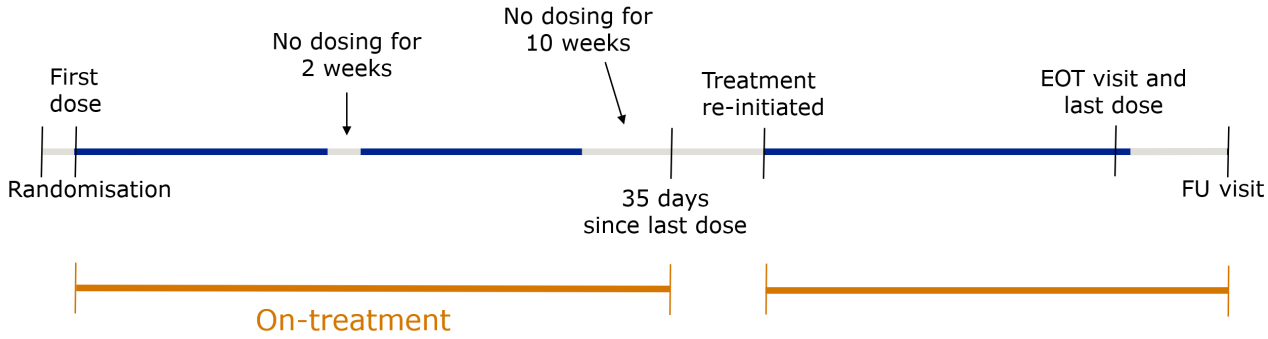


Abbreviations: EOT = end of treatment; FU = follow-up

On-treatment observation period

The on-treatment period was defined as the *sum of* all time points in the in-trial period where a subject had taken trial product within the previous 5 weeks. The on-treatment observation period for a subject could thus consist of several time intervals with gaps between, if treatment had been paused for >35 consecutive days, as illustrated in the example in Figure **3**.

Figure 3 Illustration of on-treatment observation period for sample subject

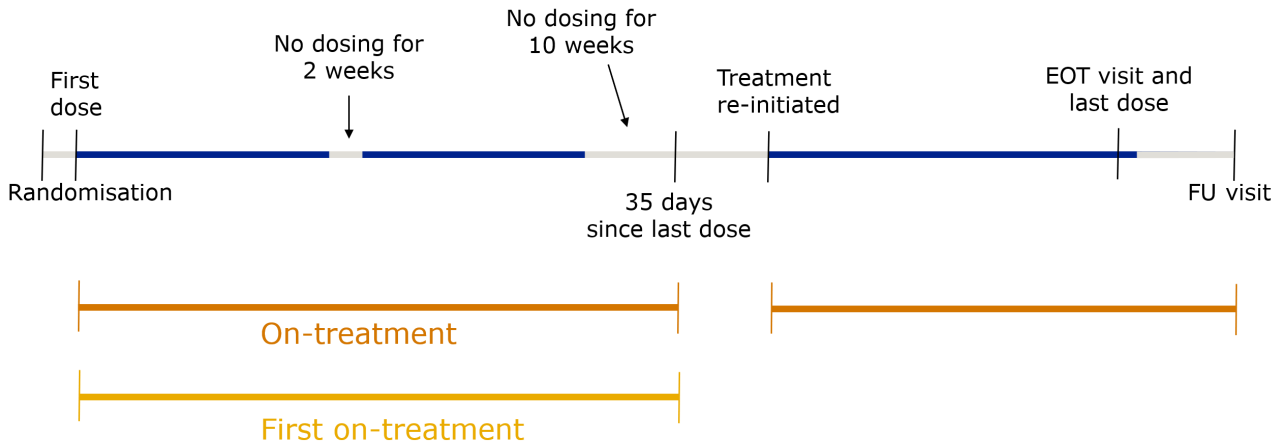


Abbreviations: EOT = end of treatment; FU = follow-up

First on-treatment observation period

The first on-treatment observation period was defined as the on-treatment observation period until first time being off treatment for >35 days. Thus, it was the first of the time intervals (if more than one) in the on-treatment observation period, as illustrated in the example in Figure **4**.

Figure 4 Illustration of first on-treatment observation period for sample subject



Abbreviations: EOT = end of treatment; FU = follow-up

Interim testing for superiority

One interim test evaluating superiority of the primary endpoint was prespecified to be performed 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%.

Trial integrity was ensured by using an external independent statistical service provider (independent of trial conduct and external to Novo Nordisk) to perform the interim testing. The DMC evaluated the unblinded interim test results using the group sequential stopping boundaries as guidance as well as considerations specified in the DMC charter.

Based on the interim testing, the DMC recommended to continue the trial on 19 July 2022. The interim evaluation was assessed to have no impact on the conduct of the trial or the final interpretation of results

Testing hierarchy

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 to be analysed under multiplicity control. Given superiority for the primary endpoint, the superiority hypothesis stated below was 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 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 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.

Pre-specified analyses of primary endpoint

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% 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 is rejected using the Lan-DeMets alpha spending function specified above to determine the nominal significance level.

Competing risk from non-CV death was technically handled as censorings in the Cox analysis.

Sensitivity analyses

Multiple sensitivity analyses were pre-specified to assess the robustness of the primary analysis results. An overview of the sensitivity analyses is provided in **Table 2** and further details are described in the SAP.

The primary analysis assumes independent censoring for subjects who have withdrawn consent or were LTFU. To investigate the impact of this assumption on the primary analysis, a 2-way tipping point sensitivity analysis based on the approach described in Zhao et al.[42] was prespecified.

Two additional sensitivity analyses were performed by imputing event times for subjects who were withdrawn or LTFU, either by using the event rate after discontinuation from those who permanently

discontinued treatment but remained in trial, or by using the event rate after first discontinuation for all who had at least one treatment pause (**Table 2**).

Supplementary analyses

Furthermore, the robustness and impact of the results from the primary analysis was evaluated by performing pre-specified supplementary analyses including estimation of the absolute risk difference at week 156 and first on-treatment analysis (**Table 2**). In addition, an analysis of non-CV death using the same Cox model as for the primary endpoint was done to evaluate the influence of the competing risk non-CV death on the primary results.

Supplementary analyses were pre-specified to assess the impact of the COVID-19 pandemic as well as the impact of co-participation in COVID-19 trials on the primary endpoint (**Table 2**). This is described in detail in the SAP.

Table 1 Pre-specified sensitivity and supplementary analyses for major adverse cardiovascular events

Analysis	Model	Analysis set	Observation period
Pre-specified sensitivity analyses			
Tipping point analysis • Imputation of event times for subjects who had withdrawn or were lost to follow-up using the conditional event distribution with a penalty.	Cox proportional hazards model	FAS	In-trial
Sensitivity analysis 2a – permanent treatment discontinuation • Imputation of event times for subjects who had withdrawn or were lost to follow-up using an estimated annual event rate from subjects who discontinued treatment permanently but remained in the trial.	Cox proportional hazards model	FAS	In-trial
Sensitivity analysis 2b – first treatment discontinuation • Imputation of event times for subjects who had withdrawn or were lost to follow-up using an estimated annual event rate for subjects who discontinued treatment at any point in the trial.	Cox proportional hazards model	FAS	In-trial
Pre-specified supplementary analyses			
Absolute risk difference	Cumulative incidence function for each group used to estimate the risk	FAS	In-trial

Analysis	Model	Analysis set	Observation period
First on-treatment	Cox proportional hazards model	FAS	First on-treatment period
Impact of COVID-19 and impact of co-participation in COVID-19			
First MACE without concurrent COVID-19 SAE • The definition of MACE is modified so any MACE occurring concurrently with a COVID-19 SAE in a subject is not considered a MACE.	Cox proportional hazards model	FAS	In-trial
First MACE without concurrent COVID-19 AE • The definition of MACE is modified so any MACE occurring concurrently with a COVID-19 AE in a subject is not considered a MACE.	Cox proportional hazards model	FAS	In-trial
First MACE or non-CV death occurring concurrently with a COVID-19 SAE	Cox proportional hazards model	FAS	In-trial
Impact of co-participation in COVID-19 treatment or prevention trials • All subjects co-participating in a COVID-19 treatment or prevention trial were censored at the day they receive the first trial treatment for preventing or treating COVID-19	Cox proportional hazards model	FAS	In-trial

Abbreviations: AE = adverse event, COVID = corona virus disease; FAS = full analysis set; MACE = major adverse cardiovascular event; SAE = serious adverse event

Subpopulation analyses

The consistency in the treatment effect for the primary endpoint is explored by subpopulation analyses based on baseline information (sex, age, race, ethnicity, region, HbA_{1c}, BMI, CV disease, eGFR and chronic HF). The subpopulation analyses were based on Cox proportional hazards models with an interaction between treatment group (semaglutide 2.4 mg, placebo) and the specific baseline variable as a factor.

Pre-specified analyses of secondary endpoints

The confirmatory secondary endpoints were analysed using a Cox proportional hazards model as described for the primary endpoint and addressing the primary estimand. Confirmatory secondary endpoints were analysed under multiplicity control.

Sensitivity analysis 2a and 2b with imputation from subjects off treatment were done for all confirmatory secondary endpoints. Analyses with regards to the impact of the COVID-19 pandemic for the primary endpoint were also to be done for CV death and the HF composite endpoint.

For the HF composite endpoint, a supplementary analysis was done by replacing the CV death component with all-cause death.

In addition, all-cause death was analysed using FAS and an extended in-trial observation period including the FU for vital status for subjects who withdrew consent or were LTFU. The relative risk for the binary endpoint death/alive was compared between the two treatment groups using the likelihood ratio method. The model was chosen because it doesn't depend on the observation time which is only extended for subjects withdrawn or LTFU.

An overview of the statistical methods used for each type of endpoint is available in **Table 3**.

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

Time-to-event endpoints
The time-to-event 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.
First and recurrent events endpoints
Mean number of events was analysed using a marginal mean regression model for recurrent events accounting for competing risk of dying. The model included treatment as a factor.
Binary endpoints
The binary explorative endpoints were analysed using logistic regression with treatment as a factor and either the baseline status as a factor (smoking) or baseline HbA_{1c} as covariate (glycaemic status).
Sensitivity analyses
In all sensitivity analyses for TTE endpoints subjects in the two treatment groups who withdrew consent or were LTFU had event times imputed. If the imputed event time occurred after the subjects planned end-of-trial time the subjects were censored at the planned end-of-trial time. Multiple imputed data sets were analysed with separate Cox regressions including treatment as factor and the results were combined using Rubin's rule. For body weight a sensitivity analysis using multiple imputation from the placebo arm only was done.

Total number of hospital days
Total length of stay (days) in hospital as a function of study time was estimated using methods for multi-state models. Comparisons of treatment groups at the planned time points were done using the method of pseudo-observations.
All-cause death and extended in-trial period
All-cause death was analysed using FAS and the extended in-trial observation period including the FU for vital status for subjects who withdrew consent or were LTFU. For subjects who completed the trial their end-of-trial vital status was used. For subjects who were LTFU or withdrew consent, the vital status as collected at trial closure was used and subjects with unknown vital status were excluded from the analysis. The relative risk between the two treatment groups for the endpoint death/alive was calculated non-parametrically. The test and CI were derived using likelihood methods.

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; HbA_{1c} = glycated haemoglobin; FAS = full analysis set; FU = follow-up; LTFU = lost to follow-up; TTE=time-to-event

Results

Participant flow

Subject disposition

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 (1:1) to treatment with semaglutide 2.4 mg (8,805 subjects) or placebo (8,804 subjects), **Table 4**. 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).

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.

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 4

Table 2-1 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.

Cross-reference: Trial 4388 (M 5.3.5.1), Table 14.1.1

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. Exposure across races and ethnic groups was ensured by including subjects from North America, Europe, Asia and other regions. 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%) **Table 5**.

Table 5

Table 2-2 Baseline characteristics and demographics

	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)

%: percentage of subjects in full analysis set, N: number of subjects, SD: standard deviation

Cross-reference: Trial 4388 (M 5.3.5.1), Tables 14.1.14 and 14.1.15

Randomised subjects were to have established CV disease in accordance with inclusion criteria. 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.

CV history was overall well balanced across treatment groups and the distribution of the CV diseases was as expected for this population. Overall, 24.3% of patients had a history of chronic heart failure, including 12.9% categorised by the investigator as heart failure with preserved ejection fraction and 7.7% as heart failure with reduced ejection fraction.

The types of CV-related medications ongoing at randomisation were similar between the two treatment groups. At randomisation, approximately 92% of subjects in each treatment group were receiving CV medication, primarily beta blockers, ACE inhibitors or angiotensin receptor blockers, as expected for a population with established CV disease. Approximately 90% of subjects were receiving lipid-lowering medication, primarily statins. Approximately 86% of subjects were receiving platelet aggregation inhibitor, mainly acetylsalicylic acid (approximately 78%). Diuretics, mainly thiazides, loop diuretics and aldosterone antagonists were received by approximately 34% of subjects.

Eligible subjects were to have a BMI ≥27 kg/m^2, and thus, the trial population included subjects with overweight (BMI ≥27 to <30 kg/m^2) or obesity (BMI ≥30 kg/m^2). A total of 71.5% of the trial

population had a BMI ≥30 kg/m^2 at baseline. Mean BMI was 33.34 kg/m^2, mean body weight was 96.68 kg and mean waist circumference was 111.3 cm at baseline with no noteworthy differences between treatment groups.

The proportions of subjects with weight related comorbidities at screening were similar for the two treatment groups, and the distribution of the comorbidities was as expected for the population.

At baseline, 66.4% of subjects had HbA_{1c} ≥5.7%, indicative of prediabetes (≥5.7% to <6.5%), and 33.5% of subjects had HbA_{1c} <5.7% with no noteworthy difference between the two treatment groups.

Baseline HbA_{1c} was similar between the two treatment groups with a mean HbA_{1c} of 5.78% (39.71 mmol/mol).

The distribution of subjects with mild, moderate and severe renal impairment at baseline was similar across treatment groups. Most subjects had normal renal function or mild renal impairment at baseline. Overall, 10.4% of subjects had moderate renal impairment and 0.4% had severe renal impairment, with no imbalance across treatment groups.

Outcomes and estimation

Evaluation of cardiovascular and other efficacy outcomes

An overview of results from the predefined confirmatory endpoints analyses are provided in **Table 6.** The results are presented in the order defined by the testing hierarchy.

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

Superiority of semaglutide 2.4 mg to placebo was not confirmed for the confirmatory secondary mortality endpoint EAC-confirmed CV death. Superiority of semaglutide 2.4 mg to placebo was not tested for the confirmatory secondary endpoint of time to first EAC-confirmed composite HF outcome comprising the component 'HF requiring hospitalisation or urgent HF visit' or the component 'CV death'. Furthermore, superiority of semaglutide 2.4 mg to placebo was not tested for the confirmatory secondary mortality endpoint EAC-confirmed all-cause death.

Table 6

Table 2-3 Superiority testing of confirmatory endpoints

	Estimate 95% CI	p-value	Nominal significance level	Hypothesis	Conclusion
Time to first EAC-confirmed MACE					
HR (Sema 2.4 mg/Placebo:	0.80 [0.72; 0.89]	<.0001	0.02281	Superiority	Confirmed
	0.80 [0.72; 0.90][a]				
Time to EAC-confirmed CV death					
HR (Sema 2.4 mg/Placebo:	0.85 [0.71; 1.01]	0.0327	0.01148	Superiority	Not confirmed
Time to first EAC-confirmed composite heart failure outcome					
HR (Sema 2.4 mg/Placebo:	0.82 [0.71; 0.96]	NA	NA	Superiority	Not tested
Time to EAC-confirmed all-cause death					
HR (Sema 2.4 mg/Placebo:	0.81 [0.71; 0.93]	NA	NA	Superiority	Not tested

Notes: Results from confirmatory analyses of primary endpoint EAC-confirmed MACE and confirmatory secondary endpoints CV death, composite heart failure outcome and all-cause death following the order of the pre-specified testing hierarchy. The nominal significance level was updated based on available number of events using pre-specified alpha spending functions. For the primary endpoint (EAC-confirmed MACE) the Lan-DeMets alpha spending function was used and for the confirmatory secondary endpoints (CV death, composite heart failure outcome and all-cause death) a separate alpha spending function, as described in the SAP, was used.

[a] Adjustment for GSD was done using likelihood ratio ordering.

The presented confidence intervals are two-sided and the p-values are one-sided.

Abbreviations: CI: confidence interval, CV: cardiovascular, EAC: event adjudication committee, GSD: group sequential design; MACE: major adverse cardiovascular event, NA: not applicable; SAP: statistical analysis plan.

Cross-reference: based on Trial 4388 (M 5.3.5.1), Table 14.2.1 and Table 14.2.3

Cardiovascular outcomes

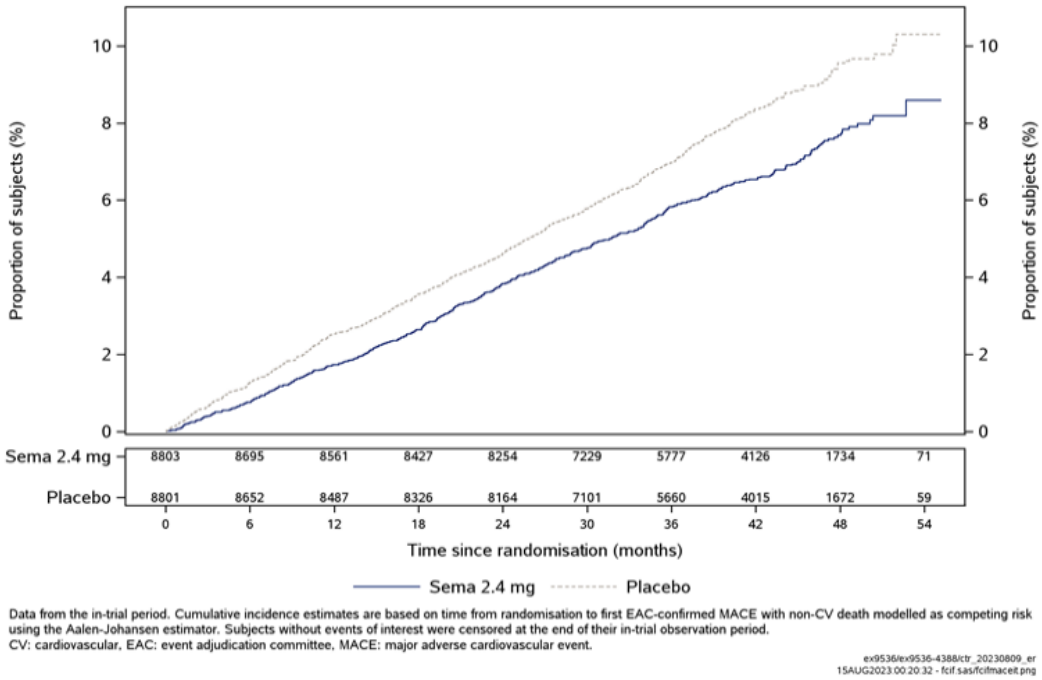
Three-component MACE and individual components

In Trial 4388 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.

A total of 1,455 MACEs in 1,270 subjects (of which not all were first events) were confirmed during the in-trial observation period. MACE occurred less frequently and at a lower rate with semaglutide 2.4 mg (6.5% of subjects, 2.2 events per 100 PYO) than with placebo (8.0% of subjects, 2.8 events per 100 PYO).

The estimated risk of experiencing a first MACE within any certain time from randomisation was lower for semaglutide 2.4 mg compared with placebo as reflected in the separation of the curves after trial initiation, and throughout the trial (**Figure 5**).

Figure 5 **Cumulative incidence plot of time to first EAC-confirmed MACE (CV death, non-fatal MI, or non-fatal stroke)**



Data from the in-trial period. Cumulative incidence estimates are based on time from randomisation to first EAC-confirmed MACE with non-CV death modelled as competing risk using the Aalen-Johansen estimator. Subjects without events of interest were censored at the end of their in-trial observation period.
CV: cardiovascular, EAC: event adjudication committee, MACE: major adverse cardiovascular event.

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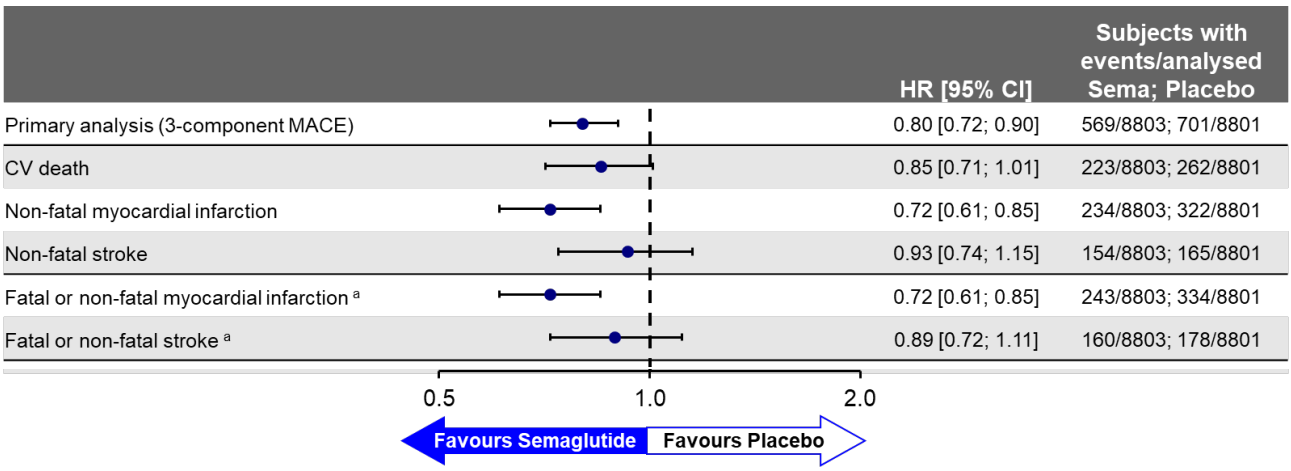
The primary analysis of time to first EAC-confirmed MACE resulted in an estimated HR of 0.80 [0.72; 0.90]$_{95\% \text{ CI}}$ (p <0.0001) for semaglutide 2.4 mg relative to placebo (**Figure 6**). The absolute risk difference between semaglutide 2.4 mg and placebo at week 156 was −0.011 [−0.019; −0.004]$_{95\% \text{ CI}}$.

Each of the components of MACE contributed to the superior MACE reduction and the components (CV death, non-fatal MI and non-fatal stroke) had HRs below 1.0 favouring semaglutide.

Figure 6 **Time to first MACE and components**



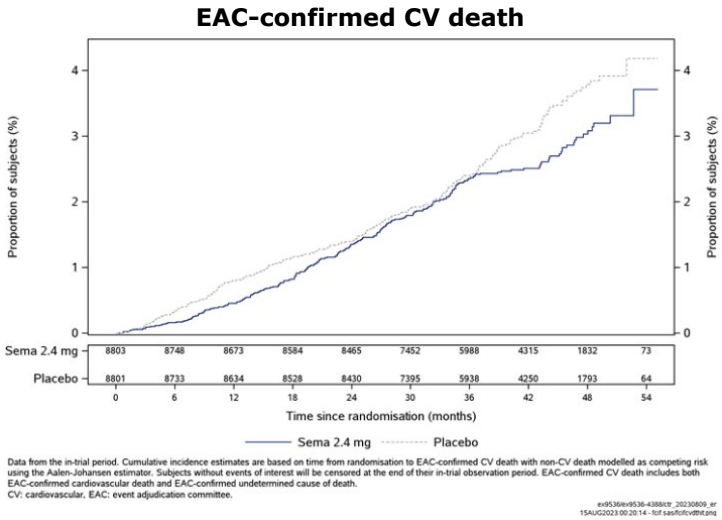
Notes: FAS in-trial. Estimated HRs and corresponding CIs are from separate Cox proportional hazards models with treatment as fixed factor. For the primary analysis (first MACE), the HR and CI are adjusted for the group sequential design using the likelihood ratio ordering. Subjects without events of interest were censored at the end of their in-trial observation period. Based on the available number of events for analysis, the nominal significance level was updated to 0.02281 using the Lan-DeMets alpha spending function. EAC-confirmed CV death includes both EAC-confirmed cardiovascular death and EAC-confirmed undetermined cause of death.

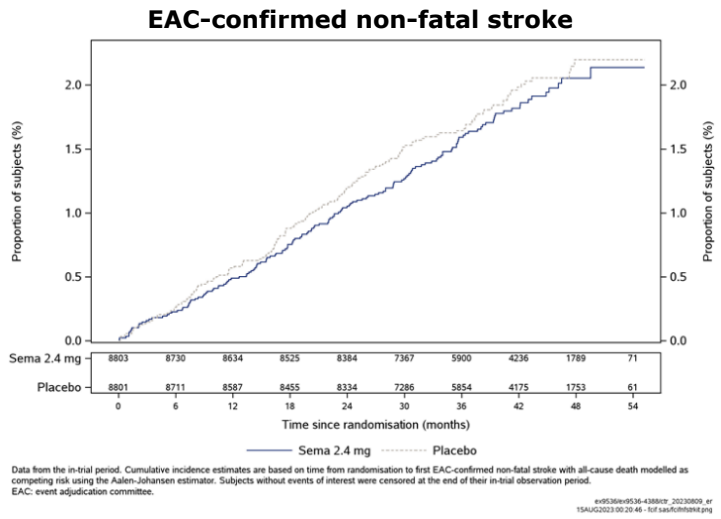
[a] From supplementary analysis.

Abbreviations: CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MACE: major adverse cardiovascular event; sema: semaglutide.

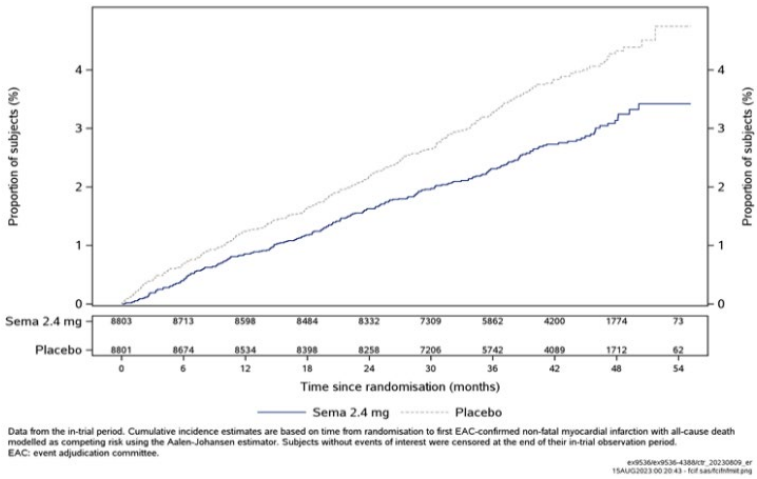
The cumulative incidence curves of the individual components generally followed a pattern similar to that seen for overall MACE with immediate separation of the curves after trial initiation, and throughout the trial (**Figure 7**). Analyses of time to first fatal or non-fatal MI and first fatal or non-fatal stroke (supplementary analyses) were consistent with the results for the non-fatal components (**Figure 6**).

Figure 7 **Cumulative incidence plot of time to CV death, first non-fatal stroke and first non-fatal MI**





EAC-confirmed non-fatal MI



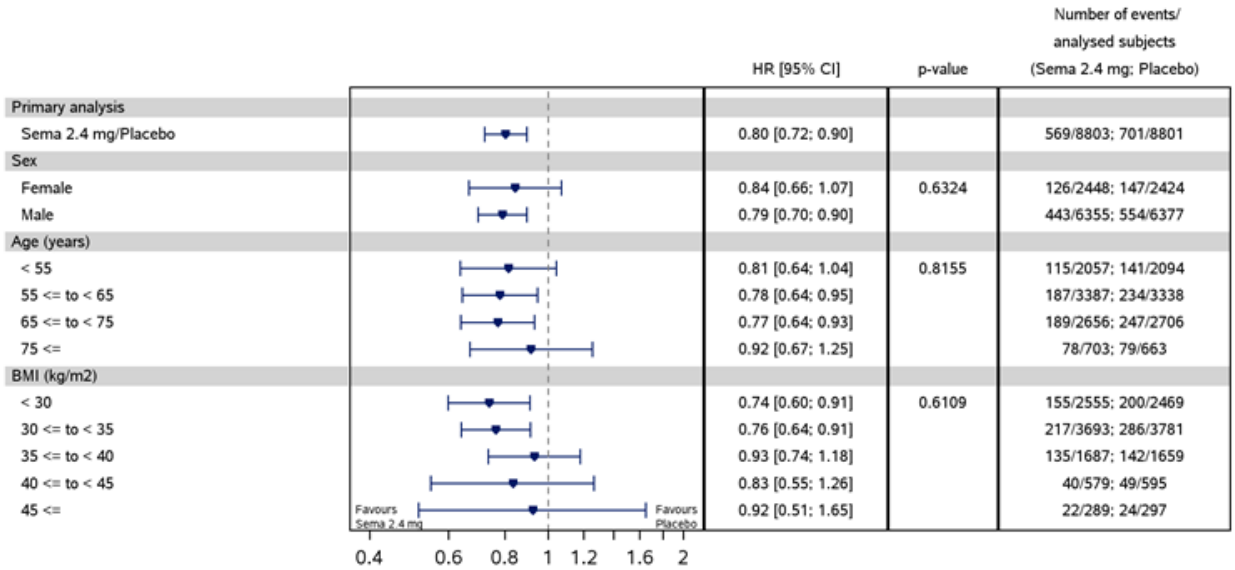
Data from the in-trial period. Cumulative incidence estimates are based on time from randomisation to first EAC-confirmed non-fatal myocardial infarction with all-cause death modelled as competing risk using the Aalen-Johansen estimator. Subjects without events of interest were censored at the end of their in-trial observation period.
EAC: event adjudication committee.

Subpopulation analyses of 3-component MACE

The consistency in the treatment effect for the primary endpoint was assessed separately by the prespecified subpopulations defined by baseline demographics (sex, age, race, ethnicity, region) and baseline prognostic disease characteristics (CV disease, BMI, renal function, HbA_{1c} status and chronic heart failure status).

The results of the predefined subpopulation analyses (**Figure 8**, **Figure 9** and **Figure 10**) were overall consistent with the results from the primary analysis with point estimates of HR <1 indicative of beneficial effect of semaglutide 2.4 mg vs placebo across all subpopulations. Note that in some of the subpopulations, the number of subjects with events were low and therefore the results should be interpreted with caution.

Figure 8 Subpopulation analyses of time to first MACE by baseline sex, age, BMI



Data from the in-trial period. For the primary analysis, the hazard ratio and confidence interval are adjusted for the group sequential design using the likelihood ratio ordering. For the subgroup analyses, estimated hazard ratios and corresponding confidence intervals are calculated in a Cox proportional hazards model with interaction between treatment group and the relevant subgroup as fixed factor.
p-value: p-value for test of no interaction effect.
CI: confidence interval, EAC: event adjudication committee, HR: hazard ratio, MACE: major adverse cardiovascular event.

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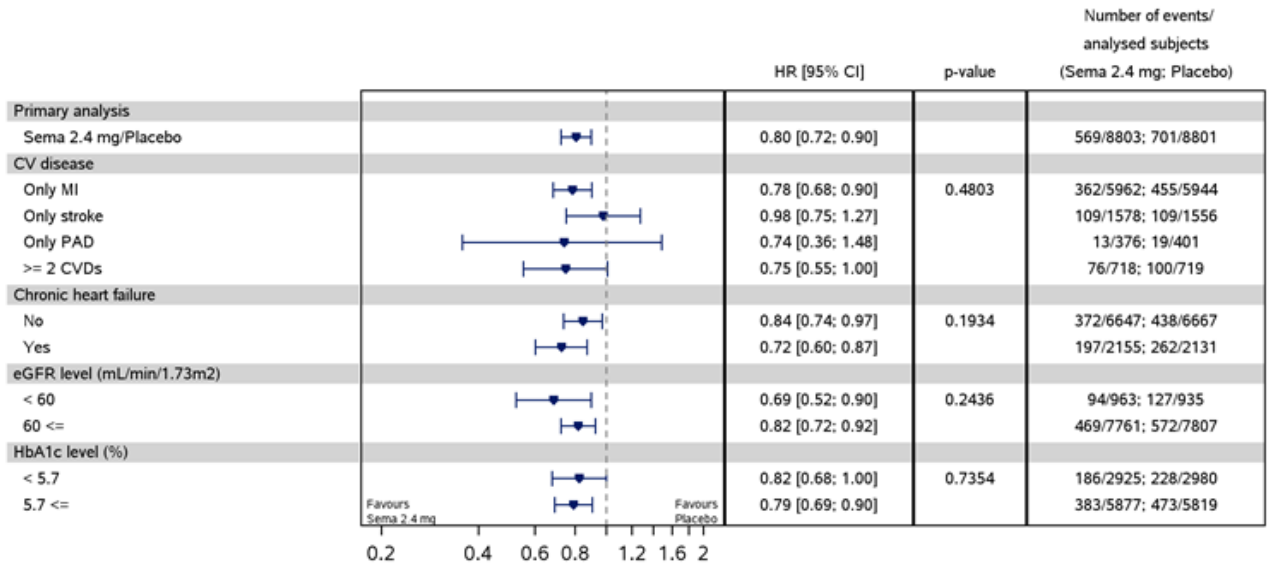
Figure 9 Subpopulation analyses of time to first MACE by baseline CV disease, chronic heart failure, eGFR level, and HBA_{1c} level



Data from the in-trial period. For the primary analysis, the hazard ratio and confidence interval are adjusted for the group sequential design using the likelihood ratio ordering. For the subgroup analyses, estimated hazard ratios and corresponding confidence intervals are calculated in a Cox proportional hazards model with interaction between treatment group and the relevant subgroup as fixed factor.
p-value: p-value for test of no interaction effect.
CI: confidence interval, CV: cardiovascular, EAC: event adjudication committee, eGFR: estimated glomerular filtration rate, HR: hazard ratio, MACE: major adverse cardiovascular event, MI: myocardial infarction, PAD: peripheral arterial disease.

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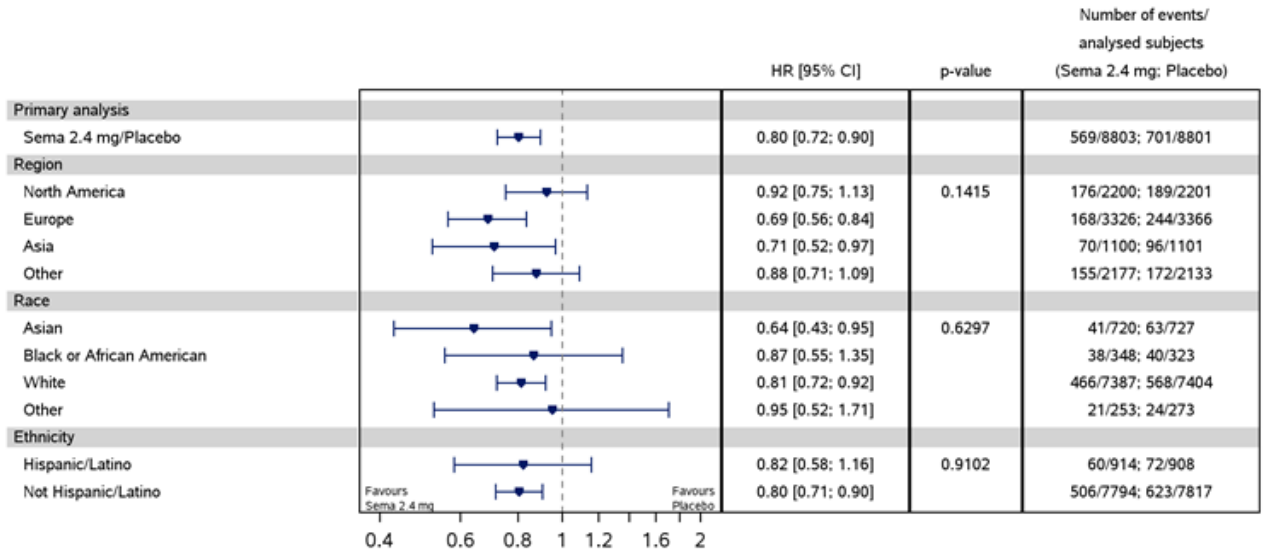
Figure 10 Subpopulation analyses of time to first MACE by baseline region, race and ethnicity



Data from the in-trial period. For the primary analysis, the hazard ratio and confidence interval are adjusted for the group sequential design using the likelihood ratio ordering. For the subgroup analyses, estimated hazard ratios and corresponding confidence intervals are calculated in a Cox proportional hazards model with interaction between treatment group and the relevant subgroup as fixed factor.
p-value: p-value for test of no interaction effect.
CI: confidence interval, EAC: event adjudication committee, HR: hazard ratio, MACE: major adverse cardiovascular event.

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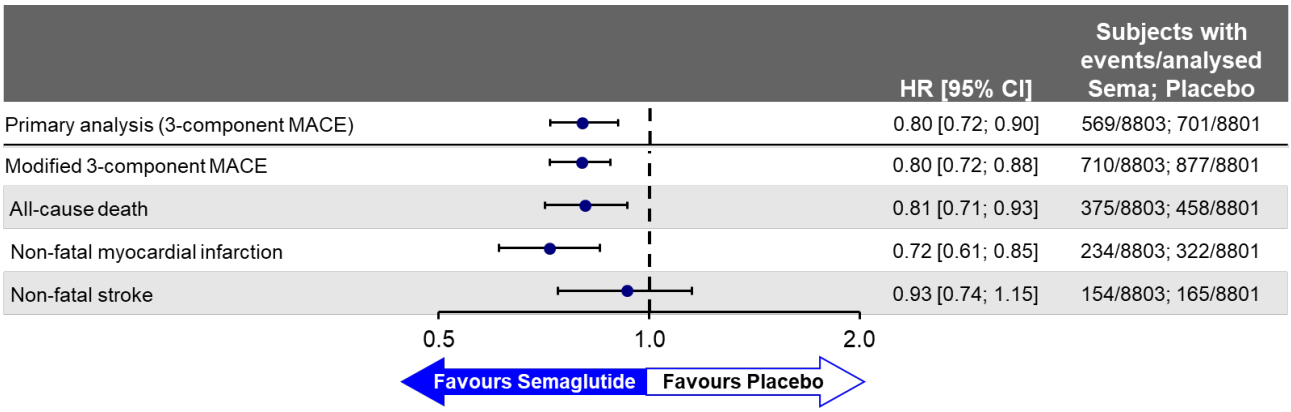
Modified MACE (all-cause death, non-fatal MI and non-fatal stroke)

A modified MACE endpoint (all-cause death, non-fatal MI, non-fatal stroke) evaluated the impact on all deaths and not only deaths due to CV causes.

The proportion of subjects with first events and event rates were lower with semaglutide 2.4 mg than with placebo; a total of 710 subjects (8.1%) experienced events with semaglutide 2.4 mg corresponding to event rates of 2.5 events per 100 person-years of observation (PYO) vs 877 subjects (10.0%) with placebo corresponding to event rates of 3.1 events per 100 PYO.

The results for time to first modified MACE (all-cause death, non-fatal MI or non-fatal stroke): HR: 0.80 [0.72; 0.88]$_{95\% \text{ CI}}$ were in line with the results for the primary MACE analysis with a HR and an upper bound of the confidence interval below 1 (**Figure 11**).

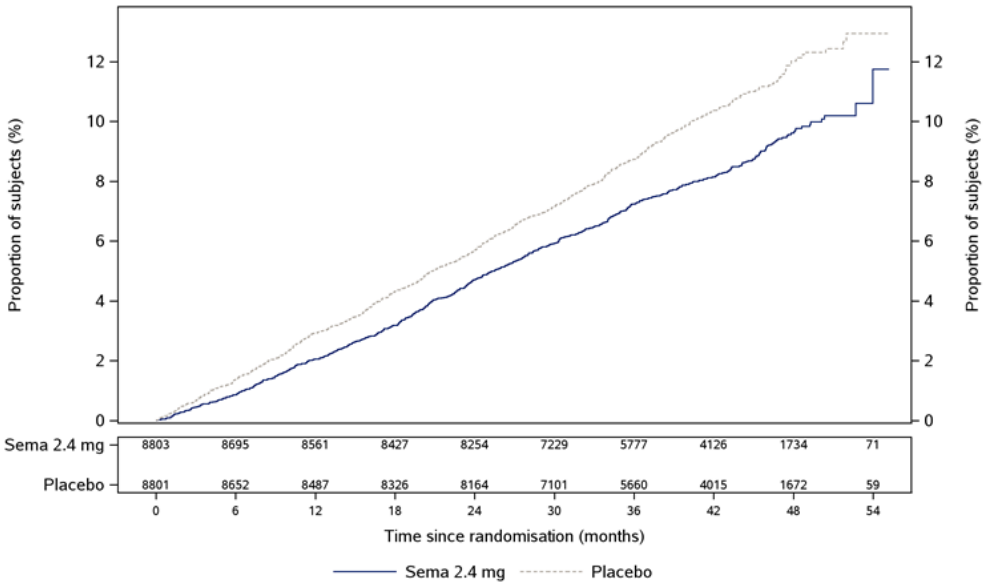
Figure 11 Time to first modified MACE (all-cause death, non-fatal MI or non-fatal stroke)



Notes: FAS in-trial. Estimated HRs and corresponding CIs are from separate Cox proportional hazards models with treatment as fixed factor. For the primary analysis (first MACE), the HR and CI are adjusted for the group sequential design using the likelihood ratio ordering. Subjects without events of interest were censored at the end of their in-trial observation period. Based on the available number of events for analysis, the nominal significance level was updated to 0.02281 using the Lan-DeMets alpha spending function. Modified MACE comprises all-cause death, non-fatal MI and non-fatal stroke.
Abbreviations: CI: confidence interval; CV: cardiovascular; EAC: event adjudication committee; HR: hazard ratio; MACE: major adverse cardiovascular event; sema: semaglutide.

The cumulative incidence curves of modified MACE generally followed the same pattern as that seen for the overall MACE analysis with immediate separation of the curves after trial initiation, and throughout the trial (**Figure 12**). Thus, the addition of the non-CV related deaths to the MACE endpoint led to the same conclusion as for the primary MACE analysis.

Figure 12 First EAC-confirmed modified MACE (all-cause death, non-fatal MI or non-fatal stroke)



Data from the in-trial period. Cumulative incidence estimates are based on time from randomisation to first EAC-confirmed all-cause death, non-fatal myocardial infarction or non-fatal stroke using the Aalen-Johansen estimator. Subjects without events of interest were censored at the end of their in-trial period.
EAC: event adjudication committee.

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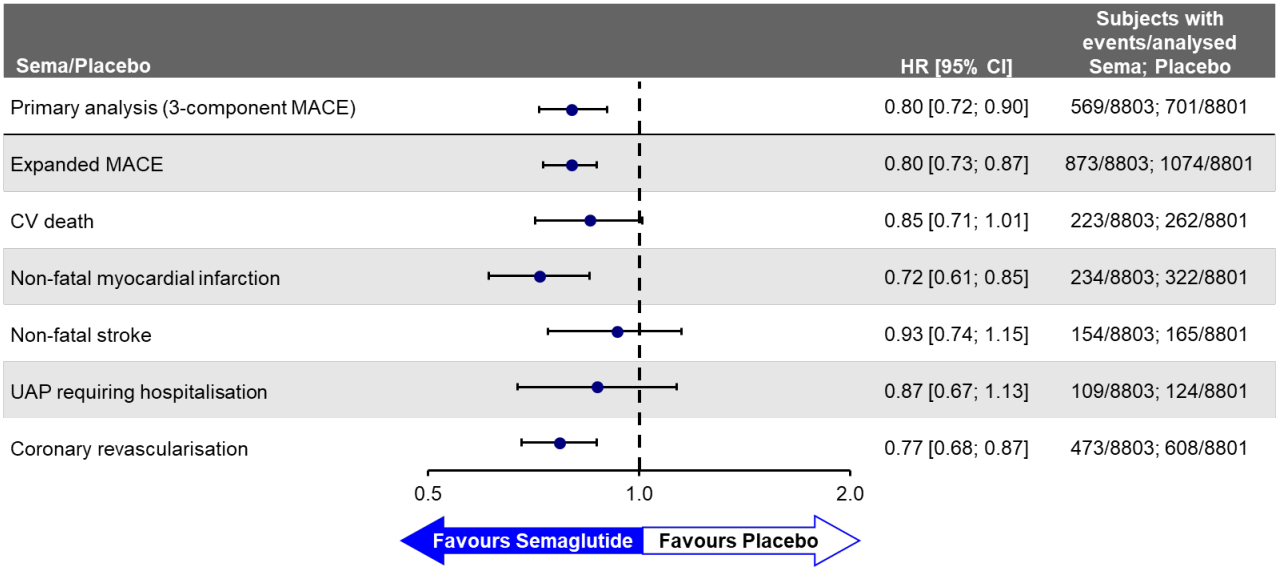
Expanded MACE

The primary analyses were supported by results based on pre-specified endpoints using a broader definition of MACE (expanded MACE, comprising CV death, non-fatal MI, non-fatal stroke, UAP requiring hospitalisation and coronary revascularisation).

The results for time to first EAC-confirmed expanded MACE, HR: 0.80 [0.73; 0.87]$_{95\% \text{ CI}}$ were in line with the results for the primary MACE analysis, with a HR and an upper bound of the confidence interval below 1 (**Figure 13**).

Figure 13 Time to first EAC-confirmed expanded MACE and components



Notes: FAS in-trial. Estimated HRs and corresponding CIs are from a Cox proportional hazards model with treatment as fixed factor. The analyses shown are time from randomisation to first EAC-confirmed event, both for expanded MACE and for the individual components.
Abbreviations: CI = confidence interval; EAC = event adjudication committee; HR = hazard ratio; MACE = major adverse cardiovascular events; sema = semaglutide; UAP = unstable angina pectoris.

Notably, all components included in MACE and expanded MACE are closely related to atherosclerotic disease (i.e., non-fatal MI, non-fatal stroke, revascularisation, and UAP requiring hospitalisation), and the hazard ratio point estimates were below 1, supporting an overall beneficial atherosclerosis-modifying effect of semaglutide.

The results were consistent (supplementary analysis), when substituting CV death with all-cause death in expanded MACE and, thus, inclusion of all-cause death in expanded MACE did not change the conclusion.

Mortality outcomes

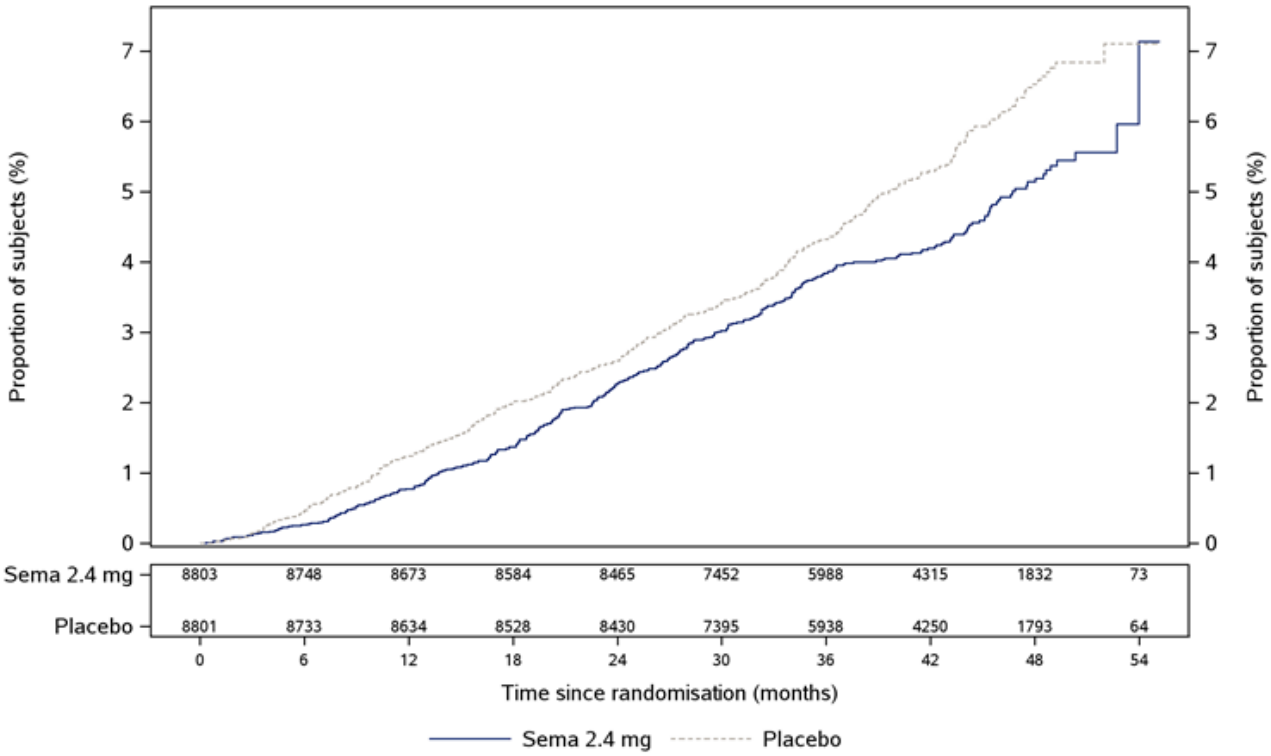
Time from randomisation to CV death and all-cause death were two confirmatory secondary endpoints addressing the primary and secondary objectives of the trial, respectively.

A total of 223 subjects (2.5%) randomised to semaglutide 2.4 mg died during the in-trial observation period due to EAC-confirmed- CV death (including undetermined cause of death) vs 262 subjects (3.0%) with placebo, corresponding to rates of 0.8 events per 100 PYO with semaglutide 2.4 mg vs 0.9 events per 100 PYO with placebo. The estimated risk of CV death was lower for semaglutide 2.4 mg compared with placebo as reflected in the separation of the curves from shortly after trial initiation, and throughout the trial (**Figure 7**). Analysis of time to CV death showed an estimated HR for semaglutide 2.4 mg vs placebo of 0.85 [0.71; 1.01]$_{95\% \text{ CI}}$ (**Figure 6**). Superiority of semaglutide

2.4 mg vs placebo was not confirmed; p=0.0327 (nominal significance level: 0.01148) for the confirmatory secondary mortality endpoint of time to EAC-confirmed CV death (**Table 6**). Hence, due to the testing hierarchy superiority of semaglutide 2.4 mg vs placebo was not tested for the confirmatory secondary mortality endpoint of time to EAC-confirmed all-cause death (**Table 6)**.

The number of all-cause deaths was lower with semaglutide 2.4 mg than with placebo; 375 (4.3%) subjects died during the in-trial observation period with semaglutide 2.4 mg vs 458 (5.2%) with placebo, corresponding to mortality rates of 1.3 events per 100 PYO with semaglutide 2.4 mg vs 1.6 events per 100 PYO with placebo 100 PYO. The estimated risk of all-cause death was lower for semaglutide 2.4 mg compared with placebo as reflected in the separation of the curves from shortly after trial initiation, and throughout the trial (**Figure 14**). Analysis of time to all-cause death showed an estimated HR for semaglutide 2.4 mg vs placebo of 0.81 $[0.71; 0.93]_{95\% \text{ CI}}$ (**Figure 15**).

Figure 14 Cumulative incidence plot of time to all-cause death



Data from the in-trial period. Cumulative incidence estimates are based on time from randomisation to EAC-confirmed all-cause death using the Aalen-Johansen estimator.
Subjects without events of interest were censored at the end of their in-trial period.
EAC: event adjudication committee.

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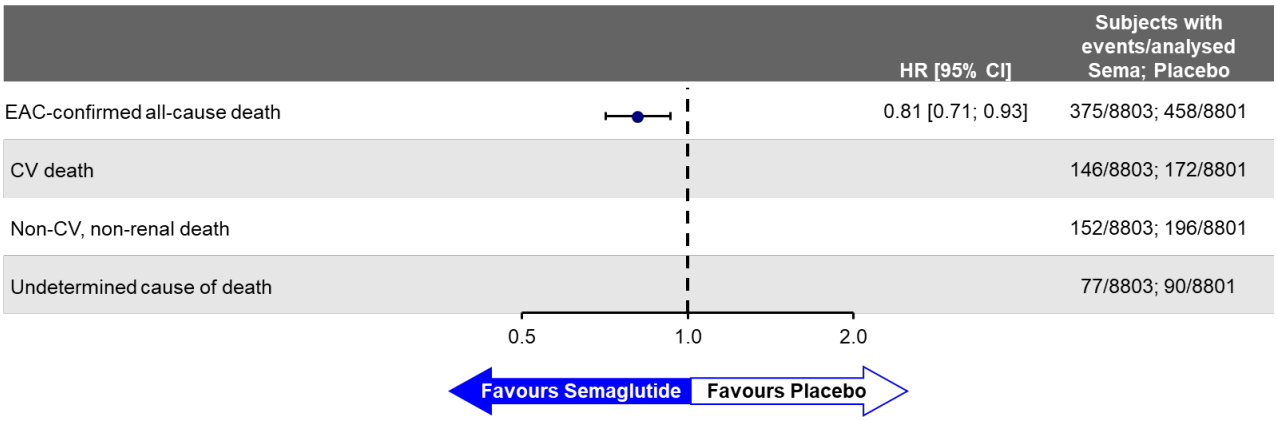
Figure 15 Time to all-cause death



Notes: FAS in-trial. Estimated HRs and corresponding CIs are from a Cox proportional hazards model with treatment as fixed factor. Deaths of undetermined cause (i.e., deaths for which the EAC could not determine the cause) were categorised as CV death.
Abbreviations: CI: confidence interval; CV: cardiovascular; HR: hazard ratio; sema: semaglutide.

Heart failure outcomes

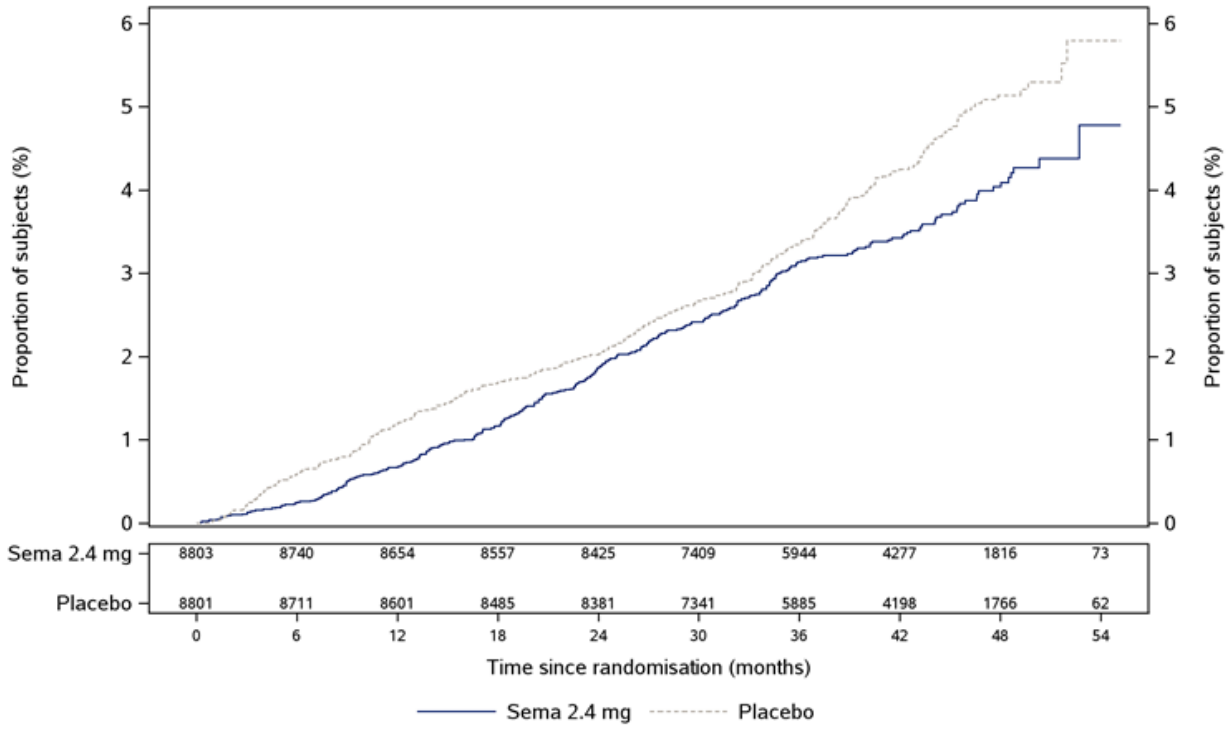
Composite heart failure outcome

Time from randomisation to first EAC-confirmed composite HF outcome comprising the component 'HF requiring hospitalisations or urgent HF visits' and the component 'CV death' was a confirmatory secondary endpoint addressing the primary objective.

The proportion of subjects with an EAC-confirmed first composite HF event were lower with semaglutide 2.4 mg than with placebo: a total of 300 subjects (3.4%) experienced events with semaglutide 2.4 mg vs 361 subjects (4.1%) with placebo. The proportions of subjects with event rates were lower with semaglutide 2.4 mg than with placebo: event rates of 1.0 events per 100 PYO for semaglutide 2.4 mg vs 1.2 events per 100 PYO for placebo.

The estimated risk of experiencing a first composite HF event within any certain time from randomisation was lower for semaglutide 2.4 mg compared with placebo as reflected in the immediate separation of the curves after trial initiation, and throughout the trial (**Figure 16**).

Figure 16 Cumulative incidence plot of time to first composite heart failure outcome



Data from the in-trial period. Cumulative incidence estimates are based on time from randomisation to first EAC-confirmed composite heart failure outcome with non-CV death modelled as competing risk using the Aalen-Johansen estimator. Subjects without events of interest were censored at the end of their in-trial observation period.
CV: cardiovascular, EAC: event adjudication committee.

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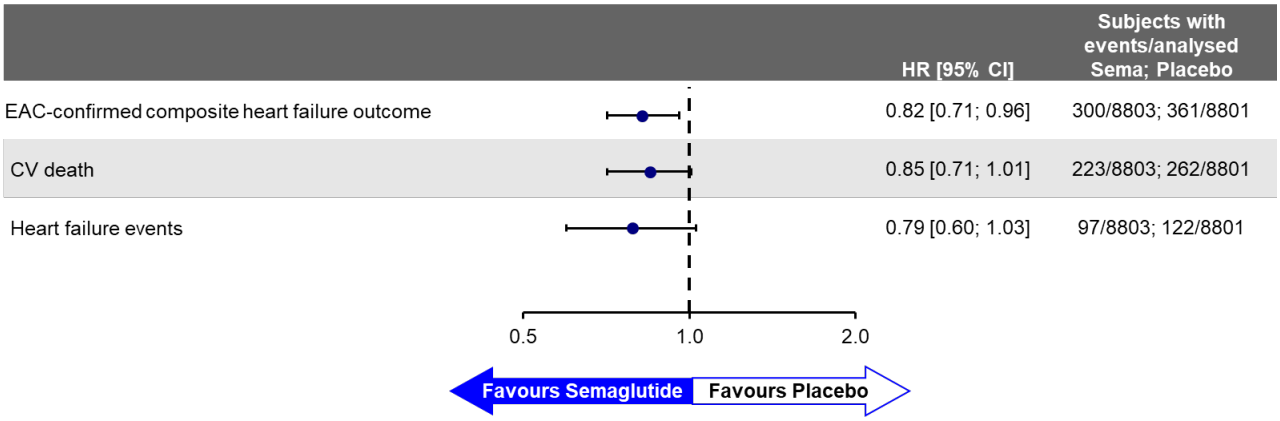
Analysis of time to first composite HF outcome showed an estimated HR for semaglutide 2.4 mg vs placebo of 0.82 [0.71; 0.96]$_{95\% \text{ CI}}$ (**Figure 17**). Due to the testing hierarchy, superiority of semaglutide 2.4 mg vs placebo was not tested for the confirmatory secondary endpoint of time to first EAC-confirmed composite HF outcome (**Table 6**). Each of the components of the composite HF outcome contributed to the reduction and the components (CV death and HF events) had HRs below 1.0 favouring semaglutide (**Figure 17**).

Figure 17 Time to first EAC-confirmed composite heart failure outcome and components



Notes: FAS in-trial. Estimated HRs and corresponding CIs are from a Cox proportional hazards model with treatment as fixed factor. The analyses shown are time from randomisation to first EAC-confirmed event, both for EAC-confirmed composite heart failure outcome and for the individual components.
Abbreviations: CI: confidence interval; CV: cardiovascular; HR: hazard ratio; sema: semaglutide.

Sensitivity and supplementary analyses

The results of the pre-specified sensitivity and supplementary analyses of the composite HF endpoint were consistent with the results from the main analysis.

Furthermore, the results were consistent (supplementary analysis), when substituting CV death with all-cause death in the composite HF endpoint and, thus, inclusion of all-cause death in the composite HF endpoint did not change the conclusion.

The result of the pre-specified COVID-19 analysis of the composite HR outcome was consistent with the result from the main analysis, indicating no impact of COVID-19 on the confirmatory secondary endpoint of composite HF outcome.

Kidney function outcomes

The potential effect of semaglutide 2.4 mg on kidney function in subjects 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 nephropathy components 'initiation of chronic renal replacement therapy' and 'renal death' were evaluated by the EAC.

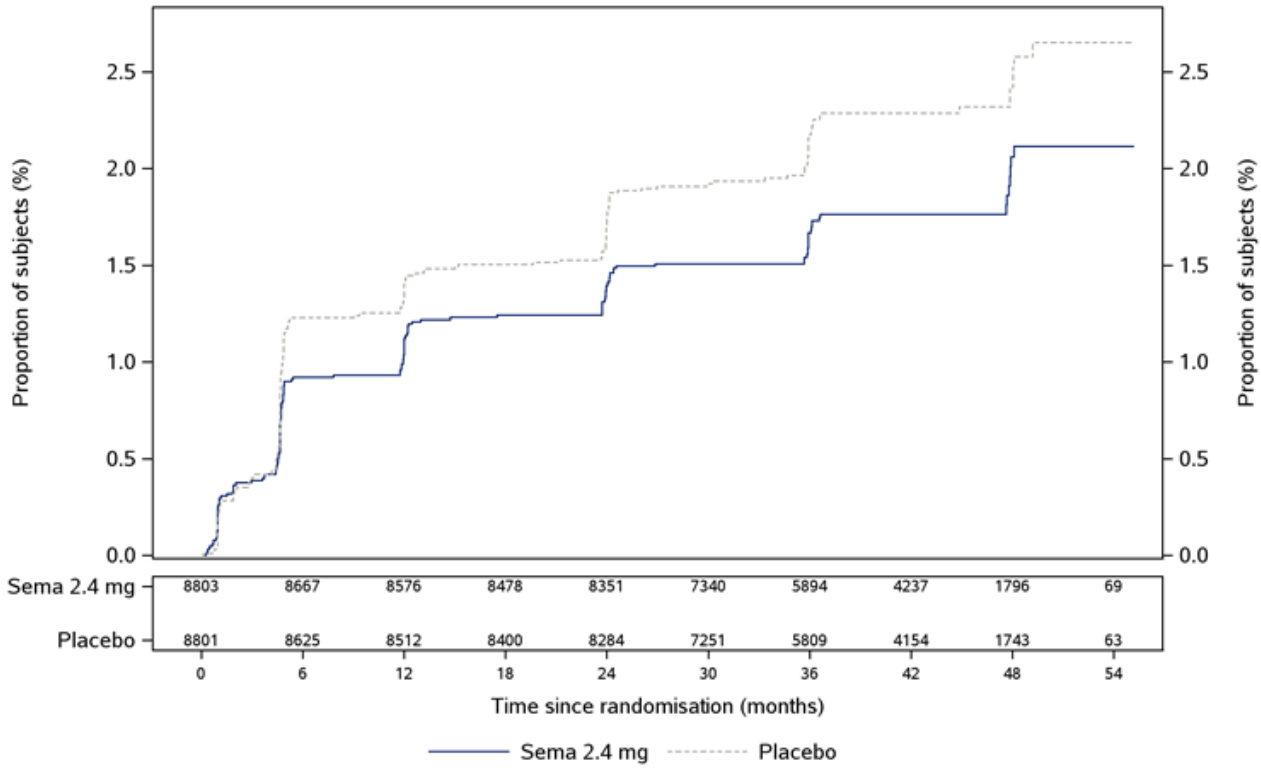
First composite nephropathy event

A total of 353 first composite nephropathy events with onset during the in-trial observation period occurred, corresponding to event rates of 0.5 events per 100 PYO (semaglutide 2.4 mg) and 0.7 events per 100 PYO (placebo). The proportion of subjects with first composite nephropathy events was lower with semaglutide 2.4 mg (155 subjects, 1.8%) than with placebo (198 subjects, 2.2%). The difference between treatments in overall number of subjects with composite nephropathy events was primarily attributable to a smaller number of persistent macroalbuminuria with semaglutide 2.4 mg than with placebo.

Time to first composite nephropathy events

Composite nephropathy events had onset throughout the entire observation period, with clustering of events at times of scheduled assessment of albumin and eGFR (**Figure 18**). The estimated risk of experiencing a composite nephropathy event was lower for semaglutide 2.4 mg compared with placebo as reflected in the separation of the curves.

Figure 18 Time from randomisation to first-composite nephropathy event – cumulative incidence plot – FAS in-trial



Data from the in-trial period. Cumulative incidence estimates are based on time from randomisation to first nephropathy outcome with non-renal death as competing risk using the Aalen-Johansen estimator. Subjects without events of interest were censored at the end of their in-trial observation period.

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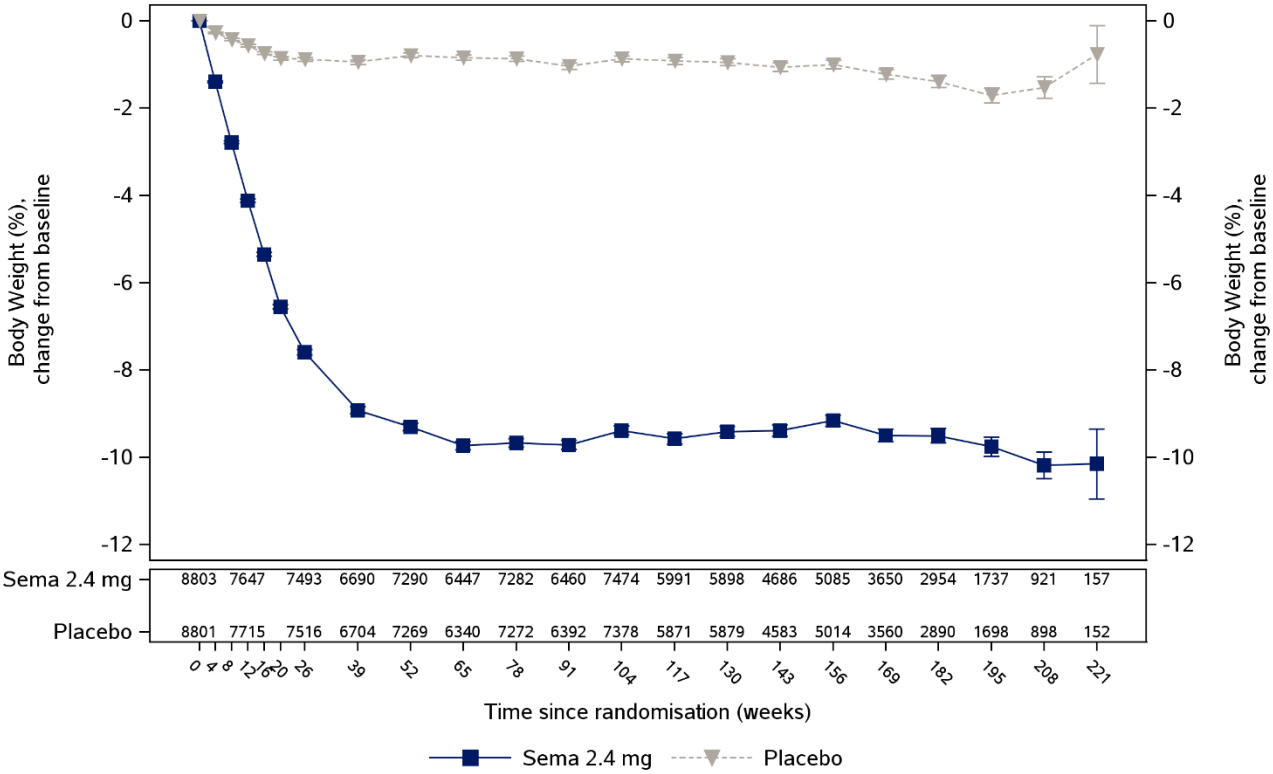
The analysis of time to first composite nephropathy events resulted in an estimated HR of 0.78 $[0.63; 0.96]_{95\% \text{ CI}}$ for semaglutide 2.4 mg relative to placebo (Trial 4388 [M 5.3.5.1], Table 14.2.87) hence, the risk of deterioration in kidney function was significantly lower with semaglutide 2.4 mg than with placebo. The reduction in risk was mainly driven by the component persistent macroalbuminuria.

Body weight and waist circumference

At baseline, mean body weight was 96.53 kg for the semaglutide 2.4 mg group and 96.82 kg for the placebo group.

Change in body weight (%) from baseline by week for each of the two treatment groups are presented in **Figure 19**. Body weight decreased from baseline through to week 65 with semaglutide 2.4 mg, after which a plateau was reached and sustained for the remainder of the trial.

Figure 19 Body weight (%) change from baseline by week – mean plot – FAS in-trial



Observed data from the in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel represent the number of subjects contributing to the means.

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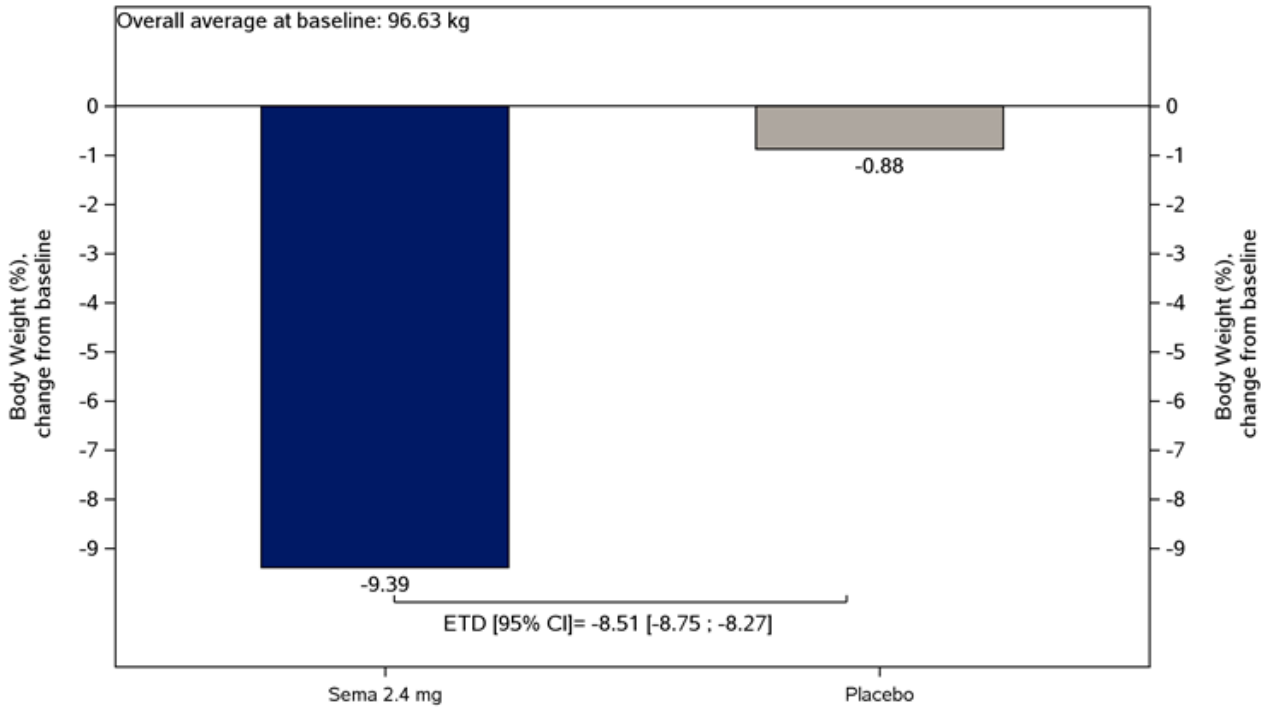
Change in body weight (%) from baseline at week 104

Change in body weight (%) from baseline at week 104 was a supportive secondary endpoint. The estimated change in mean body weight (%) from baseline at week 104 for each of the two treatment groups and the estimated treatment difference (ETD) are presented in **Figure 20** showing that the ETD was in favour of semaglutide 2.4 mg.

Figure 20 Body weight (%) change from baseline at week 104 – bar plot – estimated – FAS in-trial



Data from the in-trial period. Mean estimates are from an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and includes baseline value as a covariate and was fitted to all subjects with a measurement regardless of treatment status at week 104. The fitted model was used to impute values for subjects without a measurement at week 104. Mean estimates were adjusted according to observed baseline distribution. The solid line is the overall average value at baseline.
CI: confidence interval, ETD: estimated treatment difference

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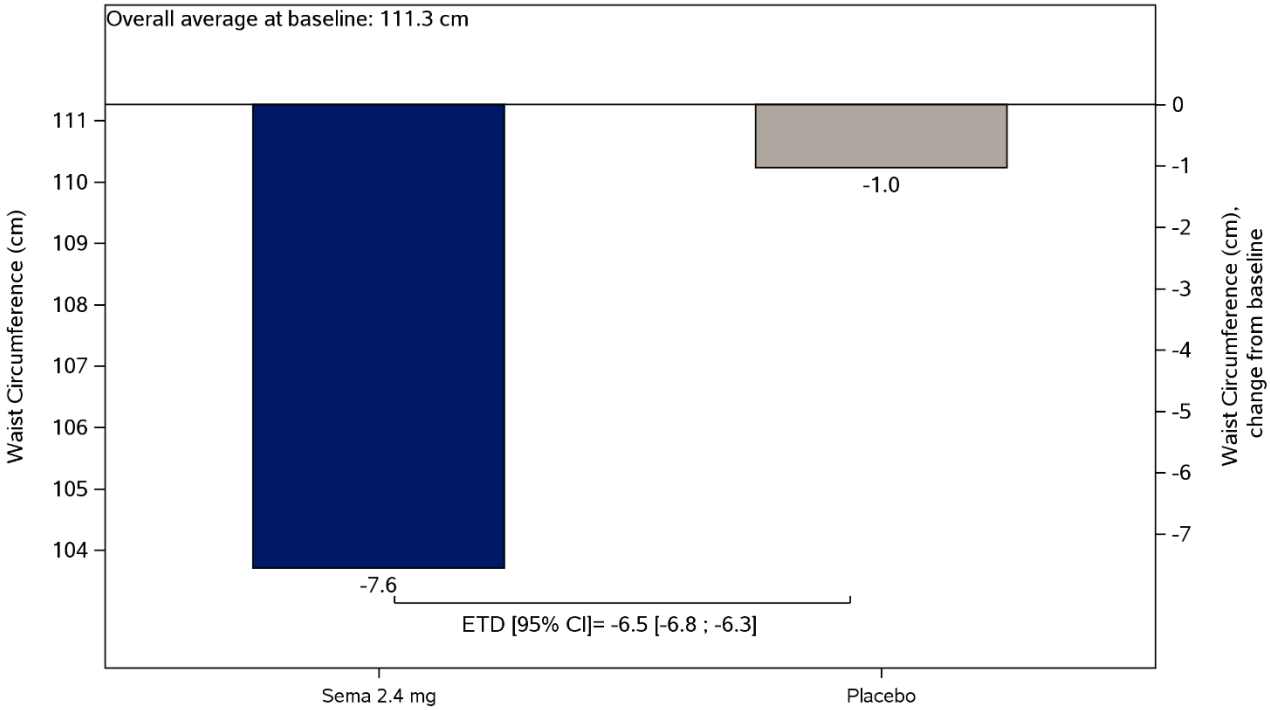
Change from baseline in waist circumference

At baseline, mean waist circumference was 111.3 cm for the semaglutide 2.4 mg group and 111.4 cm for the placebo group.

Change in waist circumference (cm) from baseline at week 104 was a supportive secondary endpoint. The estimated change in mean waist circumference (cm) from baseline at week 104 for the two treatment groups as well as the ETD are presented in **Figure 21**, showing that the ETD was in favour of semaglutide 2.4 mg.

Figure 21 Waist circumference (cm) change from baseline at week 104 – bar plot – estimated – FAS in-trial



Data from the in-trial period. Mean estimates are from an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all subjects with a measurement regardless of treatment status at week 104. The fitted model was used to impute values for subjects without a measurement at week 104. Mean estimates were adjusted according to observed baseline distribution. Solid line is the overall average value at baseline.
CI: confidence interval, ETD: estimated treatment difference

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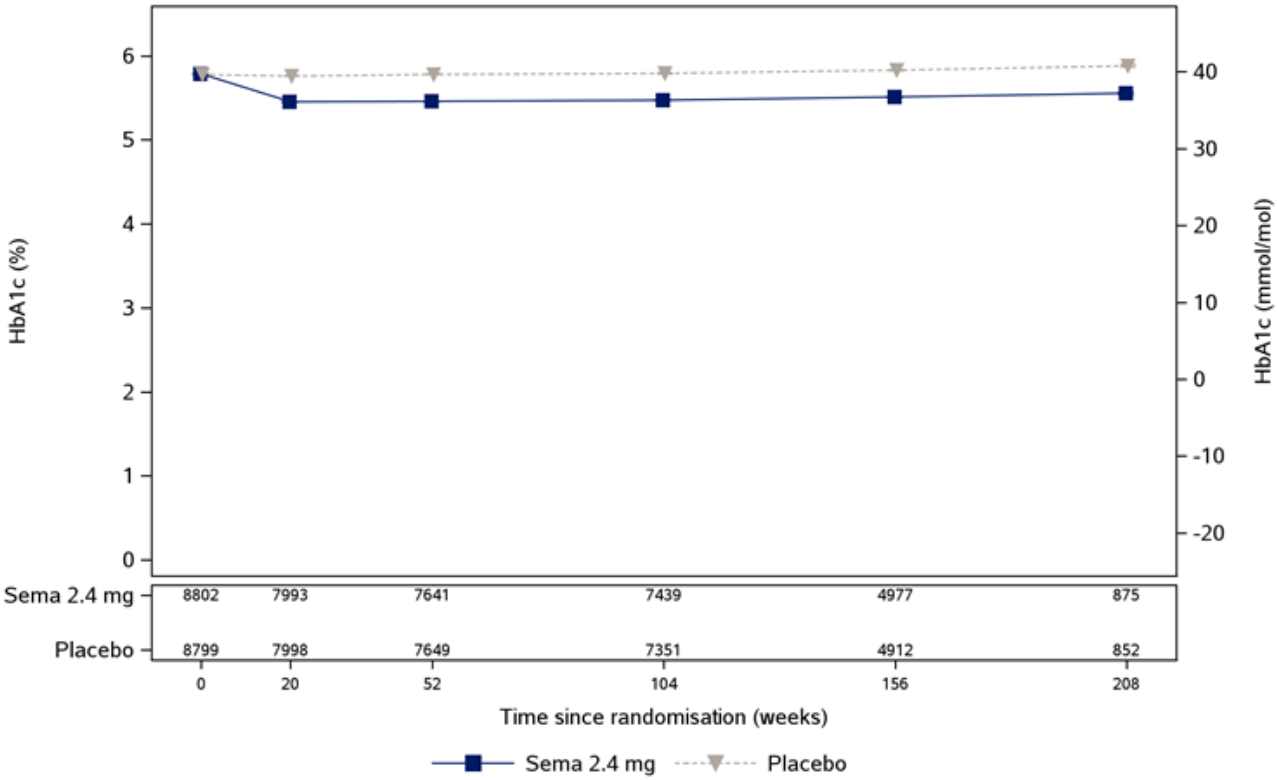
Glucose metabolism

Change from baseline in HbA_{1c} – observed data

Subjects with diabetes were not eligible for this trial and subjects with HbA_{1c} ≥6.5% (≥48 mmol/mol) as measured by the central laboratory at screening were to be excluded (**Figure 22**).

Mean HbA_{1c} decreased from baseline with semaglutide with an estimated treatment difference at Week 104 of-0.32 ([-0.33 ; -0.31] <.0001).

Figure 22 HbA_{1c} (%) by week – mean plot – FAS in-trial



Observed data from the in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel represent the number of subjects contributing to the means.

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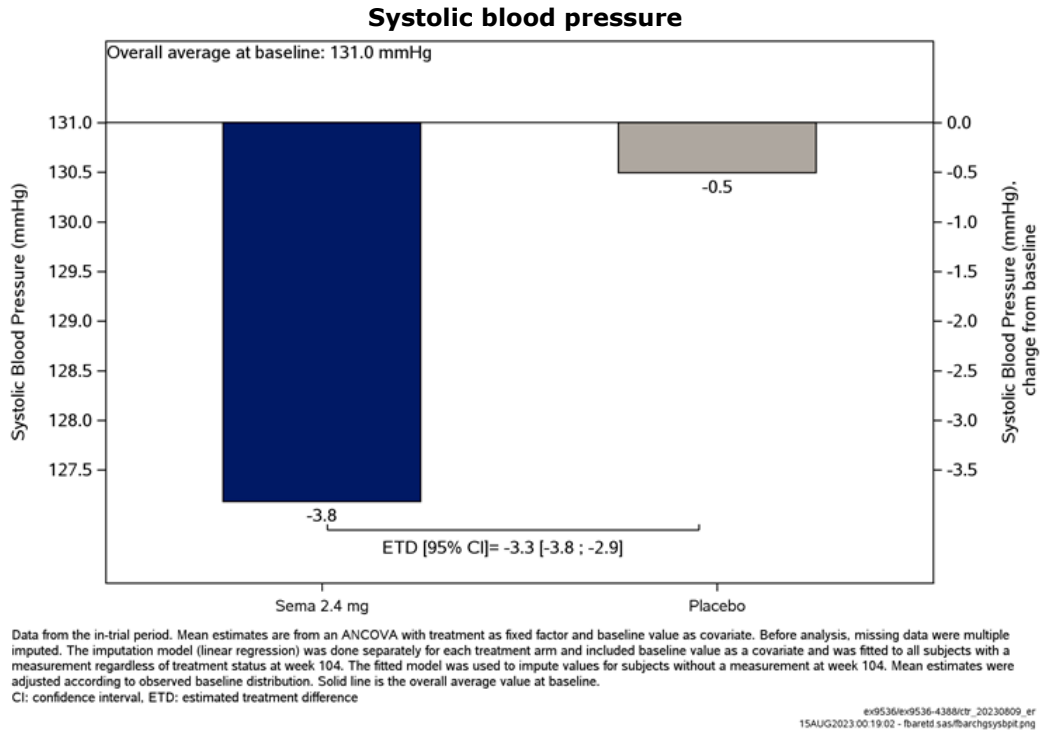
Blood pressure and heart rate

Blood pressure

At baseline, mean observed SBP and DBP (mmHg) were similar across the two treatment groups. At randomisation, approximately 92% of subjects in each treatment group were receiving CV medication, primarily beta blockers or ACE inhibitors.

Change in SBP and DBP (mmHg) from baseline at week 104 were supportive secondary endpoints. The estimated change in SBP and DBP (mmHg) from baseline at week 104 for the two treatment groups as well as the ETDs are shown in **Figure 23**, showing larger reductions in blood pressure for the semaglutide 2.4 mg group compared to the placebo group.

Figure 23 Blood pressure (mmHg) change from baseline at week 104 – bar plot – estimated – FAS in-trial



Data from the in-trial period. Mean estimates are from an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all subjects with a measurement regardless of treatment status at week 104. The fitted model was used to impute values for subjects without a measurement at week 104. Mean estimates were adjusted according to observed baseline distribution. Solid line is the overall average value at baseline.
CI: confidence interval, ETD: estimated treatment difference

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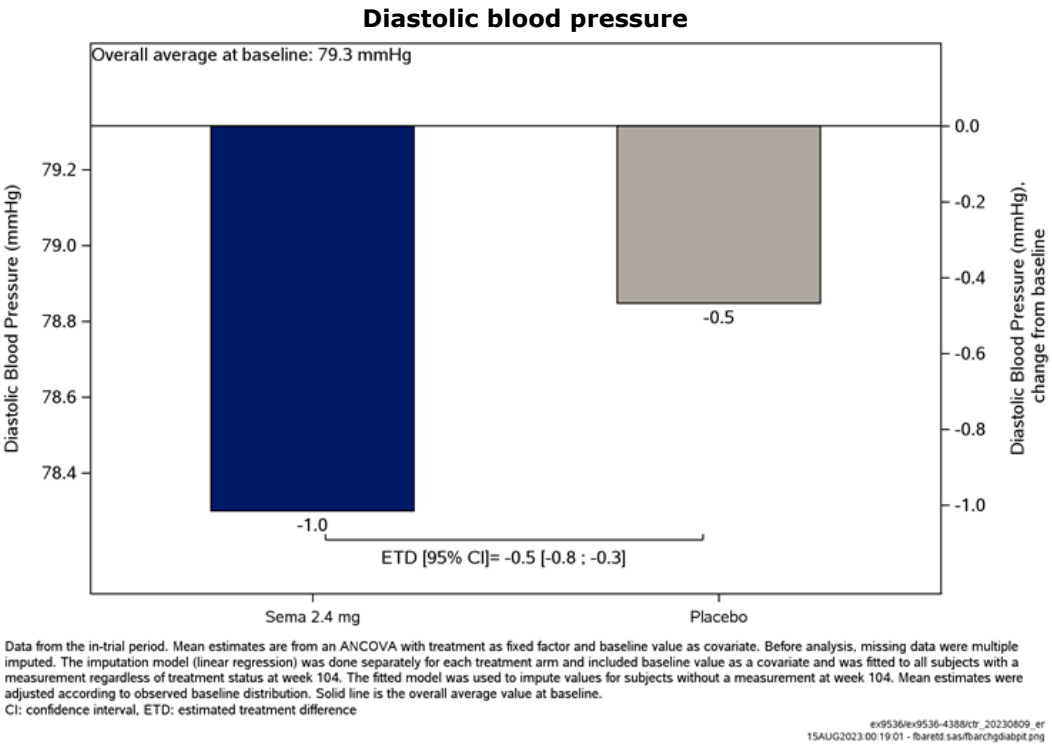

Data from the in-trial period. Mean estimates are from an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all subjects with a measurement regardless of treatment status at week 104. The fitted model was used to impute values for subjects without a measurement at week 104. Mean estimates were adjusted according to observed baseline distribution. Solid line is the overall average value at baseline.
CI: confidence interval, ETD: estimated treatment difference

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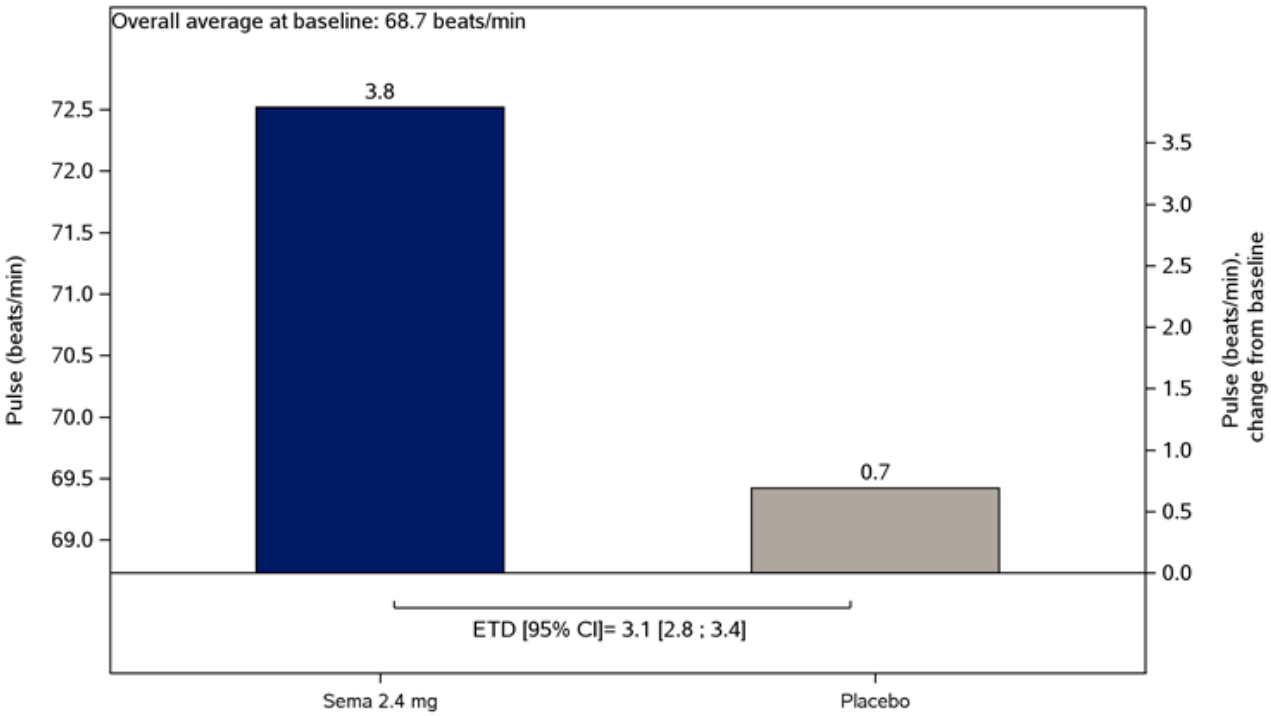
Heart rate

At baseline, mean observed heart rate (bpm) was similar across the two treatment groups. Heart rate increase is a well-known side effect associated with GLP-1 RA treatment. Change in heart rate (bpm) from baseline at week 104 was a supportive secondary endpoint. The estimated change in heart rate (bpm) from baseline at week 104 for the two treatment groups and the ETD are presented in

Figure 24, showing that the estimated change in heart rate was higher for the semaglutide 2.4 mg group compared to the placebo group, as expected.

Figure 24 Heart rate (bpm) change from baseline at week 104 – bar plot – estimated – FAS in-trial



Data from the in-trial period. Mean estimates are from an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all subjects with a measurement regardless of treatment status at week 104. The fitted model was used to impute values for subjects without a measurement at week 104. Mean estimates were adjusted according to observed baseline distribution. Solid line is the overall average value at baseline.
CI: confidence interval, ETD: estimated treatment difference

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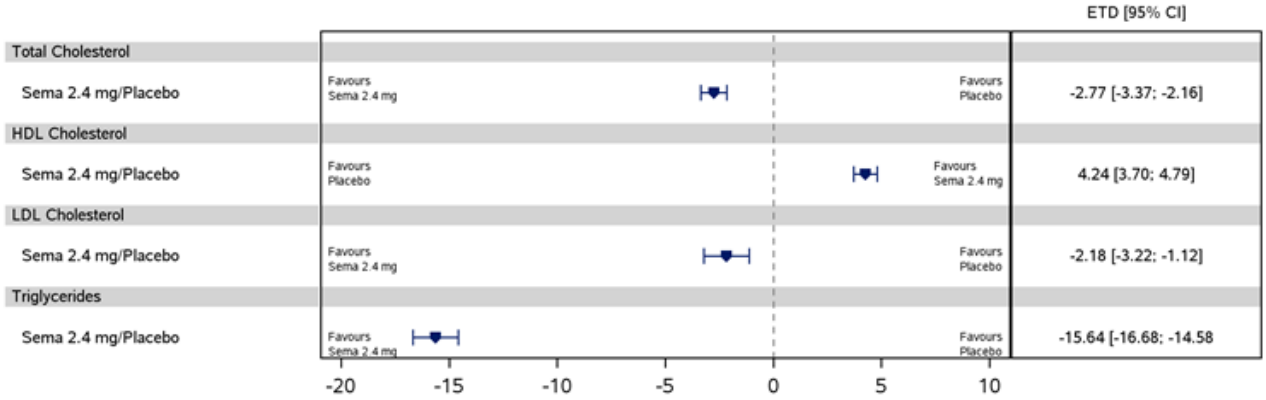
Lipids

At baseline, mean observed lipid levels (mmol/L, mg/dL) were overall within normal range and similar across the two treatment groups. A total of 90.1% of subjects were receiving lipid-lowering medication, primarily statins.

Analyses of lipids were done on a logarithmic scale and change from baseline at week 104 were supportive secondary endpoints.

Lipids ETDs are available in **Figure 25**, showing an overall slight improvement in lipid profile with semaglutide 2.4 mg as compared to placebo.

Figure 25 Lipids (%)-change from baseline at week 104 – forest plot – FAS in-trial



Data from the in-trial period.

The responses were analysed using an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all subjects with a measurement regardless of treatment status at week 104. The fitted model was used to impute values for subjects without a measurement at week 104. The ratio to baseline and the corresponding baseline value were log-transformed prior to analysis. Mean estimates were adjusted according to observed baseline distribution. The approximate relative changes/differences were derived from estimated ratios by subtracting 1 and multiplying by 100.

ETD: estimated treatment difference

CI: confidence interval

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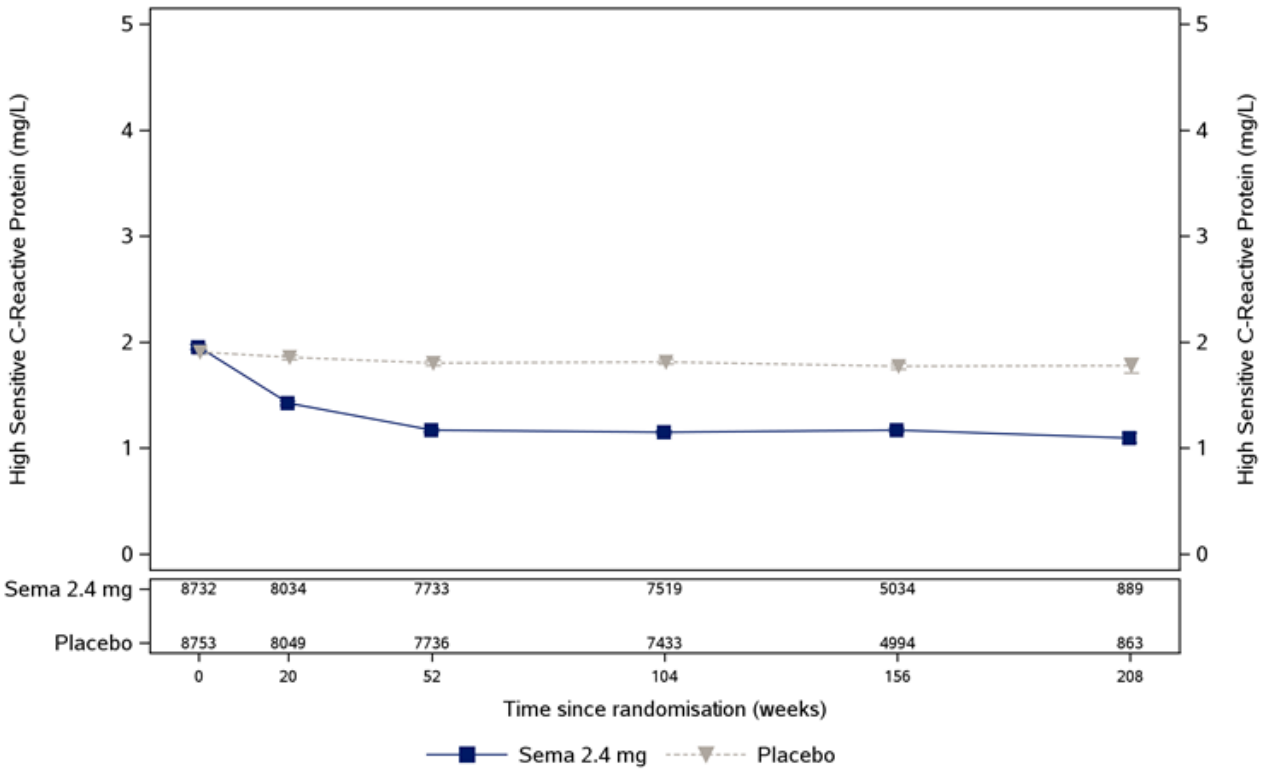
High sensitivity C-reactive protein

At baseline, geometric mean hsCRP was 1.96 mg/L for the semaglutide 2.4 mg group and 1.91 mg/L for the placebo group.

Mean hsCRP decreased from baseline through to week 52 with semaglutide 2.4 mg after which the level remained stable and mean hsCRP was unchanged throughout for placebo **Figure 26**.

Figure 26 High sensitivity C-Reactive Protein (mg/L) by week – geometric mean plot – in-trial – full analysis set



Observed data from the in-trial period. Error bars are +/- standard error of the mean on the logarithmic scale and back transformed to natural scale with the exponential. Numbers shown in the lower panel represent the number of subjects contributing to the means.

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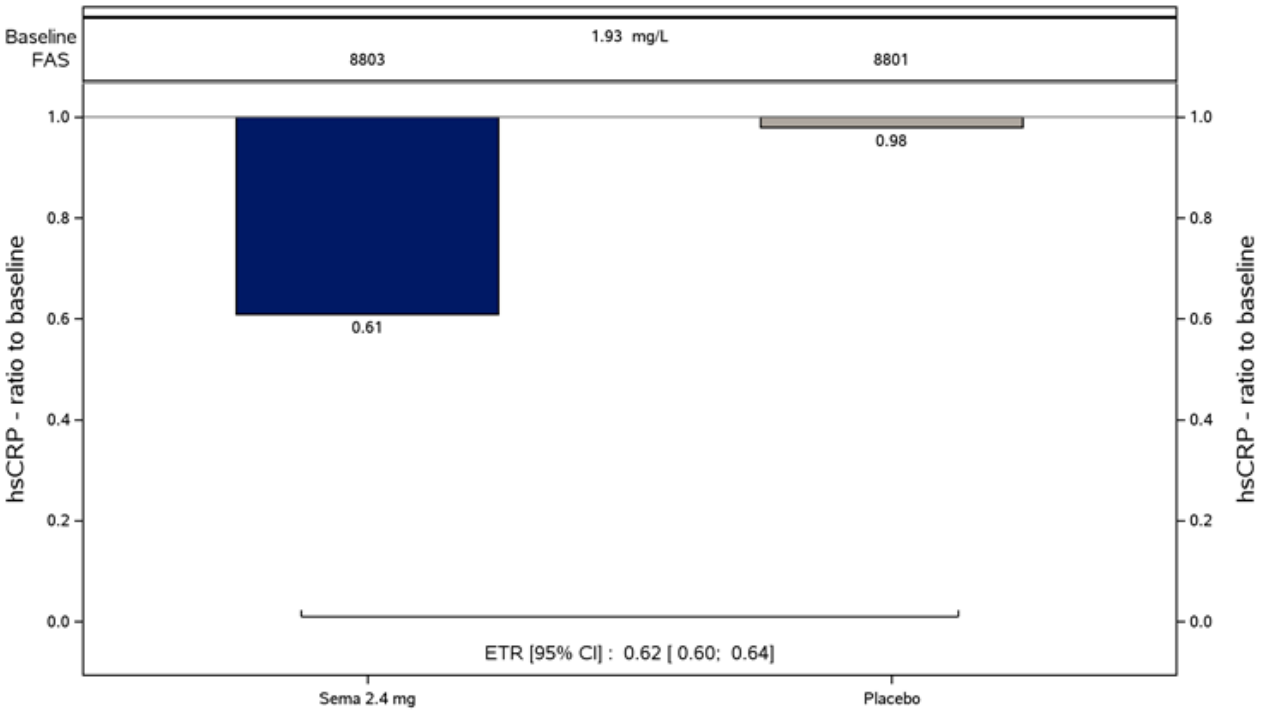
Analysis of hsCRP was done on a logarithmic scale and ratio to baseline at week 104 was a supportive secondary endpoint. The estimated geometric mean hsCRP ratio to baseline at week 104 for the two treatment groups as well as the estimated treatment ratio (ETR) are presented in **Figure 27**, showing that the ETR was in favour of semaglutide 2.4 mg.

Figure 27 High sensitivity C-Reactive Protein ratio to baseline at week 104 – bar plot – estimated – FAS in-trial



Data from the in-trial period. Mean estimates were analysed using an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all subjects with a measurement regardless of treatment status at week 104. The fitted model was used to impute values for subjects without a measurement at week 104. The ratio to baseline and the corresponding baseline value were log-transformed prior to analysis. Mean estimates were adjusted according to observed baseline distribution.
CI: confidence interval, ETR: estimated treatment ratio, FAS: Full analysis set.

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Smoking status

At baseline, the proportion of smokers was 16.9% for the semaglutide 2.4 mg group and 16.6% for the placebo group.

Smoking status (being a current smoker: yes/no) was analysed separately at week 52 and week 104 as exploratory endpoints. The risk of being a smoker at week 104 was similar with semaglutide 2.4 mg compared with placebo and a similar result was seen when analysed at week 52.

Other efficacy outcomes

EuroQol five dimensions five level (EQ 5D 5L)

The EuroQol five dimensions five level (EQ-5D-5L) questionnaire is a PRO tool. The tool was used to estimate the impact on subjects' health-related quality of life and provided a description of subjects' problems by dimensions (descriptive system), a score for overall self-rated health (visual analogue scale [VAS, range 0-100]) as well as an index score (EQ-5D-5L index [range 0-1]). A higher score indicates better self-reported health status.

The estimated change in mean EQ-5D-VAS score from baseline at week 104 was in favour of semaglutide 2.4 mg (ETD 1.60 [1.16; 2.04]$_{95\% \text{ CI}}$). The estimated change in EQ-5D-5L index score from baseline at week 104 was also in favour of semaglutide 2.4 mg (ETD 0.01 [0.01; 0.02]$_{95\% \text{ CI}}$).

Ancillary analyses

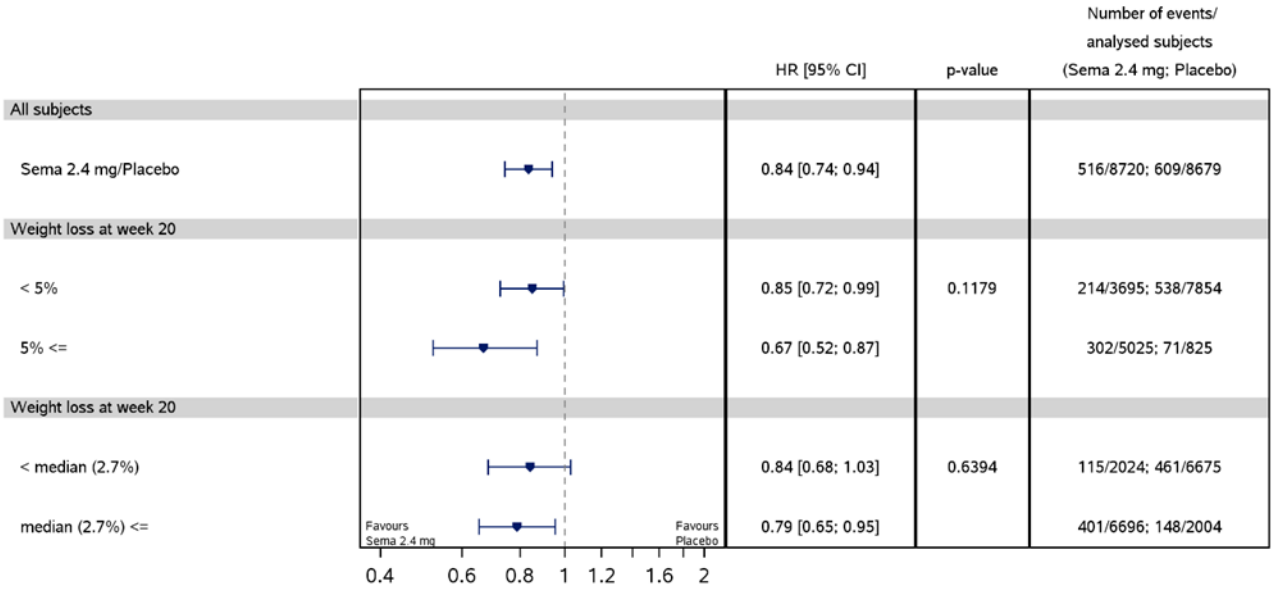
Mediation analyses

Post-baseline subpopulation analysis

The potential effect of weight loss on MACE was explored by a *post-hoc* mediation-like analysis based on post-baseline subpopulations defined by weight loss at week 20. Subjects with MACEs or withdrawal from trial before their week 20 visit were excluded from the analysis. Weight loss was derived as the last available observation from baseline to 20 weeks. EAC-confirmed

The results of the subpopulation analyses by weight loss at week 20 showed estimated HRs below 1 across the weight loss categories (**Figure** 28). The HRs obtained among the groups with the highest weight loss at week 20 (0.67 and 0.79) were slightly lower but within the same range as the HRs (0.85 and 0.84) in the groups with less weight loss at week 20, and the interaction p-value within each subgroup analysis was not significant, supporting that there may be a CV benefit of semaglutide in individuals in both weight loss groups.

Figure 28 Time from week 20 to first EAC-confirmed MACE by weight loss category at week 20 – SELECT



Time to event was analysed using a Cox proportional hazards model including treatment, subgroup and treatment by subgroup interaction as categorical fixed factors. Subjects with events or withdrawn from trial before their week 20 visit were excluded from analysis. Subjects without events during trial were censored at the end of their in-trial period. Weight loss was derived as the last available observation from baseline to 20 weeks.
p-value: p-value for test of no interaction effect.
CI: confidence interval, EAC: event adjudication committee, HR: hazard ratio, MACE: major cardiovascular event.

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07AUG2023:09:59:20 - fforest.sas/fforestmacesubgr.png

Vansteelandt method

Mediation analyses were performed *post-hoc* to explore to what extent the effect of semaglutide on CV risk reduction can be explained by an effect on another variable acting as a mediator. Semaglutide has consistently been associated with beneficial effect on various cardiometabolic risk factors. The variables body weight, HbA_{1c}, systolic blood pressure, LDL cholesterol and hsCRP were examined as potential mediators since they could plausibly have a relation to MACE.

Applying the Vansteelandt method indicated some mediation through the selected candidates, with an estimated percentage mediation ranging from approximately 10 to 40%; the strongest indicated mediator was hsCRP followed by HbA_{1c}, body weight, SBP and LDL-cholesterol.

When all potential mediators were included in the model the estimated percent mediated was approximately 40%, hence, a substantial proportion of the effect of semaglutide 2.4 mg does not appear to be explained by any of the potential mediators. Note that the percentage mediated by all mediators does not equal the sum of the percentage mediated by the individual mediator due to dependencies among the mediators. The results should be interpreted with caution since, in contrast to the primary analysis of the trial, the mediation analyses were not protected against confounding through randomisation of participants. Furthermore, the estimates of percentage mediation were subject to substantial uncertainty reflected by the wide confidence intervals.

In summary, the effect of semaglutide on CV risk reduction is likely multifactorial and partly explained by the beneficial effect on cardiometabolic risk factors related to atherosclerosis including improvements in systolic blood pressure, lipid profile, hsCRP, body weight, and HbA_{1c}, and thereby provide considerable improvements in subject's health. A substantial proportion of the effect of semaglutide 2.4 mg on CV risk reduction was not explained by effects on well-established cardiometabolic risk factors and may be ascribed to other potentially unique effects of semaglutide.

2.4.2. Discussion on clinical efficacy

Semaglutide is a GLP-1 analogue with a high degree of homology to human GLP-1. It is approved under the tradename Ozempic® for treatment of T2D. Semaglutide 2.4 mg has been approved under the tradename Wegovy® for weight management. Available data indicate that semaglutide s.c. reduces the risk of MACE in patients with T2D and high CV risk (SUSTAIN 6) and improves cardiometabolic risk factors in patients with obesity and/or T2D (STEP and SUSTAIN phase 3a development programmes). The effect of semaglutide on the risk of MACE in patients with obesity without diabetes was unknown.

Design and conduct of clinical studies

Design

Trial 4388 was a multinational, multicentre, randomised, double blind, parallel group, placebo controlled trial. The trial was designed to demonstrate superiority of semaglutide 2.4 mg once weekly vs placebo, both added to CV standard of care in subjects with established CV disease and overweight or obesity, but without history of T1D or T2D. This is a very important trial. No dedicated weight management CVOTs have been able to demonstrate a link between weight loss and CV risk reduction. There is an unmet medical need for weight management drugs targeting the residual CV risk in people with overweight or obesity.

The study was well designed, overall, to meet its objectives. It is noted that the dosing of the study drug followed the recommended titration steps, and all patients received healthy lifestyle counselling. It is further noted that the trial employed a group sequential design with one interim test for superiority of the primary endpoint evaluated by the Data Monitoring Committee (DMC).

Objectives and endpoints

Primary objective was to demonstrate that semaglutide s.c. 2.4 mg once weekly lowers the incidence of MACE vs placebo, both added to standard of care in subjects with established CV disease and overweight or obesity. Primary endpoint was the time from randomisation to first occurrence of a composite endpoint consisting of CV death, non-fatal MI, or non-fatal stroke.

It is noted that CV mortality rather than all-cause mortality was chosen as a component of the primary composite endpoint: CV mortality, non-fatal MI or non-fatal stroke. This is accepted, although in the

scientific advice on 26 April 2018 (EMEA/H/SA/3657/2/2018/II), the CHMP clearly advocated the use of the combined endpoint consisting of MI, stroke, and all-cause mortality. It was discussed in the scientific advice that weight loss would be expected to influence not only CV mortality, but also other components of the overall mortality risk.

The secondary endpoints designated by the Applicant as "confirmative" secondary endpoints, i.e. the subset of secondary endpoints that are managed with respect to multiplicity thorough a pre-specified hierarchical testing sequence, include 1) time to CV death, 2) time to a composite of heart failure events, and 3) time to all-cause death. This is acceptable.

The choice of the primary and confirmatory secondary endpoints is acceptable. However, there is a very long list of explorative and supportive secondary endpoints (26 endpoints). These are all of relevant clinical and scientific interest and accepted, although they should, by way of design, not be seen as confirmative.

Statistical methods

The methods and strategies employed in this trial appear to be well-planned and executed.

In the semaglutide arm, there were 152 (1.7%) instances of non-CV death. However, the decision to censor non-CV deaths as competing risks raises questions. Since the time to EAC-confirmed CV death was not significant, the issue of competing risk censoring was not further addressed.

Despite this, the observed cumulative sum of standardized residuals over time showed considerable fluctuation around the zero line, indicating a potential violation of the proportional hazards assumption. However, the Schoenfeld residuals test showed no evidence of violation of the proportional hazard's assumption (p=0.4874).

Population

Eligible subjects were randomised (1:1) to treatment with semaglutide 2.4 mg (8,805 subjects) or placebo (8,804 subjects). It is remarkable that 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). Given the large size of the study, the number of 5 subject identifiers not included in the FAS is small and not likely to cause significant issues with respect to the analyses and results.

In total, 96.9% of randomised subjects in the FAS completed the trial. The overall median time in-trial was 41.8 months, and overall median on treatment time was 38.2 months. Subjects were on treatment on average 85.1% of the planned on-treatment period.

In the semaglutide group, 30.6% of the individuals permanently discontinued treatment. Trial product was permanently discontinued due to adverse events in 16.3% individuals in the semaglutide group (vs 7.9% in the placebo-group). This high number emphasizes the high number of important side effects.

The mean age of the subjects at baseline was 61.6 years. In total, 38.2% of the subjects was ≥65 years and 7.8% was ≥75 years. In total, 72.3% of subjects were male. The trial population included subjects with overweight (BMI ≥27 to <30 kg/m^2) or obesity (BMI ≥30 kg/m^2). A total of 71.5% of the trial population had a BMI ≥30 kg/m^2 at baseline. Mean BMI was 33.34 kg/m^2, mean body weight was 96.68 kg. The most prevalent race was White (84.0% of subjects). Only a small proportion was Asian (8.2% of subjects) and Black or African American (3.8% of subjects). Only 10% were of Hispanic or Latino ethnicity.

CV history was overall well balanced across treatment groups and the distribution of the CV diseases was as expected for this population. At randomisation, approximately 92% of subjects in each treatment group were receiving CV medication, primarily beta blockers, ACE inhibitors or angiotensin receptor blockers, as expected for a population with established CV disease.

The trial population represents a clinically relevant population. The patient population selected for this study according to the in- and exclusion criteria is, in fact, already part of the overall target patient population for the approved weight management indication of Wegovy in adults. Therefore, it is not convincingly proven that the beneficial effects on CV risk, as shown in the SELECT study, can be separated from the already approved effects of semaglutide on weight management.

Efficacy data and additional analyses

Primary endpoint MACE

MACE occurred less frequently and at a lower rate with semaglutide 2.4 mg (6.5% of subjects, 2.2 events per 100 PYO) than with placebo (8.0% of subjects, 2.8 events per 100 PYO). 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.

These findings are statistically significant, but the number needed to treat is high (NNT 88 for 3 years), especially taking into account that this is a combined endpoint and the study population is a selection of a high risk overweight/obese population. In lower risk populations, the NNT would be much higher.

The beneficial effect of semaglutide on MACE was primarily due to effects on first fatal or non-fatal MI. The effects of semaglutide on stroke (fatal and or non-fatal) in the total population were small and non-significant.

Primary endpoint MACE in subgroups

The results of the predefined subpopulation analyses were overall consistent with the results from the primary analysis, but there were 2 exceptions.

The beneficial effects of semaglutide on MACE are less evident in individuals with BMI>35 kg/m2. However, efficacy of semaglutide was not significantly influenced by subgroups of BMI or BMI as a continuous variable. In addition, it is not likely that a lower efficacy in individuals with a higher BMI is due to the fact that the dose in these individuals is too low. The hypothesis of a lower exposure to semaglutide in these subgroups was explored by analysing weight change by baseline body weight, used as proxy of semaglutide exposure. The percentage of weight loss (placebo-adjusted) was stable (~8%) across the range of baseline body weight. Further, subjects with baseline BMI 35-40 kg/m2, 40-45 kg/m2, and $\geqslant$45 kg/m2 had a larger % weight loss at week 104 (-9.01%, -9.18%, and -9.33% respectively), compared to subjects with baseline BMI <30 kg/m2, 30-35 kg/m2 (-7.52% and -8.78% respectively).

In individuals with only stroke at baseline (no MI, PAD or other CVD) the beneficial effect of semaglutide on MACE was absent. However, there was no evidence of interaction effect across CV inclusion criteria and the atherosclerotic risk factor burden among subjects with the CV inclusion criterion of stroke only was less pronounced compared with subjects with other CV inclusion.

Modified and expanded MACE

The results for time to first modified MACE (all-cause death, non-fatal MI or non-fatal stroke) (HR: 0.80 $[0.72; 0.88]_{95\% CI}$) and the results for time to first EAC-confirmed expanded MACE (CV death,

non-fatal MI, non-fatal stroke, UAP requiring hospitalisation and coronary revascularisation) (HR: 0.80 [0.73; 0.87]$_{95\% CI}$) were in line with the results for the primary MACE analysis.

All-cause mortality and CV mortality

A total of 223 subjects (2.5%) randomised to semaglutide 2.4 mg died during the in-trial observation period due to EAC-confirmed CV death (including undetermined cause of death) vs 262 subjects (3.0%) with placebo, corresponding to rates of 0.8 events per 100 PYO with semaglutide 2.4 mg vs 0.9 events per 100 PYO with placebo. Analysis of time to CV death showed an estimated HR for semaglutide 2.4 mg vs placebo of 0.85 [0.71; 1.01]95% CI. Superiority of semaglutide 2.4 mg vs placebo was not confirmed; p=0.0327 (nominal significance level: 0.01148).

Due to the testing hierarchy superiority of semaglutide 2.4 mg vs placebo was not tested for the confirmatory secondary mortality endpoint of time to EAC-confirmed all-cause death.

The number of all-cause deaths was lower with semaglutide 2.4 mg than with placebo; 375 (4.3%) subjects died during the in-trial observation period with semaglutide 2.4 mg vs 458 (5.2%) with placebo, corresponding to mortality rates of 1.3 events per 100 PYO with semaglutide 2.4 mg vs 1.6 events per 100 PYO with placebo 100 PYO. Analysis of time to all-cause death showed an estimated HR for semaglutide 2.4 mg vs placebo of 0.81 [0.71; 0.93]95% CI.

Heart failure

Due to the testing hierarchy, superiority of semaglutide 2.4 mg vs placebo was not tested for the confirmatory secondary endpoint of time to first EAC confirmed composite HF outcome.

The proportion of subjects with an EAC-confirmed first composite HF event were lower with semaglutide 2.4 mg than with placebo: a total of 300 subjects (3.4%) experienced events with semaglutide 2.4 mg vs 361 subjects (4.1%) with placebo. The proportions of subjects with event rates were lower with semaglutide 2.4 mg than with placebo: event rates of 1.0 events per 100 PYO for semaglutide 2.4 mg vs 1.2 events per 100 PYO for placebo. Analysis of time to first composite HF outcome showed an estimated HR for semaglutide 2.4 mg vs placebo of 0.82 [0.71; 0.96]95% CI.

Nephropathy

The 5 component composite nephropathy endpoint consisted 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 m2, initiation of chronic renal replacement therapy (dialysis or transplantation) or renal death). A total of 353 first composite nephropathy events (with onset during the in-trial observation period occurred, corresponding to event rates of 0.5 events per 100 PYO (semaglutide 2.4 mg) and 0.7 events per 100 PYO (placebo). The proportion of subjects with first composite nephropathy events was lower with semaglutide 2.4 mg (155 subjects, 1.8%) than with placebo (198 subjects, 2.2%). The analysis of time to first composite nephropathy events resulted in an estimated HR of 0.78 [0.63; 0.96]95% CI for semaglutide 2.4 mg relative to placebo hence, the risk of deterioration in kidney function was significantly lower with semaglutide 2.4 mg than with placebo.

The reduction in risk was mainly driven by the component persistent macroalbuminuria. Only few subjects experienced an event of persistent reduction in eGFR, onset of eGFR<15 ml/min/1.73m2, and initiation of RRT. No events of renal death were observed.

Body weight

Change in body weight (%) from baseline at week 104 was a supportive secondary endpoint. The estimated treatment difference of the change in mean body weight (%) from baseline at week 104 was

-8.51 kg (95% CI -8.75 to -8.27 kg). This is less than could be expected on the basis of the results of previous studies with semaglutide in obese individuals that showed average weight loss of >10 kg vs placebo.

Other endpoints

There were slight improvements in systolic and diastolic blood pressure, lipids and hs CRP levels.

Similar to previous studies with GLP-1 RA's, heart rate increased with semaglutide (ETD +3.1 bpm, 95% CI 2.8-3.4 bpm).

The risk of being a smoker was similar with semaglutide 2.4 mg compared with placebo.

The EuroQol five dimensions five level (EQ 5D 5L) questionnaire showed small improvements in overall self-rated health (ETD 1.60 [1.16; 2.04]95% CI). The EQ 5D 5L is a well-known widely used quality of life assessment instrument. In addition, The EQ 5D 5L can be used to support payer (i.e. HTA bodies) submissions and negotiation.

Additional analyses

Statistically, a proportion of the effect of semaglutide 2.4 mg on CV risk reduction was not explained by effects on well-established cardiometabolic risk factors. The MAH interpret their mediation analyses as supportive for an independent CV risk reducing effect of semaglutide by itself, but these analyses are prone to bias because they are based on a limited number of identified mediating factors. The variables body weight, HbA1c, systolic blood pressure, LDL cholesterol and hsCRP were examined as potential mediators since they could plausibly have a relation to MACE. Inherently, these analyses do not account for any potential mediating factors related to weight-loss and contributing to CV risk reduction that are not identified and included in the mediation analyses. In addition, as stated by the Applicant, the results should be interpreted with caution since, in contrast to the primary analysis of the trial, the mediation analyses were not protected against confounding through randomisation of participants. Furthermore, the estimates of percentage mediation were subject to substantial uncertainty reflected by the wide confidence intervals. These concerns notwithstanding, the mechanism by which semaglutide is supposed to act independently and directly to reduce CV risk is not established. Therefore, mediation analyses may be considered hypothesis generating, but they are not considered an appropriate basis for a separate indication for the prevention of CV disease.

2.4.3. Conclusions on the clinical efficacy

Trial 4388 is a very relevant and large clinical trial. No previous dedicated weight management CVOTs have been able to demonstrate a link between weight loss and CV risk reduction. The trial demonstrated that semaglutide s.c. 2.4 mg once weekly lowers the incidence of MACE vs placebo, both added to standard of care in subjects with established CV disease and overweight or obesity.

These findings are statistically significant, but the number needed to treat is high (NNT 88 for 3 years), especially taking into account that this is a combined endpoint and the study population is a selection of a high risk overweight/obese population. In lower risk populations, the NNT would be much higher.

The patient population selected for this study is already a part of the target patient population for the weight loss indication in adults already approved for Wegovy. Also the mechanism of action of semaglutide for cardiovascular risk reduction is likely multifactorial, in part driven by weight loss effects and effects on known cardiovascular risk factors (reduction in blood pressure, improvements in lipid profile and glucose metabolism, and anti-inflammatory effects as demonstrated by reductions in high-sensitivity C-reactive protein (hsCRP)). The exact mechanism of cardiovascular risk reduction has not been established.

Mediation analyses are presented to support an independent effect of semaglutide on reduction of CV risk. However, mediation analyses may be considered hypothesis generating, but they are not considered an appropriate basis for a separate indication for the prevention of CV disease. Nonetheless, it is considered relevant to add the results of the SELECT trial in section 5.1 of the SmPC of Wegovy, since they demonstrate a link between weight loss and CV risk reduction. The beneficial effect of semaglutide on MACE is considered clinically important, as well as the fact that the result was primarily due to effects on first fatal or non-fatal MI, while the effects of semaglutide on stroke (fatal and or non-fatal) in the total population were small and non-significant. However, the SELECT trial was not powered to evaluate the mono components for the composite endpoint.

2.5. Clinical safety

Introduction and exposure

Data from SELECT has not been pooled with data from the STEP phase 3a trials included in the initial Wegovy® application. This was due to differences in the populations included in the trials; SELECT included a population of people above 45 years- of-age with established CV disease and overweight or obesity, the duration of the trials, and the difference in collection of safety data (SELECT employed targeted safety data collection).

Trial 4388 was event-driven and consequently, the observation time and treatment time varied between subjects depending on when they were recruited into the trial. 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. 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.

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 1 3). Most subjects (60.5%) did not have any treatment discontinuation periods.

With a sample size of 17,604 subjects, the exposure in SELECT (58,395 PYO) is considered sufficient to allow for a robust safety evaluation based on this single trial. Furthermore, SELECT provides additional information on safety in a population with ASCVD and on treatment differences for infrequent events compared to the STEP phase 3a trials.

Adverse events

The safety evaluation is based on the FAS using the in-trial observation period.

Trial 4388 applied a targeted approach for collection of safety data as the safety profile of semaglutide is well characterised. Systematically collected events included all SAEs as well as selected predefined categories of AEs regardless of seriousness (i.e., AEs leading to discontinuation of trial product, COVID-19 AEs, AEs in scope for additional data collected via specific event forms and events for adjudication). The selected events supported the collection of endpoint information and helped to further characterise the safety profile in specific areas, based on the identified and potential risks for semaglutide and other GLP-1 receptor agonists.

Deaths

The evaluation of deaths for efficacy is primarily based on adjudication by the EAC and described under mortality endpoints in the efficacy section. All deaths were in scope for adjudication with the objective to attribute deaths to CV death (including undetermined cause of death), renal death or non-CV, non-renal death. A total of 375 subjects in the semaglutide 2.4 mg group and 458 subjects in the placebo group died during the in-trial observation period, based on EAC-determined day of death.

Investigator-reported SAEs with fatal outcome

This section summarises SAEs with a fatal outcome with onset during the in-trial observation period, as reported by the investigator. The investigator could report more than one event with a fatal outcome for the same subject. The date of onset for these events represents the onset of the SAE leading to the fatal outcome as assigned by the investigator.

A total of 371 subjects in the semaglutide 2.4 mg group and 460 subjects in the placebo group had an SAE with a fatal outcome with onset during the in-trial observation period. The proportion of subjects with SAEs with a fatal outcome and the corresponding event rate were lower with semaglutide 2.4 mg (4.21% of subjects with 1.64 events per 100 PYO) than with placebo (5.23% of subjects with 2.04 events per 100 PYO).

The types of SAEs with a fatal outcome were generally similar with semaglutide 2.4 mg and placebo. Overall, the most frequent fatal events across both treatment groups by SOC were Cardiac disorders, General disorders and administration site conditions (primarily PTs of death, sudden death and sudden cardiac death) and Infections and infestations (primarily PTs of COVID-19 pneumonia and COVID-19). Lower frequencies were observed with semaglutide 2.4 mg vs placebo for fatal events of Cardiac disorders (1.32% vs 1.50%), General disorders and administration site conditions (0.87% vs 1.11%) and Infections and infestations (0.82% vs 1.15%).

Other serious adverse events

The proportion of subjects reporting SAEs (including events with fatal outcome) with onset during the in-trial observation period and the corresponding event rate were lower with semaglutide 2.4 mg (33.41% of subjects and 22.61 events per 100 PYO) than with placebo (36.40% of subjects and 25.79 events per 100 PYO) (**Table 4**).

Most of the reported SAEs were of severe or moderate severity and most were assessed by the investigator as unlikely related to trial product, both with semaglutide 2.4 mg and placebo. Most SAEs had an outcome of recovered at the end of the trial. The proportion of subjects with action taken 'drug withdrawn' or 'drug interrupted' and the corresponding event rates were similar in the semaglutide 2.4 mg and placebo groups.

Table 3 Overview of SAEs – FAS in-trial

	Sema 2.4 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	8803	(100)			8801	(100)		
Observation time (year)	29283				29112			
Events	2941	(33.41)	6622	22.61	3204	(36.40)	7507	25.79
Severity								
Severe	1540	(17.49)	2907	9.93	1697	(19.28)	3343	11.48
Moderate	1645	(18.69)	2918	9.96	1830	(20.79)	3288	11.29
Mild	559	(6.35)	795	2.71	598	(6.79)	875	3.01
Relationship to trial product								
Probable	47	(0.53)	71	0.24	31	(0.35)	40	0.14
Possible	214	(2.43)	307	1.05	188	(2.14)	257	0.88
Unlikely	2831	(32.16)	6237	21.30	3115	(35.39)	7201	24.74
Outcome								
Fatal	371	(4.21)	480	1.64	460	(5.23)	595	2.04
Not recovered	402	(4.57)	509	1.74	436	(4.95)	578	1.99
Recovered with sequelae	125	(1.42)	138	0.47	141	(1.60)	159	0.55
Recovering	43	(0.49)	50	0.17	42	(0.48)	51	0.18
Recovered	2523	(28.66)	5433	18.55	2747	(31.21)	6111	20.99
Unknown	11	(0.12)	12	0.04	11	(0.12)	13	0.04
Action taken								
Drug withdrawn	177	(2.01)	217	0.74	176	(2.00)	213	0.73
Drug interrupted	541	(6.15)	813	2.78	627	(7.12)	950	3.26
Dose reduced	14	(0.16)	22	0.08	4	(0.05)	4	0.01
Dose increased	2	(0.02)	2	<.01	1	(0.01)	1	<.01
Dose not changed	1977	(22.46)	3671	12.54	2403	(27.30)	4925	16.92
Unknown	0				3	(0.03)	7	0.02
Not applicable	893	(10.14)	1890	6.45	674	(7.66)	1399	4.81

%: percentage of subjects, E: number of events, N: number of subjects, R: events per 100 years of observation, Relationship to trial product: as judged by the investigator.

A total of 524 subjects (740 events) had SAEs reported as SUSARs during the trial. Of these 36 subjects (49 events) had events with fatal outcome. The most frequently reported SUSARs were by SOC GI disorders, Hepatobiliary disorders, and CV disorders.

Serious adverse events by system organ class

The distribution of SAEs within each SOC was balanced or favouring semaglutide 2.4 mg (**Figure** 29). The most frequently reported SAEs for both semaglutide 2.4 mg and placebo were Cardiac disorders (11.45% vs 13.45%) and Infections and Infestations (7.09% vs 8.39%).

Figure 29 Summary of SAEs by SOC – FAS in-trial

System organ class	Sema 2.4 mg (N=8,803)				Placebo (N=8,801)			
	N	(%)	E	R	N	(%)	E	R
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 unspec.	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 complication	305	(3.46)	414	1.41	313	(3.56)	419	1.44
General disorders and adm. site conditions	273	(3.10)	298	1.02	316	(3.59)	354	1.22
Musculoskeletal and connective tissue dis.	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 dis.	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 dis.	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 dis.	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 dis.	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, family and genetic dis.	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

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.
Abbreviations: %: percentage of subjects in full analysis set, dis.: disorders, E: number of events, N: number of subjects, R: events per 100 years of observation, SAE: serious adverse event, SOC: system organ class.

There was no unexpected clustering or pattern in the type of PTs reported.

Other significant events

Adverse events leading to withdrawal from trial

To ensure complete follow-up, subjects were encouraged to stay in Trial 4388 even if the trial product was permanently discontinued. More than 96% of randomised subjects completed the trial, and a total of 543 randomised subjects (3.1%) did not complete the trial due to either withdrawal of consent or being lost to follow-up.

Adverse events leading to discontinuation of trial product

The proportion of subjects with AEs leading to discontinuation of trial product and the corresponding event rates were higher with semaglutide 2.4 mg than with placebo (30.32% vs 16.00%; 18.30 vs 7.62 events per 100 PYO), respectively. The difference was predominantly caused by more AEs in the SOC of GI disorders (particularly PTs of nausea, diarrhoea, and vomiting) in the semaglutide 2.4 mg group than the placebo group.

For semaglutide 2.4 mg, the proportion of subjects reporting AEs leading to discontinuation of trial product was higher during the dose-escalation period.

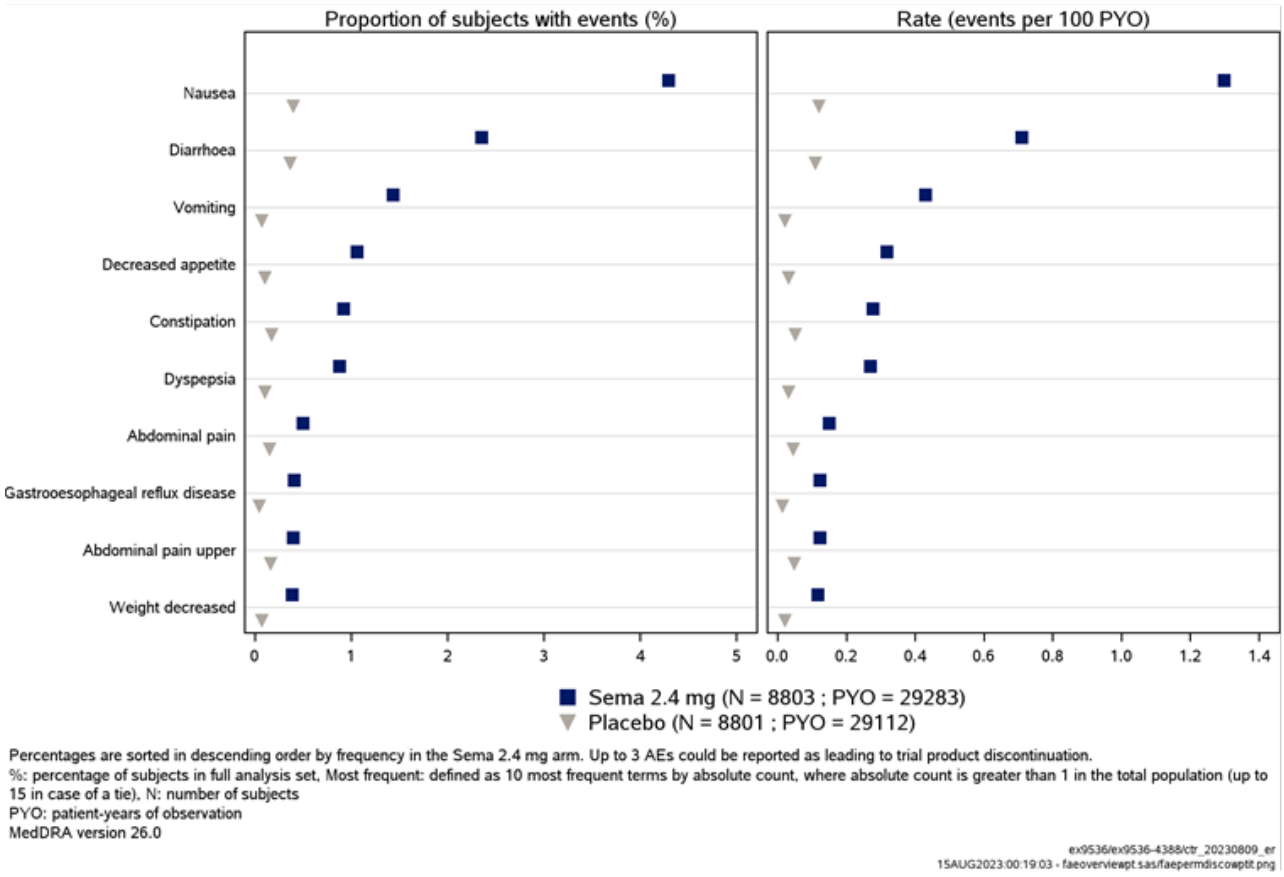
Approximately 80% of the AEs in the semaglutide 2.4 mg group and 50% of the events in the placebo group that led to discontinuation of trial product (drug interrupted or drug withdrawn) were non-serious. The proportion of subjects with SAEs leading to discontinuation of trial product was similar across treatment groups.

Adverse events leading to permanent discontinuation of trial product

The proportion of subjects with AEs leading to permanent discontinuation of trial product (i.e., events indicated on the dose change form as being primary reason for treatment discontinuation and where treatment was not resumed), was higher with semaglutide 2.4 mg than with placebo (16.60% vs 8.16%). This was predominantly driven by AEs in the SOCs of GI disorders (including PTs of nausea, vomiting, diarrhoea, constipation, dyspepsia and GERD), Nervous system disorders (including PTs of dizziness, headache), as well as Metabolism and general disorders (including PTs of decreased appetite, weight decreased, asthenia and fatigue). Most frequent PTs leading to permanent trial product discontinuation are presented in **Figure 30**.

For semaglutide 2.4 mg, the proportion of subjects reporting AEs leading to permanent discontinuation of trial product was higher in the initial 6 months during dose-escalation, whereas a time pattern was less apparent with placebo.

Figure 30 AEs leading to permanent trial product discontinuation by PT – most frequent – FAS in-trial



Percentages are sorted in descending order by frequency in the Sema 2.4 mg arm. Up to 3 AEs could be reported as leading to trial product discontinuation.
%: percentage of subjects in full analysis set, Most frequent: defined as 10 most frequent terms by absolute count, where absolute count is greater than 1 in the total population (up to 15 in case of a tie), N: number of subjects
PYO: patient-years of observation
MedDRA version 26.0

ex9536/ex9536-4388/ctr_20230809_er
15AUG2023:00:19:03 - faeoverviewpt.sas/faepermdiscowptlt.png

The proportion of subjects with SAEs leading to the permanent discontinuation of trial product was similar in both treatment groups (semaglutide 2.4 mg: 3.57%; placebo: 4.12%). Among subjects with

SAEs leading to permanent discontinuation of trial product, more subjects had events of mild or moderate severity with semaglutide 2.4 mg vs placebo. The majority of subjects with SAEs leading to permanent discontinuation of trial product recovered from the event (semaglutide 2.4 mg: 78% of subjects with events; placebo: 59% of subjects with events).

Overview of results for safety focus areas

A summary of results for all safety focus areas evaluated in Trial 4388 is provided in **Figure 31**. For most of the predefined safety focus areas there were little or no differences between semaglutide 2.4 mg and placebo, including similar proportion of subjects in each treatment group reporting AEs of acute renal failure (MedDRA search), malignant neoplasms (MedDRA search), pancreatitis (MedDRA search) and COVID-19 (MedDRA search) and SAEs of gastrointestinal disorders (MedDRA search). The proportion of subjects reporting SAEs of Cardiac disorders (SOC) was lower with semaglutide 2.4 mg than with placebo. The proportion of subjects reporting AEs of Gallbladder-related disorders (MedDRA search) was higher with semaglutide 2.4 mg than with placebo, mainly driven by an imbalance in cholelithiasis (PT).

No pregnancies were reported by women enrolled in Trial 4388.

Figure 31 Overview of events based on pre-defined MedDRA searches for each safety focus area

Predefined MedDRA Search	Sema 2.4 mg (N=8803)				Placebo (N=8801)			
	N	(%)	E	R	N	(%)	E	R
COVID-19	2108	(23.95)	2323	8.86	2150	(24.43)	2365	9.08
Cardiac disorders (SAEs)	1008	(11.45)	1414	4.83	1184	(13.45)	1800	6.18
Malignant tumours	422	(4.79)	517	1.77	418	(4.75)	505	1.73
Gastrointestinal disorders (SAEs)	342	(3.89)	455	1.55	323	(3.67)	403	1.38
Gallbladder-related disorders	246	(2.79)	300	1.02	203	(2.31)	246	0.85
Acute renal failure	171	(1.94)	193	0.66	200	(2.27)	222	0.76
Rare events (SAE)	136	(1.54)	150	0.51	139	(1.58)	150	0.52
Medication errors	54	(0.61)	63	0.22	70	(0.80)	83	0.29
Eye disorders (SAEs)	41	(0.47)	49	0.17	41	(0.47)	51	0.18
Hepatic disorders (SAEs)	36	(0.41)	45	0.15	35	(0.40)	47	0.16
Pancreatitis	29	(0.33)	33	0.11	30	(0.34)	33	0.11
Allergic reactions (SAEs)	26	(0.30)	27	0.09	24	(0.27)	24	0.08
Appendicitis (SAEs)	25	(0.28)	25	0.09	25	(0.28)	27	0.09
Abuse and misuse	10	(0.11)	11	0.04	12	(0.14)	17	0.06
Suicide / self-injury (SAEs)	10	(0.11)	12	0.04	10	(0.11)	12	0.04
Hypoglycaemia (SAEs)	3	(0.03)	3	0.01	1	(0.01)	1	<.01
Suspected transmission* (SAE)	0	-	-	-	1	0.01	1	<.01

N: number of subjects with event(s), %: proportion of subjects with event(s), E: number of events, R: events per 100 patient years of observation, Sema: semaglutide, * Suspected transmission* of an infectious agent via trial product (SAE)

Malignant neoplasms

Malignant neoplasms were reported for a similar proportion of subjects with a similar event rate in the semaglutide 2.4 mg group (4.79%, 1.77 events per 100 PYO) and the placebo group (4.75%, 1.73 events per 100 PYO). Malignant neoplasms were distributed throughout the trial in both treatment groups. There was no apparent difference between treatment groups with respect to time of onset of malignant neoplasms and no clustering of events.

AEs of Pancreatic neoplasms malignant (excl. islet cell and carcinoid) (HLT) was reported by a similar proportion of subjects in the semaglutide group (0.08%, 0.02 events per 100 PYO) and in the placebo group (0.10%, 0.03 events per 100 PYO). A total of 3 events of MTC were reported; all events were in subjects in the placebo group. All 3 cases were identified based on baseline calcitonin assessments.

Suicide/self-injury

Few subjects had SAEs of suicide/self-injury with no imbalance across treatment groups (12 events in 10 (0.11%) subjects and 0.04 events per 100 PYO in both treatment groups). The SAEs of suicide/self-injury occurred throughout the trial in both treatment groups with no evidence of temporal clustering. Approximately half of the subjects with SAEs of suicide/self-injury had either depression and/or anxiety as medical history.

Acute pancreatitis

The evaluation of pancreatitis was based on predefined MedDRA search for pancreatitis among all AEs, which provides a broad evaluation of all types of investigator-reported pancreatitis including search terms (PTs) indicative of acute or chronic pancreatitis, additional information collected on a specific event form for pancreatitis and the outcome of the adjudication by the EAC, where the evaluation focuses on events of acute pancreatitis and is specific to the area of interest (acute pancreatitis).

The proportion of subjects with EAC-confirmed events of acute pancreatitis was slightly lower in the semaglutide 2.4 mg group (0.2%) than in the placebo group (0.3%). In both treatment groups, most of the confirmed events were categorised by the EAC as mild or moderate in severity based on the Atlanta criteria.[9] None of the subjects with a history of acute pancreatitis had EAC-confirmed events of acute pancreatitis during the in-trial period.

Hypoglycaemia

The number of events and corresponding proportion of subjects with hypoglycaemia SAEs (MedDRA search) were low but numerically higher in the semaglutide 2.4 mg group compared to the placebo group (3 events in 3 subjects corresponding to 0.03% in the semaglutide 2.4 mg group and 1 event in1 subject corresponding to 0.01% in the placebo group).

All reported adverse events

Adverse events were reported by a larger proportion of subjects in the semaglutide 2.4 mg group than in the placebo group (71.01% vs 67.03%).

Gastrointestinal adverse were reported by a larger proportion of subjects in the semaglutide 2.4 mg group than in the placebo group (39.21% vs 18.66%).

Infections and infestations were reported for a similar proportion of subjects in the semaglutide 2.4 mg group and the placebo group (34.99% vs 36.65%). Nervous system disorders were reported for a similar proportion of subjects in the semaglutide 2.4 mg group and the placebo group (14.63% vs 13.51%). Musculoskeletal and connective tissue disorders were reported for a similar proportion of subjects in the semaglutide 2.4 mg group and the placebo group (14.03% vs 15.42%). General disorders and administration site reactions were reported for a similar proportion of subjects in the semaglutide 2.4 mg group and the placebo group (13.34% vs 11.66%). Specifically, administration site reactions were reported for a similar proportion of subjects in the semaglutide 2.4 mg group and the placebo group (1.02% vs 1.18%).

The lack of systematic collection precludes any firm conclusions. However, no new safety concerns or potential safety issues were identified based on all AEs.

Laboratory findings

Clinical laboratory data were assessed at baseline and throughout the trial at selected visits.

Kidney function parameters, hepatic biochemistry parameters and calcitonin were all evaluated as part of a safety focus area. Assessed kidney function parameters were eGFR, creatinine and UACR. Assessed hepatic biochemistry parameters were alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase and gamma-glutamyl transferase (GGT). Calcitonin was evaluated under malignant neoplasms safety focus area. The biochemistry parameters not included under a safety focus area were albumin, calcium, albumin corrected calcium, potassium, sodium and urea. The haematology parameters measured included erythrocytes, haematocrit, haemoglobin, leucocytes, thrombocytes and differential cell counts (basophils, eosinophils, lymphocytes, monocytes and neutrophils).

Overall, treatment with semaglutide 2.4 mg did not have an impact on the evaluated laboratory parameters.

Other observations related to safety

Post-baseline hypotension, defined as minimum SBP <90 mmHg or minimum DBP <60 mmHg at any visit after baseline, was observed for similar proportions in the two treatment groups (15.6% of subjects in the semaglutide 2.4 mg group and for 15.8% of subjects in the placebo group) A maximum increase in heart rate from baseline of ≥20 bpm was observed for 35.3% of subjects in the semaglutide 2.4 mg group and for 24.7% of subjects in the placebo group To ensure that any potential unexpected adverse effects related to the magnitude of weight loss, post-baseline hypotension and increase in heart rate were evaluated, the safety profile (SAEs) of semaglutide 2.4 mg was assessed for subpopulations based on maximum post-baseline body weight loss (<20%; ≥20%), post-baseline hypotension (yes; no) and maximum post-baseline heart rate (<10 bpm; ≥10 to <20 bpm; ≥20 bpm).

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. 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.

Safety in subgroups

Intrinsic and extrinsic factors

The potential impact of intrinsic factors and extrinsic factors on the safety profile of semaglutide 2.4 mg was evaluated based on data from the in-trial period of Trial 4388.

The prespecified intrinsic and extrinsic factors (baseline subpopulations) evaluated in Trial 4388 were:

- Sex (Males; Females)
- Baseline age (<55 years, ≥55 to <65 years, ≥65 to <75 years; ≥75 years)
- Race (Asian; Black or African American; White; Other)
- Ethnic origin (Hispanic/Latino; Not Hispanic/Latino)
- Baseline BMI (<30 kg/m^2; ≥30 to <35 kg/m^2; ≥35 to <40 kg/m^2; ≥40 to <45 kg/m^2; ≥45 kg/m^2)
- Baseline kidney function (<60 mL/min/1.73 m^2; ≥60 mL/min/1.73 m^2)

- Baseline HbA_{1c} (<5.7%; ≥5.7%)
- Baseline chronic heart failure status (Yes; No)
- Baseline CVD status (Only MI; Only stroke; Only PAD; ≥ 2 CV diseases [any combination of MI, stroke and PAD])
- Region (Europe; North America [Canada and United States]; Asia; Other [Africa, South America and Other])

While there were minor differences in some PTs between subpopulations, there were no marked exceptions within any given HLGT or SOC to the overall observed treatment differences for any of the evaluated prespecified intrinsic or extrinsic factors. This also included baseline age, which also evaluated the subpopulation of subjects ≥75 years (with accounted for 1366 subjects in total).

2.5.1. Discussion on clinical safety

With a sample size of 17,604 subjects and an overall median on treatment time of more than 3 years, the exposure in SELECT (58,395 PYO) is considered sufficient to allow for a robust safety evaluation. Furthermore, SELECT provides additional information on safety in a population with ASCVD and on treatment differences for infrequent events compared to the STEP phase 3a trials. However, experience with semaglutide 2.4 mg is still limited in subjects ≥ 85 years of age (n=23 in SELECT).

SAE's

The proportion of subjects reporting SAEs (including events with fatal outcome) with onset during the in-trial observation period and the corresponding event rate were lower with semaglutide 2.4 mg (33.41% of subjects and 22.61 events per 100 PYO) than with placebo (36.40% of subjects and 25.79 events per 100 PYO) The distribution of SAEs within each SOC was balanced or favouring semaglutide 2.4 mg.

The proportion of subjects with AEs leading to discontinuation of trial product and the corresponding event rates were higher with semaglutide 2.4 mg than with placebo (30.32% vs 16.00%; 18.30 vs 7.62 events per 100 PYO), respectively. The difference was predominantly caused by more AEs in the SOC of GI disorders (particularly PTs of nausea, diarrhoea, and vomiting) in the semaglutide 2.4 mg group than the placebo group. The proportion of subjects with AEs leading to permanent discontinuation of trial product, was higher with semaglutide 2.4 mg than with placebo (16.60% vs 8.16%). This was also predominantly driven by AEs in the SOCs of GI disorders (including PTs of nausea, vomiting, diarrhoea, constipation, dyspepsia and GERD).

Adverse events

Adverse events were reported by a larger proportion of subjects in the semaglutide 2.4 mg group than in the placebo group (71.01% vs 67.03%). Especially, gastrointestinal adverse were reported by a larger proportion of subjects in the semaglutide 2.4 mg group than in the placebo group (39.21% vs 18.66%).

Administration site reactions were reported for a similar proportion of subjects in the semaglutide 2.4 mg group and the placebo group (1.02% vs 1.18%).

The lack of systematic collection precludes any firm conclusions. However, no new safety concerns or potential safety issues were identified based on all AEs.

Safety focus areas

For most of the predefined safety focus areas there were little or no differences between semaglutide 2.4 mg and placebo.

Malignant neoplasms were recorded for a similar proportion of subjects and with similar event rates for semaglutide (4.79%, 1.77 events per 100 PYO) and placebo (4.75%, 1.73 events per 100 PYO). No marked between-group imbalance in specific cancer PTs or temporal clustering was apparent.

Non-clinical data have indicated a potential association between GLP-1 analogues and pancreatic as well as medullary thyroid neoplasms. AEs of Pancreatic neoplasms malignant (excl. islet cell and carcinoid) (HLT) was reported by a similar proportion of subjects in the semaglutide group (0.08%, 0.02 events per 100 PYO) and in the placebo group (0.10%, 0.03 events per 100 PYO). A total of 3 events of MTC were reported; all events were in subjects in the placebo group. All 3 cases were identified based on baseline calcitonin assessments.

Few subjects had SAEs of suicide/self-injury with no imbalance across treatment groups (12 events in 10 (0.11%) subjects and 0.04 events per 100 PYO in both treatment groups).

In the phase 3a pool of the initial Wegovy MAA, 5 EAC-confirmed events of acute pancreatitis were recorded in 4 subjects (0.2%) treated with semaglutide 2.4 mg vs. 1 such event (< 0.1%) with placebo. Conversely, in SELECT, the proportion of subjects with EAC-confirmed events of acute pancreatitis was slightly lower in the semaglutide 2.4 mg group (0.19%) than in the placebo arm (0.27%). The MAH's proposed inclusion of the latter data in SmPC section 4.8 is endorsed.

The proportion of subjects reporting SAEs of Cardiac disorders (SOC) was lower with semaglutide 2.4 mg than with placebo.

The proportion of subjects reporting AEs of Gallbladder-related disorders (MedDRA search) was slightly higher with semaglutide (2.79%) than with placebo (2.31%), mainly driven by an imbalance in cholelithiasis (1.40% vs. 1.14% in respective groups) and with grouped cholecystitis PTs (cholecystitis, cholecystitis acute or cholecystitis infective) balanced between treatment groups (0.56% vs. 0.59% for semaglutide and placebo, respectively). Risk of gallstones and cholecystitis are addressed in currently approved SmPC wordings.

The proportion of subjects with SAEs in the Eye disorders SOC and the event rates were balanced between the two treatment groups (0.47% vs 0.47% and 0.17 vs 0.18 events per 100 PYO for semaglutide and placebo, respectively). In addition, no significant between-group imbalances were observed regarding Eye disorder PTs which may be mapped under 'Retinal disorders'.

The proportion of subjects with SAEs of acute renal failure was 1.00% in the semaglutide 2.4 mg group and 1.28% in the placebo group.

There was a similar proportion of subjects in each treatment group reporting AEs of COVID-19 (MedDRA search) and SAEs of gastrointestinal disorders (MedDRA search).

The proportion of subjects with SAEs of hypoglycaemia SAEs was numerically higher in the semaglutide 2.4 mg group compared to the placebo group (0.03% in the semaglutide 2.4 mg group and 0.01% in the placebo group). In the previous studies with semaglutide 2.4 mg, no SAEs of hypoglycaemia have been reported.

Subgroup analyses

The safety profile of semaglutide 2.4 mg was not affected to any clinically relevant extent by the intrinsic factors (sex, baseline age, race, ethnic origin, baseline BMI, baseline kidney function, baseline HbA1c, baseline chronic HF status and baseline CV disease status) or the extrinsic factors (region) evaluated in Trial 4388. However, the number of Asian; Black or African American and Hispanic/Latino patients was small.

2.5.2. Conclusions on clinical safety

With a sample size of 17,604 subjects and an overall median on treatment time of more than 3 years, the exposure in SELECT (58,395 PYO) is considered sufficient to allow for a robust safety evaluation. In general, the safety and tolerability profile of semaglutide 2.4 mg in people with established CV disease and overweight or obesity observed in SELECT is in line with the safety profile previously reported for semaglutide and no new safety concerns were identified for semaglutide 2.4 mg.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

3.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- The changes to the patient leaflet are not significant (ref. Guideline on the readability of the labelling and package leaflet of medicinal products for human use, January 2009)
- A user consultation was made for semaglutide during the marketing authorisation application approved in 2022 (Readability test report [M 1.3.4], seq. 0004)
- A user consultation was made for the additional pen-presentation (PDS290) approved in 2022 (Readability test report [M 1.3.4], seq. 0007)

3.1.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Wegovy (semaglutide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

4. Benefit-Risk Balance

4.1. Therapeutic Context

4.1.1. Disease or condition

The global prevalence of obesity is rising, at present more than 760 million people live with obesity globally and, by 2030 it is predicted that more than 1 billion people will be living with obesity.

Obesity is associated with several health-related complications including an increased risk of CV disease. CV disease is the leading cause of death and morbidity worldwide and currently accounts for more than 17.6 million deaths each year and this number is expected to increase to more than 22.2 million deaths by 2030. Overall, CV disease is more prevalent in individuals living with obesity and the lifetime risk for incident CV disease increases exponentially in both men and women with higher BMI. Moreover, most deaths associated with high BMI are caused by CV disease. Despite improvements in cardiometabolic risk factors, patients with obesity continue to be at considerable increased CV risk.

Semaglutide is a GLP-1 analogue with a high degree of homology to human GLP-1. It is approved under the tradename Ozempic® for treatment of T2D. Semaglutide 2.4 mg has been approved under the tradename Wegovy® for weight management. Available data indicate that semaglutide s.c. reduces the risk of MACE in patients with T2D and high CV risk (SUSTAIN 6) and improves cardiometabolic risk factors in patients with obesity and/or T2D (STEP and SUSTAIN phase 3a development programmes. The effect of semaglutide on the risk of MACE in patients with obesity without diabetes is unknown.

The MAH requested an extension of indication to include risk reduction of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and BMI ≥27 kg/m2.

4.1.2. Main clinical studies

Design and conduct of clinical studies

Design

Trial 4388 was a multinational, multicentre, randomised, double blind, parallel group, placebo controlled trial. The trial was designed to demonstrate superiority of semaglutide 2.4 mg once weekly vs placebo, both added to CV standard of care in subjects with established CV disease and overweight or obesity, but without history of T1D or T2D. This is a very important trial. No dedicated weight management CVOTs have been able to demonstrate a link between weight loss and CV risk reduction. There is an unmet medical need for weight management drugs targeting the residual CV risk in people with overweight or obesity.

Objectives and endpoints

Primary objective was to demonstrate that semaglutide s.c. 2.4 mg once weekly lowers the incidence of MACE vs placebo, both added to standard of care in subjects with established CV disease and

overweight or obesity. Primary endpoint was the time from randomisation to first occurrence of a composite endpoint consisting of CV death, non fatal MI, or non fatal stroke.

Confirmatory secondary endpoints were time from randomisation to CV death and time from randomisation to first occurrence of a composite HF endpoint consisting of: HF hospitalisation, urgent HF visit or CV death. These endpoints were managed with respect to multiplicity thorough a pre-specified hierarchical testing sequence.

The choice of the primary and confirmatory secondary endpoints is acceptable. However, there is a very long list of explorative and supportive secondary endpoints (26 endpoints). The results with respect to these endpoints should be interpreted with caution. The company used a hierarchical testing strategy.

Population

Eligible subjects were randomised (1:1) to treatment with semaglutide 2.4 mg (8,805 subjects) or placebo (8,804 subjects).

In total, 96.9% of randomised subjects in the FAS completed the trial. The overall median time in-trial was 41.8 months, and overall median on treatment time was 38.2 months. Subjects were on treatment on average 85.1% of the planned on-treatment period.

30.6% of the individuals in the semaglutide group permanently discontinued treatment. Trial product was permanently discontinued due to adverse events in 16.3% individuals in the semaglutide group (vs 7.9% in the placebo group). This high number emphasizes the high number of important side effects.

The mean age of the subjects at baseline was 61.6 years. In total, 38.2% of the subjects was ≥65 years and 7.8% was ≥75 years. In total, 72.3% of subjects were male. The trial population included subjects with overweight (BMI ≥27 to <30 kg/m^2) or obesity (BMI ≥30 kg/m^2). A total of 71.5% of the trial population had a BMI ≥30 kg/m^2 at baseline. Mean BMI was 33.34 kg/m^2, mean body weight was 96.68 kg. The most prevalent race was White (84.0% of subjects). Only a small proportion was Asian (8.2% of subjects) and Black or African American (3.8% of subjects). Only 10% were of Hispanic or Latino ethnicity.

CV history was overall well balanced across treatment groups and the distribution of the CV diseases was as expected for this population. At randomisation, approximately 92% of subjects in each treatment group were receiving CV medication, primarily beta blockers, ACE inhibitors or angiotensin receptor blockers, as expected for a population with established CV disease. The trial population represents a clinically relevant population, it is a selected subgroup of the total overweight/obese population.

The patient population selected for this study is already a part of the target patient population for the weight loss indication in adults already approved for Wegovy. Also the mechanism of action of semaglutide for cardiovascular risk reduction is likely multifactorial, in part driven by weight loss effects and effects on known cardiovascular risk factors. The exact mechanism of cardiovascular risk reduction has not been established.

4.2. Favourable effects

Primary endpoint MACE

MACE occurred less frequently and at a lower rate with semaglutide 2.4 mg (6.5% of subjects, 2.2 events per 100 PYO) than with placebo (8.0% of subjects, 2.8 events per 100 PYO). 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.

Modified and expanded MACE

The results for time to first modified MACE (all-cause death, non-fatal MI or non-fatal stroke) (HR: 0.80 [0.72; 0.88]$_{95\% CI}$) and the results for time to first EAC-confirmed expanded MACE (CV death, non-fatal MI, non-fatal stroke, UAP requiring hospitalisation and coronary revascularisation) (HR: 0.80 [0.73; 0.87]$_{95\% CI}$) were in line with the results for the primary MACE analysis

Body weight

Change in body weight (%) from baseline at week 104 was a supportive secondary endpoint. The estimated treatment difference of the change in mean body weight (%) from baseline at week 104 was -8.51 kg (95% CI -8.75 to -8.27 kg). This is less than could be expected on the basis of the results of previous studies with semaglutide in obese individuals that showed average weight loss of >10 kg vs placebo.

Other endpoints

There were slight improvements in systolic and diastolic blood pressure, lipids and hs CRP levels.

Similar to previous studies with GLP-1 RA's, heart rate increased with semaglutide (ETD +3.1 bpm, 95% CI 2.8-3.4 bpm).

The risk of being a smoker was similar with semaglutide 2.4 mg compared with placebo.

The EuroQol five dimensions five level (EQ 5D 5L) questionnaire showed small improvements in overall self-rated health (ETD 1.60 [1.16; 2.04]95% CI). The EQ 5D 5L is a well-known widely used quality of life assessment instrument. In addition, The EQ 5D 5L can be used to support payer (i.e. HTA bodies) submissions and negotiation.

4.3. Uncertainties and limitations about favourable effects

Separate components of the primary endpoint

The beneficial effect of semaglutide on MACE was primarily due to effects on first fatal or non-fatal MI. The effects of semaglutide on stroke (fatal and or non-fatal) in the total population were small and non-significant. However, the SELECT trial was not powered to evaluate the mono components for the composite endpoint.

Primary endpoint MACE in subgroups

The results of the predefined subpopulation analyses were overall consistent with the results from the primary analysis, but there were 2 exceptions.

In the BMI subgroup analyses the beneficial effects of semaglutide on MACE were lower in individuals with BMI>35 kg/m2. However, efficacy of semaglutide was not significantly influenced by subgroups of BMI or BMI as a continuous variable. In addition, it is not likely that a lower efficacy in individuals with a higher BMI is due to the fact that the dose in these individuals is too low. Subjects with baseline BMI 35-40 kg/m2, 40-45 kg/m2, and ≥45 kg/m2 had a larger % weight loss at week 104 (-9.01%, -9.18%, and -9.33% respectively), compared to subjects with baseline BMI <30 kg/m2, 30-35 kg/m2 (-7.52% and -8.78% respectively).

In individuals with only stroke at baseline (no MI, PAD or other CVD) the beneficial effect of semaglutide on MACE was absent. However, there was no evidence of interaction effect across CV inclusion criteria (p=0.4803). In addition, evaluating possible explanations as to why a numerically lower MACE risk reduction was seen for subjects with a history of stroke compared to other CV inclusion criteria, there are important differences in the baseline subject composition to consider that may make them less likely to develop MACE compared to other CV inclusion criteria subgroups. For example, among subjects across both treatment groups with a history of stroke, only 51.7% were male (versus 72.3% male overall in SELECT), were more likely to have never smoked (51.3% versus 34.8% overall in SELECT), less likely to have prediabetes (58.9% versus 64.5% overall in SELECT), less coronary heart disease (20.9% versus 82.1% overall in SELECT), less heart failure (18% versus 24.3% overall in SELECT), and less likely to receive lipid lowering treatment (75.6% versus 90.1% overall in SELECT).

All-cause mortality and CV mortality

A total of 223 subjects (2.5%) randomised to semaglutide 2.4 mg died during the in-trial observation period due to EAC-confirmed CV death (including undetermined cause of death) vs 262 subjects (3.0%) with placebo, corresponding to rates of 0.8 events per 100 PYO with semaglutide 2.4 mg vs 0.9 events per 100 PYO with placebo. Analysis of time to CV death showed an estimated HR for semaglutide 2.4 mg vs placebo of 0.85 [0.71; 1.01]95% CI. Superiority of semaglutide 2.4 mg vs placebo was not confirmed; p=0.0327 (nominal significance level: 0.01148).

Due to the testing hierarchy superiority of semaglutide 2.4 mg vs placebo was not tested for the confirmatory secondary mortality endpoint of time to EAC-confirmed all-cause death.

The number of all-cause deaths was lower with semaglutide 2.4 mg than with placebo; 375 (4.3%) subjects died during the in-trial observation period with semaglutide 2.4 mg vs 458 (5.2%) with placebo, corresponding to mortality rates of 1.3 events per 100 PYO with semaglutide 2.4 mg vs 1.6 events per 100 PYO with placebo 100 PYO. Analysis of time to all-cause death showed an estimated HR for semaglutide 2.4 mg vs placebo of 0.81 [0.71; 0.93]95% CI.

Heart failure

Due to the testing hierarchy, superiority of semaglutide 2.4 mg vs placebo was not tested for the confirmatory secondary endpoint of time to first EAC confirmed composite HF outcome.

The proportion of subjects with an EAC-confirmed first composite HF event were lower with semaglutide 2.4 mg than with placebo: a total of 300 subjects (3.4%) experienced events with semaglutide 2.4 mg vs 361 subjects (4.1%) with placebo. The proportions of subjects with event rates were lower with semaglutide 2.4 mg than with placebo: event rates of 1.0 events per 100 PYO for semaglutide 2.4 mg vs 1.2 events per 100 PYO for placebo. Analysis of time to first composite HF outcome showed an estimated HR for semaglutide 2.4 mg vs placebo of 0.82 [0.71; 0.96]95% CI.

Nephropathy

Due to the testing hierarchy, superiority of semaglutide 2.4 mg vs placebo was not tested for the supportive secondary endpoint of time to first EAC confirmed composite nephropathy outcome.

The 5 component composite nephropathy endpoint consisted 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 m2, initiation of chronic renal replacement therapy (dialysis or transplantation) or renal death). A total of 353 first composite nephropathy events (with onset during the in-trial observation period occurred, corresponding to event rates of 0.5 events per 100 PYO (semaglutide 2.4 mg) and 0.7 events per 100 PYO (placebo). The proportion of subjects with first

composite nephropathy events was lower with semaglutide 2.4 mg (155 subjects, 1.8%) than with placebo (198 subjects, 2.2%). The analysis of time to first composite nephropathy events resulted in an estimated HR of 0.78 [0.63; 0.96]95% CI for semaglutide 2.4 mg relative to placebo.

The reduction in risk was mainly driven by the component persistent macroalbuminuria. Only few subjects experienced an event of persistent reduction in eGFR, onset of eGFR<15 ml/min/1.73m2, and initiation of RRT. No events of renal death were observed.

Additional analyses

Statistically, a proportion of the effect of semaglutide 2.4 mg on CV risk reduction was not explained by effects on well-established cardiometabolic risk factors. The company believes that this may be ascribed to other potentially unique effects of semaglutide. However, mediation analyses may be considered hypothesis generating, but they are not considered an appropriate basis for a separate indication for the prevention of CV disease.

4.4. Unfavourable effects

With a sample size of 17,604 subjects and an overall median on treatment time of more than 3 years, the exposure in SELECT (58,395 PYO) is considered sufficient to allow for a robust safety evaluation. Furthermore, SELECT provides additional information on safety in a population with ASCVD and on treatment differences for infrequent events compared to the STEP phase 3a trials.

SAE's

The proportion of subjects reporting SAEs (including events with fatal outcome) with onset during the in-trial observation period and the corresponding event rate were lower with semaglutide 2.4 mg (33.41% of subjects and 22.61 events per 100 PYO) than with placebo (36.40% of subjects and 25.79 events per 100 PYO) The distribution of SAEs within each SOC was balanced or favouring semaglutide 2.4 mg.

The proportion of subjects with AEs leading to discontinuation of trial product and the corresponding event rates were higher with semaglutide 2.4 mg than with placebo (30.32% vs 16.00%; 18.30 vs 7.62 events per 100 PYO), respectively. The difference was predominantly caused by more AEs in the SOC of GI disorders (particularly PTs of nausea, diarrhoea, and vomiting) in the semaglutide 2.4 mg group than the placebo group. The proportion of subjects with AEs leading to permanent discontinuation of trial product, was higher with semaglutide 2.4 mg than with placebo (16.60% vs 8.16%). This was also predominantly driven by AEs in the SOCs of GI disorders (including PTs of nausea, vomiting, diarrhoea, constipation, dyspepsia and GERD).

Adverse events

Adverse events were reported by a larger proportion of subjects in the semaglutide 2.4 mg group than in the placebo group (71.01% vs 67.03%). Especially, gastrointestinal adverse were reported by a larger proportion of subjects in the semaglutide 2.4 mg group than in the placebo group (39.21% vs 18.66%).

Administration site reactions were reported for a similar proportion of subjects in the semaglutide 2.4 mg group and the placebo group (1.02% vs 1.18%).

The lack of systematic collection precludes any firm conclusions. However, no new safety concerns or potential safety issues were identified based on all AEs.

Safety focus areas

For most of the predefined safety focus areas there were little or no differences between semaglutide 2.4 mg and placebo.

AEs of Pancreatic neoplasms malignant (excl. islet cell and carcinoid) (HLT) was reported by a similar proportion of subjects in the semaglutide group (0.08%, 0.02 events per 100 PYO) and in the placebo group (0.10%, 0.03 events per 100 PYO). A total of 3 events of MTC were reported; all events were in subjects in the placebo group. All 3 cases were identified based on baseline calcitonin assessments.

Few subjects had SAEs of suicide/self-injury with no imbalance across treatment groups (12 events in 10 (0.11%) subjects and 0.04 events per 100 PYO in both treatment groups).

The proportion of subjects with EAC-confirmed events of acute pancreatitis was slightly lower in the semaglutide 2.4 mg group (0.2%) than in the placebo group (0.3%).

The proportion of subjects reporting SAEs of Cardiac disorders (SOC) was lower with semaglutide 2.4 mg than with placebo.

The proportion of subjects reporting AEs of Gallbladder-related disorders (MedDRA search) was higher with semaglutide 2.4 mg than with placebo, mainly driven by an imbalance in cholelithiasis (PT).

The proportion of subjects with SAEs of acute renal failure was 1.00% in the semaglutide 2.4 mg group and 1.28% in the placebo group.

There was a similar proportion of subjects in each treatment group reporting AEs of COVID-19 (MedDRA search) and SAEs of gastrointestinal disorders (MedDRA search).

4.5. Uncertainties and limitations about unfavourable effects

SAEs

The proportion of subjects with SAEs of hypoglycaemia SAEs was numerically higher in the semaglutide 2.4 mg group compared to the placebo group (0.03% in the semaglutide 2.4 mg group and 0.01% in the placebo group). In the previous studies with semaglutide 2.4 mg, no SAEs of hypoglycaemia have been reported.

There was a notably higher frequency of AEs leading to permanent treatment discontinuation with semaglutide in SELECT (16.6%) compared to previous studies with semaglutide 2.4 mg for weight management (5.7% in the phase 3a pool of the initial Wegovy MAA and occurring primarily during the dose escalation phase). The proportion of subjects with AEs leading to permanent discontinuation of trial product was higher in SELECT trial due to the longer duration of the trial compared to previous studies. However, in SELECT, the proportion of subjects that overall, permanently discontinued trial product was similar with semaglutide 2.4 mg (30.6%) and placebo (27.0%).

Eye disorders were evaluated based on the SOC of Eye disorders among SAEs, and the number of subjects reporting such events were balanced across treatment groups. In addition, no significant between-group imbalances were observed regarding Eye disorder PTs which may be mapped under 'Retinal disorders'.

Subgroup analyses

The safety profile of semaglutide 2.4 mg was not affected to any clinically relevant extent by the intrinsic factors (sex, baseline age, race, ethnic origin, baseline BMI, baseline kidney function, baseline HbA1c, baseline chronic HF status and baseline CV disease status) or the extrinsic factors (region)

evaluated in Trial 4388. However, the number of Asian; Black or African American and Hispanic/Latino patients was small. Considering the consistency in effect, this issue is not pursued.

Experience with semaglutide 2.4 mg is still limited in subjects ≥ 85 years of age (n=23 in SELECT).

4.6. Effects Table

Table. Effects Table for Wegovy and CV risk based on SELECT trial

Effect	Unit	Treatment	Control	Uncertainties / Strength of evidence
Randomised	N	8803	8801	median on treatment time 38.2 months
Favourable Effects				
				Primary composite endpoint
MACE	N(%)	569 (6.5)	701 (8.0)	HR 0.80 (CI 0.72 to 0.90); P<0.001
				Confirmatory secondary endpoints
CV Death	N(%)	223 (2.5)	262 (3.0)	HR 0.85 (0.71 to 1.01); P=0.07
Heart failure	N(%)	300 (3.4)	361 (4.1)	HR 0.82 (CI 0.71 to 0.96); P=NT
All cause death	N(%)	375 (4.3)	458 (5.2)	HR 0.81 (CI 0.71 to 0.93); P=NT
Body weight	kg	−9.39±0.09	−0.88±0.08	−8.51 (−8.75 to −8.27)
Unfavourable Effects				
Serious adverse events	%	33.4%	36.4%	
AEs leading to permanent discontinuation	%	16.60%	8.16%	
Gastrointestinal adverse events	%	39.21%	18.66%	

Note: MACE: Major adverse Cardiovascular Event, a composite of cardiovascular mortality, non-fatal stroke or non-fatal myocardial infarction. NT = Not Tested.

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Obesity is associated with several health-related complications including an increased risk of CV disease. The lifetime risk for incident CV disease increases exponentially in both men and women with higher BMI. Moreover, most deaths associated with high BMI are caused by CV disease. Despite improvements in cardiometabolic risk factors, persons living with obesity continue to be at considerably increased CV risk. A beneficial effect on CV outcomes is therefore highly relevant.

Trial 4388 is a very relevant and large clinical trial. No previous dedicated weight management CVOTs have been able to demonstrate a link between weight loss and CV risk reduction. The trial demonstrated that semaglutide s.c. 2.4 mg once weekly lowers the incidence of MACE vs placebo, both added to standard of care in subjects with established CV disease and overweight or obesity. The trial population represents a clinically relevant subgroup of the total overweight/obese population.

The beneficial effect of semaglutide on MACE is considered clinically significant and was primarily due to effects on first fatal or non-fatal MI, while the effect of semaglutide on stroke (fatal and/or non-fatal) in the total population was absent. Although the SELECT trial was not powered to evaluate the mono components for the composite endpoint, these data are important from a clinical viewpoint and

have been included in section 5.1 of the SmPC. In addition, subgroup analyses demonstrated that efficacy (MACE) was absent in individuals with stroke at baseline. However, there was no evidence of interaction effect across CV inclusion criteria and the atherosclerotic risk factor burden among subjects with the CV inclusion criterion of stroke only was less pronounced compared with subjects with other CV inclusion.

With a sample size of 17,604 subjects and an overall median on treatment time of more than 3 years, the exposure in SELECT (58,395 PYO) is considered sufficient to allow for a robust safety evaluation. In general, the safety and tolerability profile of semaglutide 2.4 mg in people with established CV disease and overweight or obesity observed in SELECT is in line with the safety profile previously reported for semaglutide and no new safety concerns were identified for semaglutide 2.4 mg.

Malignant neoplasms were reported for a similar proportion of subjects with a similar event rate in the semaglutide 2.4 mg group (4.79%, 1.77 events per 100 PYO) and the placebo group (4.75%, 1.73 events per 100 PYO). Although obesity is a well-known risk factor for cancer, no beneficial effect was attributable to semaglutide.

In reference to an ongoing signal assessment, it is noted that few subjects had SAEs of suicide/self-injury with no imbalance across treatment groups (12 events in 10 (0.11%) subjects and 0.04 events per 100 PYO in both treatment groups).

4.7.2. Balance of benefits and risks

The beneficial effect on CV risk shown in SELECT is clinically very important, as semaglutide s.c. 2.4 mg once weekly lowers the incidence of MACE vs placebo, both added to standard of care in subjects with established CV disease and overweight or obesity. The trial population represents a clinically relevant subgroup of the total overweight/obese population, for which Wegovy is already approved. Therefore, the proposed separate indication for the prevention of CV disease in obese/overweight individuals at high risk is not agreed.

The most important health parameters associated with obesity/overweight are cardiovascular risk factors (such as type 2 diabetes mellitus and hypertension) and cardiovascular outcomes (including myocardial infarction, stroke and heart failure). As such, a crucial aim of weight loss interventions is to improve these comorbidities. This aim is independent of the exact pathophysiological mechanisms. Mediation analyses may be considered hypothesis generating, but they are not considered an appropriate basis for a separate indication for the prevention of CV disease. In the submitted data, body weight and related CV comorbidities were improved in a high risk subgroup of the obese/overweight population. However, there was no extension of the target population as such as compared to the already authorised patient population. Therefore, the beneficial effect of semaglutide on CV risk is already considered sufficiently covered by the current obesity/overweight indication in section 4.1 of the SmPC**.** Nevertheless, it is acknowledged that the beneficial effect on CV risk is very important from a clinical viewpoint and the data have therefore been appropriately reflected in section 5.1 of the SmPC, and an editorial amendment has been made in section 4.1 in order to include a cross reference to SmPC section 5.1. This approach is in line with previous CHMP decisions concerning CVOT's of GLP-1 RA's and SGLT2i's in patients with diabetes.

During the procedure, the MAH proposed the use of semaglutide 0.5/1 mg (Ozempic) data (SUSTAIN 6 and FLOW) to support a CV indication for semaglutide 2.4 mg (Wegovy). The CHMP considered that is not acceptable for the following reasons:

- The reduction of CV disease is already an accepted goal of treatment both in patients with type 2 diabetes and in patients with overweight (BMI ≥27 kg/m2) and CV risk. Therefore, this

treatment goal is considered covered already by the approved diabetes-indication for Ozempic, and the approved weight management indication for Wegovy, respectively. CV data in patients with diabetes (SUSTAIN 6) are already covered by the Ozempic diabetes indication and sufficiently reflected in the product information. In addition, although not yet being fully assessed for regulatory approval, the secondary results on MACE events in patients with diabetes from the FLOW study, could also be considered as covered already by the approved diabetes-indication for Ozempic. Nonetheless, in principle, although the treatment goal of the study might be covered by the approved indication, the study results might always be considered for inclusion in section 5.1 of the SmPC if clinically important.

- The proposed expanded stand-alone CV indication regardless of BMI is based on subgroups of patients with diabetes and BMI <27 kg/m2 in the SUSTAIN 6 and FLOW studies. These analyses are post-hoc in small subgroups. Therefore, these data are not considered sufficient for a separate indication.
- Besides the above, the applied extension for a stand-alone CV indication (as proposed by mixing the diabetes and obesity doses and indications) seems not to be in line with the reasons for the duplicate marketing authorisations for Wegovy and Ozempic.
- In general, the safety and tolerability profile of semaglutide 2.4 mg in people with established CV disease and overweight or obesity observed in SELECT is acceptable and in line with the safety profile previously reported for semaglutide and no new safety concerns were identified for semaglutide 2.4 mg.

Oral explanation

During an oral explanation at the CHMP plenary meeting in June 2024, the company argued that there was no scientific or legal basis for denying the use of clinical data previously used to support one marketing authorisation (Ozempic) to support the extension of the indication for another marketing authorisation (Wegovy). In addition, they argued that mixing indications and posologies is manageable for clinicians and patients. The CHMP considered that there is no substantive reason to mix the obesity and diabetes indications. Ozempic data have been used for and incorporated in the Ozempic label, and Wegovy data have been used for and incorporated into the Wegovy label. In addition, mixing the obesity and diabetes indication could be contradictory with the need to have different marketing authorizations for semaglutide (Ozempic and Wegovy).

With respect to the post-hoc subgroup analyses, the company argued that these post-hoc analyses are in line with the primary analyses of the trial. This was agreed by the CHMP, however the CHMP did not consider post-hoc subgroup analyses sufficient for a new indication.

Finally, the company argued that a separate CV indication will offer clearer guidance on the use of semaglutide as treatment option for patients with CV disease, especially for cardiologists. The CHMP also considered Wegovy an important treatment option for obese individuals with CV disease. However, the CHMP did not support the idea that explicitly mentioning CV prevention in the indication (SmPC section 4.1) is necessary to enable use in cardiovascular risk management. The Committee considered that the beneficial effect of semaglutide on CV risk is already sufficiently covered by the current obesity/overweight indication. Nonetheless, in view of the clinical importance of the results, the CHMP supported the inclusion of the data in SmPC section 5.1, and the addition of a reference to these data in SmPC section 4.1.

The MAH initially submitted a variation application under category C.I.6.a of the variation classification Guideline with the scope to include:

"Extension of indication to include risk reduction of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and BMI ≥27 kg/m2 for WEGOVY, based on results from study EX9536-4388 (SELECT); this is a randomised, double-blind, placebo-controlled, trial comparing semaglutide 2.4 mg with placebo both administered s.c. once weekly in subjects with established cardiovascular disease and overweight or obesity. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. As part of the application the MAH is requesting a 1-year extension of the market protection".

Based on the assessment of the data contained in the application, and the additional information provided during the procedure, the CHMP is of the view that the following changes to the MA should be introduced:

"*Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC based on results from study EX9536-4388 (SELECT); this is a randomised, double-blind, placebo-controlled, trial comparing semaglutide 2.4 mg with placebo both administered s.c. once weekly in subjects with established cardiovascular disease and overweight or obesity. The Package Leaflet is updated accordingly."*

These changes fall under category C.1.4 of the variation classification Guideline.

In reply to a Request for Supplementary Information during the procedure, the MAH updated the product information accordingly.

As requested, with the responses the MAH has made an editorial amendment in SmPC section 4.1 to include a cross reference to the results of the SELECT trial in SmPC section 5.1. No previous dedicated weight management CVOTs have been able to demonstrate a link between weight loss and CV risk reduction. Therefore, it is considered acceptable to add the results of SELECT trial to section 5.1 of the SmPC, and to add to the wording of the current indication a reference to SmPC section 5.1, where the cardiovascular effects are described.

4.8. Conclusions

The revised scope and the changes to the product information are agreed.

The overall B/R of Wegovy remains positive.

5. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC based on results from study EX9536-4388 (SELECT); this is a randomised, double-blind, placebo-controlled, trial comparing semaglutide 2.4 mg with placebo both administered s.c. once weekly in subjects with established cardiovascular disease and overweight or obesity. The Package Leaflet is updated accordingly.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB are recommended.

6. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Wegovy-H-C-005422-II-0017'.

Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 25 July 2024

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 09 August 2024. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 09 August 2024. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.