CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

215256Orig1s011

Trade Name:	WEGOVY
Generic or Proper Name:	semaglutide
Sponsor:	Novo Nordisk Inc.
Approval Date:	March 8, 2024

Indication:

WEGOVY is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated in combination with a reduced calorie diet and increased physical activity:

- to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight.
- to reduce excess body weight and maintain weight reduction long term in:
  - Adults and pediatric patients aged 12 years and older with obesity
  - Adults with overweight in the presence of at least one weight-related comorbid condition.

CENTER FOR DRUG EVALUATION AND RESEARCH

215256Orig1s011

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	**X**
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215256Orig1s011

APPROVAL LETTER

NDA 215256/S-011

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT(S)

Novo Nordisk Inc.
Attention: Stephanie DeChiaro
Executive Director, Regulatory Affairs
P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Stephanie DeChiaro:

Please refer to your supplemental new drug application (sNDA) dated and received September 8, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Wegovy (semaglutide) injection.

This Prior Approval sNDA provides for the addition of the following indication to the Prescribing Information, with corresponding revisions to the Medication Guide:

- Wegovy is indicated in combination with a reduced calorie diet and increased physical activity to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight.

The addition of this indication is based on the result from trial EX9536-4388, entitled "SELECT − Semaglutide effects on cardiovascular outcomes in people with overweight or obesity." This trial also addresses the following postmarketing requirement listed in the June 4, 2021, approval letter:

4081-6: Complete the ongoing randomized, double-blind, parallel-group, placebo-controlled trial in approximately 17,500 patients with established CV disease and overweight or obesity (randomized 1:1 to semaglutide 2.4 mg and placebo) to evaluate the long-term effects of semaglutide 2.4 mg on pancreatitis, gallbladder disorders, renal safety, serious hepatic events, malignant neoplasms, serious hypoglycemia, and serious gastrointestinal disorders.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with minor editorial revisions listed below and reflected in the enclosed labeling.

- A vertical line has been added to the left edge of the indication statements.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Medication Guide, and Instruction for Use), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impractical. Atherosclerotic cardiovascular disease is on FDA's list of adult-related conditions that qualify for a waiver because they rarely or never occur in pediatrics (dated February 26, 2024).

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

This sNDA contained the final report for PMR 4081-6, cited above. We have reviewed the submission and conclude that the above requirement has been fulfilled.

We remind you that there are postmarketing requirements listed in the June 4, 2021, approval letter and the July 21, 2023, supplement approval letter that are still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[6]

If you have any questions, contact Martin White, MS, Regulatory Project Manager, at 240-402-6018.

Sincerely,

{See appended electronic signature page}

John Sharretts, M.D.
Director
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use (version approved on August 24, 2022)

[6] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN M SHARRETTS
03/08/2024 12:31:07 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215256Orig1s011

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use WEGOVY safely and effectively. See full prescribing information for WEGOVY.

WEGOVY (semaglutide) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: RISK OF THYROID C-CELL TUMORS
See full prescribing information for complete boxed warning.

- **In rodents, semaglutide causes thyroid C-cell tumors at clinically relevant exposures. It is unknown whether WEGOVY causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **WEGOVY is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

·····RECENT MAJOR CHANGES·····

Indications and Usage (1)	03/2024
Dosing and Administration (2.2)	07/2023
Warnings and Precaution, Hypoglycemia (5.4)	03/2024

·····INDICATIONS AND USAGE·····

WEGOVY is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated in combination with a reduced calorie diet and increased physical activity:

- to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight (1).
- to reduce excess body weight and maintain weight reduction long term in:
    - Adults and pediatric patients aged 12 years and older with obesity
    - Adults with overweight in the presence of at least one weight-related comorbid condition (1).

Limitations of Use:

- Coadministration with other semaglutide-containing products or with any other GLP-1 receptor agonist is not recommended (1).

·····DOSAGE AND ADMINISTRATION·····

- Administer WEGOVY once weekly as an adjunct to diet and increased physical activity, on the same day each week, at any time of day, with or without meals (2.1).
- Inject subcutaneously in the abdomen, thigh or upper arm (2.1).
- In patients with type 2 diabetes, monitor blood glucose prior to starting and during WEGOVY treatment (2.1).
- Initiate at 0.25 mg once weekly for 4 weeks. Then follow the dosage escalation schedule, titrating every 4 weeks to achieve the maintenance dosage (2.2, 2.3).
- The maintenance dosage of WEGOVY in adults is either 2.4 mg (recommended) or 1.7 mg once weekly (2.2).
- The maintenance dosage of WEGOVY in pediatric patients aged 12 years and older is 2.4 mg once weekly (2.3).

·····DOSAGE FORMS AND STRENGTHS·····

Injection: pre-filled, single-dose pen that delivers doses of 0.25 mg, 0.5 mg, 1 mg, 1.7 mg or 2.4 mg (3).

·····CONTRAINDICATIONS·····

- Personal or family history of MTC or in patients with MEN2 (4).
- Known hypersensitivity to semaglutide or any of the excipients in WEGOVY (4).

·····WARNINGS AND PRECAUTIONS·····

- *Acute Pancreatitis:* Has occurred in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
- *Acute Gallbladder Disease:* Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow-up are indicated (5.3).
- *Hypoglycemia:* Concomitant use with insulin or an insulin secretagogue may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing the dose of insulin or insulin secretagogue may be necessary. Inform all patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia (5.4).
- *Acute Kidney Injury:* Has occurred. Monitor renal function when initiating or escalating doses of WEGOVY in patients reporting severe adverse gastrointestinal reactions or in those with renal impairment reporting severe adverse gastrointestinal reactions (5.5).
- *Hypersensitivity Reactions:* Anaphylactic reactions and angioedema have been reported postmarketing. Discontinue WEGOVY if suspected and promptly seek medical advice (5.6).
- *Diabetic Retinopathy Complications in Patients with Type 2 Diabetes:* Has been reported in trials with semaglutide. Patients with a history of diabetic retinopathy should be monitored (5.7).
- *Heart Rate Increase:* Monitor heart rate at regular intervals (5.8).
- *Suicidal Behavior and Ideation:* Monitor for depression or suicidal thoughts. Discontinue WEGOVY if symptoms develop (5.9).

·····ADVERSE REACTIONS·····

Most common adverse reactions (incidence ≥ 5%) in adults or pediatric patients aged 12 years and older are: nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia in patients with type 2 diabetes, flatulence, gastroenteritis, gastroesophageal reflux disease, and nasopharyngitis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc., at 1-833-934-6891 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

WEGOVY delays gastric emptying. May impact absorption of concomitantly administered oral medications. Use with caution (7.2).

·····USE IN SPECIFIC POPULATIONS·····

- *Pregnancy:* May cause fetal harm. When pregnancy is recognized, discontinue WEGOVY (8.1).
- *Females and Males of Reproductive Potential:* Discontinue WEGOVY at least 2 months before a planned pregnancy because of the long half-life of semaglutide (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2024

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: RISK OF THYROID C-CELL TUMORS

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

- **In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether WEGOVY causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.**
- **WEGOVY is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Contraindications (4)]*. Counsel patients regarding the potential risk for MTC with the use of WEGOVY and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with WEGOVY *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

WEGOVY is indicated in combination with a reduced calorie diet and increased physical activity:

- to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight.

- to reduce excess body weight and maintain weight reduction long term in:
  - Adults and pediatric patients aged 12 years and older with obesity
  - Adults with overweight in the presence of at least one weight-related comorbid condition.

Limitations of Use

- WEGOVY contains semaglutide. Coadministration with other semaglutide-containing products or with any other GLP-1 receptor agonist is not recommended.

2 DOSAGE AND ADMINISTRATION

2.1 Important Monitoring and Administration Instructions

- In patients with type 2 diabetes, monitor blood glucose prior to starting WEGOVY and during WEGOVY treatment *[see Warnings and Precautions (5.4)]*.
- Prior to initiation of WEGOVY, train patients on proper injection technique. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations.
- Inspect WEGOVY visually prior to each injection. Only use if solution is clear, colorless, and contains no particles.
- Administer WEGOVY in combination with a reduced-calorie diet and increased physical activity.
- Administer WEGOVY once weekly, on the same day each week, at any time of day, with or without meals.
- Inject WEGOVY subcutaneously in the abdomen, thigh, or upper arm. The time of day and the injection site can be changed without dose adjustment.

2.2 Recommended Dosage in Adults

Dosage Initiation and Escalation

- Initiate WEGOVY with a dosage of 0.25 mg injected subcutaneously once weekly. Then follow the dose escalation schedule presented in Table 1 to minimize gastrointestinal adverse reactions *[see Adverse Reactions (6.1)]*.

- If patients do not tolerate a dose during dosage escalation, consider delaying dosage escalation for 4 weeks.

Table 1. Recommended Dosage Regimen for Adults

Treatment	Weeks	Once weekly Subcutaneous Dosage
Initiation	1 through 4	0.25 mg
Escalation	5 through 8	0.5 mg
	9 through 12	1 mg
	13 through 16	1.7 mg
Maintenance	17 and onward	1.7 mg or 2.4 mg

Maintenance Dosage

- The maintenance dosage of WEGOVY in adults is either 2.4 mg (recommended) or 1.7 mg once weekly. Consider treatment response and tolerability when selecting the maintenance dosage *[see Clinical Studies (14.2)]*.

2.3 Recommended Dosage in Pediatric Patients Aged 12 Years and Older

Dosage Initiation and Escalation

- Initiate WEGOVY according to the dosage escalation schedule in Table 2 to minimize gastrointestinal adverse reactions *[see Adverse Reactions (6.1)]*.
- If patients do not tolerate a dose during dosage escalation, consider delaying dosage escalation for 4 weeks.
- The 0.25 mg. 0.5 mg, and 1 mg once-weekly dosages are initiation and escalation dosages and are not approved as maintenance dosages.

Table 2. Recommended Dosage Regimen for Pediatric Patients Aged 12 Years and Older

Treatment	Weeks	Once weekly Subcutaneous Dosage
Initiation	1 through 4	0.25 mg[a]
Escalation	5 through 8	0.5 mg[a]
	9 through 12	1 mg[a]
	13 through 16	1.7 mg[b]
Maintenance	17 and onward	2.4 mg

[a]Not approved as maintenance dosages
[b]See *Dosage Modifications for Adverse Reactions*

Maintenance Dosage

- The maintenance dosage of WEGOVY in pediatric patients aged 12 years and older is 2.4 mg once weekly.

Dosage Modifications for Adverse Reactions

- If patients do not tolerate the 2.4 mg once-weekly maintenance dosage, the maintenance dosage may be reduced to 1.7 mg once weekly.
- Discontinue WEGOVY if the patient cannot tolerate the 1.7 mg once-weekly dosage.

2.4 Recommendations Regarding Missed Dose

- If one dose is missed and the next scheduled dose is more than 2 days away (48 hours), administer WEGOVY as soon as possible. If one dose is missed and the next scheduled dose is less than 2 days away (48 hours), do not administer the dose. Resume dosing on the regularly scheduled day of the week.
- If 2 or more consecutive doses are missed, resume dosing as scheduled or, if needed, reinitiate WEGOVY and follow the dose escalation schedule, which may reduce the occurrence of gastrointestinal symptoms associated with reinitiation of treatment.

3 DOSAGE FORMS AND STRENGTHS

Injection: clear, colorless solution available in 5 pre-filled, disposable, single-dose pens:

- 0.25 mg/0.5 mL
- 0.5 mg/0.5 mL
- 1 mg/0.5 mL
- 1.7 mg/0.75 mL
- 2.4 mg/0.75 mL

4 CONTRAINDICATIONS

WEGOVY is contraindicated in the following conditions:

- A personal or family history of MTC or in patients with MEN 2 *[see Warnings and Precautions (5.1)]*.
- A prior serious hypersensitivity reaction to semaglutide or to any of the excipients in WEGOVY. Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with WEGOVY *[see Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-Cell Tumors

In mice and rats, semaglutide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures *[see Nonclinical Toxicology (13.1)]*. It is unknown whether WEGOVY causes thyroid C-cell tumors, including MTC, in humans, as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.

WEGOVY is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of WEGOVY and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with WEGOVY. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values greater than 50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 Acute Pancreatitis

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists, including semaglutide. Acute pancreatitis was observed in patients treated with WEGOVY in clinical trials *[see Adverse Reactions (6)]*. After initiation of WEGOVY,

observe patients carefully for signs and symptoms of acute pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, and which may or may not be accompanied by vomiting). If acute pancreatitis is suspected, WEGOVY should promptly be discontinued, and appropriate management should be initiated. If acute pancreatitis is confirmed, WEGOVY should not be restarted.

There is limited experience from clinical trials with WEGOVY in patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on WEGOVY.

5.3 Acute Gallbladder Disease

Treatment with WEGOVY is associated with an increased occurrence of cholelithiasis and cholecystitis. The incidence of cholelithiasis and cholecystitis was higher in WEGOVY-treated pediatric patients aged 12 years and older than in WEGOVY-treated adults. In randomized clinical trials in adult patients, cholelithiasis was reported by 1.6% of WEGOVY-treated patients and 0.7% of placebo-treated patients. Cholecystitis was reported by 0.6% of WEGOVY-treated adult patients and 0.2% of placebo-treated patients. In a clinical trial in pediatric patients aged 12 years and older, cholelithiasis was reported by 3.8% of WEGOVY-treated patients and 0% placebo-treated patients. Cholecystitis was reported by 0.8% of WEGOVY-treated pediatric patients and 0% placebo-treated patients *[see Adverse Reactions (6.1)]*.

Substantial or rapid weight loss can increase the risk of cholelithiasis; however, the incidence of acute gallbladder disease was greater in WEGOVY-treated patients than in placebo-treated patients, even after accounting for the degree of weight loss. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

5.4 Hypoglycemia

WEGOVY lowers blood glucose and can cause hypoglycemia.

In a trial of adult patients with type 2 diabetes and body mass index (BMI) greater than or equal to 27 kg/m^2, hypoglycemia (defined as a plasma glucose less than 54 mg/dL) was reported in 6.2% of WEGOVY-treated patients versus 2.5% of placebo-treated patients. One episode of severe hypoglycemia (requiring the assistance of another person) was reported in one WEGOVY-treated patient versus no placebo-treated patients.

Patients with diabetes mellitus taking WEGOVY in combination with insulin or an insulin secretagogue (e.g., sulfonylurea) may have an increased risk of hypoglycemia, including severe hypoglycemia. Hypoglycemia has been observed in patients treated with semaglutide at doses of 0.5 and 1 mg in combination with insulin. The use of WEGOVY (semaglutide 2.4 mg or 1.7 mg once weekly) in patients with type 1 diabetes mellitus or in combination with insulin has not been evaluated.

Inform patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. In patients with diabetes, monitor blood glucose prior to starting WEGOVY and during WEGOVY treatment. When initiating WEGOVY, consider reducing the dose of concomitantly administered insulin or insulin secretagogue (such as sulfonylureas) to reduce the risk of hypoglycemia *[see Drug Interactions (7)]*.

5.5 Acute Kidney Injury

There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which have in some cases required hemodialysis, in patients treated with semaglutide. Patients with renal impairment may be at greater risk of acute kidney injury, but some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, or diarrhea, leading to volume depletion *[see Adverse Reactions (6)]*.

Monitor renal function when initiating or escalating doses of WEGOVY in patients reporting severe adverse gastrointestinal reactions. Monitor renal function in patients with renal impairment reporting any adverse reactions that could lead to volume depletion.

5.6 Hypersensitivity

Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with WEGOVY. If hypersensitivity reactions occur, discontinue use of WEGOVY, treat promptly per standard of care, and monitor until signs and symptoms resolve. WEGOVY is contraindicated in patients with a prior serious hypersensitivity reaction to semaglutide or to any of the excipients in WEGOVY *[see Adverse Reactions (6.2)]*.

Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with WEGOVY.

5.7 Diabetic Retinopathy Complications in Patients with Type 2 Diabetes

In a trial of adult patients with type 2 diabetes and BMI greater than or equal to 27 kg/m^2, diabetic retinopathy was reported by 4.0% of WEGOVY-treated patients and 2.7% placebo-treated patients.

In a 2-year trial with semaglutide 0.5 mg and 1 mg once-weekly injection in adult patients with type 2 diabetes and high cardiovascular risk, diabetic retinopathy complications (which was a 4-component adjudicated endpoint) occurred in patients treated with semaglutide injection (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (semaglutide injection 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (semaglutide injection 0.7%, placebo 0.4%).

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

5.8 Heart Rate Increase

Treatment with WEGOVY was associated with increases in resting heart rate. Mean increases in resting heart rate of 1 to 4 beats per minute (bpm) were observed in WEGOVY-treated adult patients compared to placebo in clinical trials. More adult patients treated with WEGOVY compared with placebo had maximum changes from baseline at any visit of 10 to 19 bpm (41% versus 34%, respectively) and 20 bpm or more (26% versus 16%, respectively). In a clinical trial in pediatric patients aged 12 years and older with normal baseline heart rate, more patients treated with WEGOVY compared to placebo had maximum changes in heart rate of 20 bpm or more (54% versus 39%) *[see Adverse Reactions (6.1)]*.

Monitor heart rate at regular intervals consistent with usual clinical practice. Instruct patients to inform their healthcare providers of palpitations or feelings of a racing heartbeat while at rest during WEGOVY treatment. If patients experience a sustained increase in resting heart rate, discontinue WEGOVY.

5.9 Suicidal Behavior and Ideation

Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Monitor patients treated with WEGOVY for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue WEGOVY in patients who experience suicidal thoughts or behaviors. Avoid WEGOVY in patients with a history of suicidal attempts or active suicidal ideation.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-Cell Tumors *[see Warnings and Precautions (5.1)]*
- Acute Pancreatitis *[see Warnings and Precautions (5.2)]*
- Acute Gallbladder Disease *[see Warnings and Precautions (5.3)]*
- Hypoglycemia *[see Warnings and Precautions (5.4)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.5)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.6)]*
- Diabetic Retinopathy Complications in Patients with Type 2 Diabetes *[see Warnings and Precautions (5.7)]*
- Heart Rate Increase *[see Warnings and Precautions (5.8)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Clinical Trials in Adults with Obesity or Overweight

WEGOVY 2.4 mg Subcutaneous Weekly Dosage

WEGOVY was evaluated for safety in 3 randomized, double-blind, placebo-controlled trials that included 2,116 adult patients with obesity or overweight treated with 2.4 mg WEGOVY for up to 68 weeks and a 7 week off-drug follow-up period *[see Clinical Studies (14.2)]*. Baseline characteristics included a mean age of 48 years, 71% female, 72% White, 14% Asian, 9% Black or African American, and 5% reported as other or unknown; and 85% were not Hispanic or Latino ethnicity, 13% were Hispanic or Latino ethnicity, and 2% reported as unknown. The baseline characteristics were 42% with hypertension, 19% with type 2 diabetes, 43% with dyslipidemia, 28% with a BMI greater than 40 kg/m^2, and 4% with cardiovascular disease.

In these clinical trials, 6.8% of patients treated with 2.4 mg WEGOVY and 3.2% of patients treated with placebo permanently discontinued treatment as a result of adverse reactions. The most common adverse reactions leading to discontinuation were nausea (1.8% versus 0.2%), vomiting (1.2% versus 0%), and diarrhea (0.7% versus 0.1%) for WEGOVY and placebo, respectively.

Adverse reactions reported in clinical trials in adults and greater than or equal to 2% of WEGOVY-treated patients and more frequently than in placebo-treated patients are shown in Table 3.

Table 3. Adverse Reactions (≥ 2% and Greater Than Placebo) in WEGOVY-treated Adults with Obesity or Overweight

	Placebo N = 1,261 %	**WEGOVY 2.4 mg N = 2,116 %**
Nausea	16	44
Diarrhea	16	30
Vomiting	6	24
Constipation	11	24
Abdominal Pain[a]	10	20
Headache	10	14
Fatigue[b]	5	11
Dyspepsia	3	9
Dizziness	4	8
Abdominal Distension	5	7
Eructation	<1	7
Hypoglycemia in T2DM[c]	2	6

	Placebo N = 1,261 %	WEGOVY 2.4 mg N = 2,116 %
Flatulence	4	6
Gastroenteritis	4	6
Gastroesophageal Reflux Disease	3	5
Gastritis[d]	1	4
Gastroenteritis Viral	3	4
Hair Loss	1	3
Dysesthesia[e]	1	2

[a]Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain, abdominal tenderness, abdominal discomfort and epigastric discomfort
[b]Includes fatigue and asthenia
[c]Defined as blood glucose <54 mg/dL with or without symptoms of hypoglycemia or severe hypoglycemia (requiring the assistance of another person) in patients with type 2 diabetes not on concomitant insulin (Study 3, WEGOVY N=403, Placebo N=402). See text below for further information regarding hypoglycemia in patients with and without type 2 diabetes. T2DM = type 2 diabetes mellitus
[d]Includes chronic gastritis, gastritis, gastritis erosive, and reflux gastritis
[e]Includes paresthesia, hyperesthesia, burning sensation, allodynia, dysesthesia, skin burning sensation, pain of skin, and sensitive skin

In a cardiovascular outcomes trial, 8,803 patients were exposed to WEGOVY for a median of 37.3 months and 8,801 patients were exposed to placebo for a median of 38.6 months *[see Clinical Studies (14.1)]*. Safety data collection was limited to serious adverse events (including death), adverse events leading to discontinuation, and adverse events of special interest. Sixteen percent (16%) of WEGOVY-treated patients and 8% of placebo-treated patients, respectively, discontinued study drug due to an adverse event. Additional information from this trial is included in subsequent sections below when relevant.

Adverse Reactions in a Clinical Trial of Pediatric Patients Aged 12 Years and Older with Obesity
WEGOVY was evaluated in a 68-week, double-blind, randomized, parallel group, placebo-controlled, multi-center trial in 201 pediatric patients aged 12 years and older with obesity *[see Clinical Studies (14.3)]*. Baseline characteristics included a mean age of 15.4 years; 38% of patients were male; 79% were White, 8% were Black or African American, 2% were Asian, and 11% were of other or unknown race; and 11% were of Hispanic or Latino ethnicity. The mean baseline body weight was 107.5 kg, and mean BMI was 37 kg/m^2.

Table 4 shows adverse reactions reported in greater than or equal to 3% of WEGOVY-treated pediatric patients and more frequently than in the placebo group from a study in pediatric patients aged 12 years and older.

Table 4. Adverse Reactions (≥ 3% and Greater than Placebo) in WEGOVY-Treated Pediatric Patients Aged 12 Years and Older with Obesity

	Placebo N = 67 %	WEGOVY 2.4 mg N = 133 %
Nausea	18	42
Vomiting	10	36
Diarrhea	19	22
Headache	16	17
Abdominal Pain	6	15
Nasopharyngitis	10	12
Dizziness	3	8
Gastroenteritis	3	7
Constipation	2	6

	Placebo N = 67 %	WEGOVY 2.4 mg N = 133 %
Gastroesophageal Reflux Disease	2	4
Sinusitis	2	4
Urinary tract infection	2	4
Ligament sprain	2	4
Anxiety	2	4
Hair Loss	0	4
Cholelithiasis	0	4
Eructation	0	4
Influenza	0	3
Rash	0	3
Urticaria	0	3

Other Adverse Reactions in Adults and/or Pediatric Patients

Acute Pancreatitis

In WEGOVY clinical trials in adults, acute pancreatitis was confirmed by adjudication in 4 WEGOVY-treated patients (0.2 cases per 100 patient years) versus 1 in placebo-treated patients (less than 0.1 cases per 100 patient years). One additional case of acute pancreatitis was confirmed in a patient treated with WEGOVY in another clinical trial.

Acute Gallbladder Disease

In WEGOVY clinical trials in adults, cholelithiasis was reported by 1.6% of WEGOVY-treated patients and 0.7% of placebo-treated patients. Cholecystitis was reported by 0.6% of WEGOVY-treated adult patients and 0.2% of placebo-treated patients. In a clinical trial in pediatric patients aged 12 years and older *[see Clinical Studies (14.3)]*, cholelithiasis was reported by 3.8% of WEGOVY-treated patients and 0% placebo-treated patients. Cholecystitis was reported by 0.8% of WEGOVY-treated pediatric patients and 0% placebo-treated patients.

Hypoglycemia

Patients with Type 2 Diabetes

In a trial of adult patients with type 2 diabetes and BMI greater than or equal to 27 kg/m^2, clinically significant hypoglycemia (defined as a plasma glucose less than 54 mg/dL) was reported in 6.2% of WEGOVY-treated patients versus 2.5% of placebo-treated patients. A higher rate of clinically significant hypoglycemic episodes was reported with WEGOVY (semaglutide 2.4 mg) versus semaglutide 1 mg (10.7 vs. 7.2 episodes per 100 patient years of exposure, respectively); the rate in the placebo-treated group was 3.2 episodes per 100 patient years of exposure. In addition, one episode of severe hypoglycemia requiring intravenous glucose was reported in a WEGOVY-treated patient versus none in placebo-treated patients. The risk of hypoglycemia was increased when WEGOVY was used with a sulfonylurea.

Patients without Type 2 Diabetes

Episodes of hypoglycemia have been reported with GLP-1 receptor agonists in adult patients without type 2 diabetes mellitus. In WEGOVY clinical trials in adult patients without type 2 diabetes mellitus, there was no systematic capturing or reporting of hypoglycemia.

In a cardiovascular outcomes trial in adult patients without type 2 diabetes, 3 episodes of serious hypoglycemia were reported in WEGOVY-treated patients versus 1 episode in placebo. Patients with a history of bariatric surgery (a risk factor for hypoglycemia) had more events of serious hypoglycemia while taking WEGOVY (2.3%, 2/87) than placebo (0%, 0/97).

Acute Kidney Injury
Acute kidney injury occurred in clinical trials in 7 adult patients (0.4 cases per 100 patient years) receiving WEGOVY versus 4 patients (0.2 cases per 100 patient years of exposure) receiving placebo. Some of these adverse reactions occurred in association with gastrointestinal adverse reactions or dehydration. In addition, 2 patients treated with WEGOVY had acute kidney injury with dehydration in other clinical trials. The risk of renal adverse reactions with WEGOVY was increased in adult patients with a history of renal impairment (trials included 65 patients with a history of moderate or severe renal impairment at baseline), and occurred more frequently during dose titration.

Retinal Disorders in Patients with Type 2 Diabetes
In a trial of adult patients with type 2 diabetes and BMI greater than or equal to 27 kg/m^2, retinal disorders were reported by 6.9% of patients treated with WEGOVY (semaglutide 2.4 mg), 6.2% of patients treated with semaglutide 1 mg, and 4.2% of patients treated with placebo. The majority of events were reported as diabetic retinopathy (4.0%, 2.7%, and 2.7%, respectively) and non-proliferative retinopathy (0.7%, 0%, and 0%, respectively).

Increase in Heart Rate
Mean increases in resting heart rate of 1 to 4 beats per minute (bpm) were observed with routine clinical monitoring in WEGOVY-treated adult patients compared to placebo in clinical trials. In trials in which adult patients were randomized prior to dose-escalation, more patients treated with WEGOVY, compared with placebo, had maximum changes from baseline at any visit of 10 to 19 bpm (41% versus 34%, respectively) and 20 bpm or more (26% versus 16%, respectively). In a clinical trial in pediatric patients aged 12 years and older with normal baseline heart rate, more patients treated with WEGOVY compared to placebo had maximum changes in heart rate of 20 bpm or more (54% versus 39%).

Hypotension and Syncope
Adverse reactions related to hypotension (hypotension, orthostatic hypotension, and decreased blood pressure) were reported in 1.3% of WEGOVY-treated adult patients versus 0.4% of placebo-treated patients and syncope was reported in 0.8% of WEGOVY-treated patients versus 0.2% of placebo-treated patients. Some reactions were related to gastrointestinal adverse reactions and volume loss associated with WEGOVY. Hypotension and orthostatic hypotension were more frequently seen in patients on concomitant antihypertensive therapy. In a clinical trial in pediatric patients aged 12 years and older, hypotension was reported in 2.3% of WEGOVY-treated patients versus 0% in placebo-treated patients.

Appendicitis
Appendicitis (including perforated appendicitis) occurred in 10 (0.5%) WEGOVY-treated adult patients and 2 (0.2%) patients receiving placebo.

Gastrointestinal Adverse Reactions
In clinical trials in adults, 73% of WEGOVY-treated patients and 47% of patients receiving placebo reported gastrointestinal adverse reactions, including severe reactions that were reported more frequently among patients receiving WEGOVY (4.1%) than placebo (0.9%). The most frequently reported reactions were nausea (44% vs. 16%), vomiting (25% vs. 6%), and diarrhea (30% vs. 16%). Other reactions that occurred at a higher incidence among WEGOVY-treated adult patients included dyspepsia, abdominal pain, abdominal distension, eructation, flatulence, gastroesophageal reflux disease, gastritis, hemorrhoids, and hiccups. These reactions increased during dose escalation.

In the pediatric clinical trial, 62% of WEGOVY-treated patients and 42% of placebo-treated patients reported gastrointestinal disorders. The most frequently reported reactions were nausea (42% vs. 18%), vomiting (36% vs. 10%), and diarrhea (22% vs. 19%). Other gastrointestinal-related reactions that occurred at a higher incidence than placebo among WEGOVY-treated pediatric patients included abdominal pain, constipation, eructation, gastroesophageal reflux disease, dyspepsia, and flatulence.

Permanent discontinuation of treatment as a result of a gastrointestinal adverse reaction occurred in 4.3% of WEGOVY-treated adult patients versus 0.7% of placebo-treated patients. In a pediatric clinical trial, 2.3% of patients treated with WEGOVY versus 1.5% of patients who received placebo discontinued treatment as a result of gastrointestinal adverse reactions.

Injection Site Reactions
In clinical trials in adults, 1.4% of WEGOVY-treated patients and 1.0% of patients receiving placebo experienced injection site reactions (including injection site pruritus, erythema, inflammation, induration, and irritation).

Hypersensitivity Reactions
Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with WEGOVY.

In a pediatric clinical trial, rash was reported in 3% of WEGOVY-treated patients and 0% of placebo-treated patients, and urticaria was reported in 3% of WEGOVY-treated patients and 0% of placebo-treated patients. In adult clinical trials, allergic reactions occurred in 16% (8/50) of WEGOVY-treated patients with anti-semaglutide antibodies and in 7% (114/1659) of WEGOVY-treated patients who did not develop anti-semaglutide antibodies *[see Clinical Pharmacology (12.6)].*

Fractures
In the cardiovascular outcomes trial in adults, more fractures of the hip and pelvis were reported on WEGOVY than on placebo in female patients: 1.0% (24/2448) vs. 0.2% (5/2424), and in patients ages 75 years and older: 2.4% (17/703) vs. 0.6% (4/663), respectively.

Urolithiasis
In a cardiovascular outcomes trial, 1.2% of WEGOVY-treated patients and 0.8% of patients receiving placebo reported urolithiasis, including serious reactions that were reported more frequently among patients receiving WEGOVY (0.6%) than placebo (0.4%).

Dysgeusia
In clinical trials in adults, 1.7% of WEGOVY-treated patients and 0.5% of placebo-treated patients reported dysgeusia.

Laboratory Abnormalities
Amylase and Lipase
Adult and pediatric patients treated with WEGOVY had a mean increase from baseline in amylase of 15-16% and lipase of 39%. These changes were not observed in the placebo group. The clinical significance of elevations in lipase or amylase with WEGOVY is unknown in the absence of other signs and symptoms of pancreatitis.

Liver Enzymes
In a pediatric clinical trial, increases in alanine aminotransferase (ALT) greater than or equal to 5 times the upper limit of normal were observed in 4 (3%) WEGOVY-treated patients compared with 0% of placebo-treated patients. In some patients, increases in ALT and AST were associated with other confounding factors (such as gallstones). In the cardiovascular outcomes trial in adults, increases in total bilirubin greater than or equal to 3 times the upper limit of normal were observed in 0.3% (30/8585) of WEGOVY-treated patients versus 0.2% (14/8579) of placebo-treated patients.

6.2 Postmarketing Experience
The following adverse reactions have been reported during post-approval use of semaglutide, the active ingredient of WEGOVY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: acute pancreatitis and necrotizing pancreatitis, sometimes resulting in death; ileus
Hypersensitivity: anaphylaxis, angioedema, rash, urticaria
Renal and Urinary Disorders: acute kidney injury

7 DRUG INTERACTIONS

7.1 Concomitant Use with Insulin or an Insulin Secretagogue (e.g., Sulfonylurea)

WEGOVY lowers blood glucose and can cause hypoglycemia. The risk of hypoglycemia is increased when WEGOVY is used in combination with insulin or insulin secretagogues (e.g., sulfonylureas). The addition of WEGOVY in patients treated with insulin has not been evaluated.

When initiating WEGOVY, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]*.

7.2 Oral Medications

WEGOVY causes a delay of gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials with semaglutide 1 mg, semaglutide did not affect the absorption of orally administered medications *[see Clinical Pharmacology (12.3)]*. Nonetheless, monitor the effects of oral medications concomitantly administered with WEGOVY.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There will be a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to semaglutide during pregnancy. Pregnant women exposed to WEGOVY and healthcare providers are encouraged to contact Novo Nordisk at 1-877-390-2760 or www.wegovypregnancyregistry.com.

Risk Summary

Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. Additionally, weight loss offers no benefit to a pregnant patient and may cause fetal harm. When a pregnancy is recognized, advise the pregnant patient of the risk to a fetus, and discontinue WEGOVY *(see Clinical Considerations)*. Available pharmacovigilance data and data from clinical trials with WEGOVY use in pregnant patients are insufficient to establish a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

In pregnant rats administered semaglutide during organogenesis, embryofetal mortality, structural abnormalities and alterations to growth occurred at maternal exposures below the maximum recommended human dose (MRHD) based on AUC. In rabbits and cynomolgus monkeys administered semaglutide during organogenesis, early pregnancy losses and structural abnormalities were observed at below the MRHD (rabbit) and greater than or equal to 2-fold the MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Appropriate weight gain based on pre-pregnancy weight is currently recommended for all pregnant patients, including those who already have overweight or obesity, because of the obligatory weight gain that occurs in maternal tissues during pregnancy.

Data

Animal Data

In a combined fertility and embryofetal development study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (0.04-, 0.1-, and 0.4-fold the MRHD) were administered to males for 4 weeks prior to and throughout mating and to females for 2 weeks prior to mating, and throughout organogenesis to Gestation Day 17. In parental animals, pharmacologically mediated reductions in body weight gain and food consumption were observed at all dose levels. In the offspring, reduced growth and fetuses with visceral (heart blood vessels) and skeletal (cranial bones, vertebra, ribs) abnormalities were observed at the human exposure.

In an embryofetal development study in pregnant rabbits, subcutaneous doses of 0.0010, 0.0025 or 0.0075 mg/kg/day (0.01-, 0.1-, and 0.9-fold the MRHD) were administered throughout organogenesis from Gestation Day 6 to 19. Pharmacologically mediated reductions in maternal body weight gain and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (kidney, liver) and skeletal (sternebra) fetal abnormalities were observed at greater than or equal to 0.0025 mg/kg/day, at clinically relevant exposures.

In an embryofetal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (0.4-, 2-, and 6-fold the MRHD) were administered throughout organogenesis, from Gestation Day 16 to 50. Pharmacologically mediated, marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternebra, ribs) at greater than or equal to 0.075 mg/kg twice weekly (greater than or equal to 2 times human exposure).

In a pre- and postnatal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (0.2-, 1-, and 3-fold the MRHD) were administered from Gestation Day 16 to 140. Pharmacologically mediated marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with an increase in early pregnancy losses and led to delivery of slightly smaller offspring at greater than or equal to 0.075 mg/kg twice weekly (greater than or equal to 1 time human exposure).

8.2 Lactation

Risk Summary

There are no data on the presence of semaglutide or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Semaglutide was present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk *(see Data).* The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for WEGOVY and any potential adverse effects on the breastfed infant from WEGOVY or from the underlying maternal condition.

Data

In lactating rats, semaglutide was detected in milk at levels 3-12 fold lower than in maternal plasma.

8.3 Females and Males of Reproductive Potential

Because of the potential for fetal harm, discontinue WEGOVY in patients at least 2 months before they plan to become pregnant to account for the long half-life of semaglutide *[see Use in Specific Populations (8.1)]*.

8.4 Pediatric Use

The safety and effectiveness of WEGOVY as an adjunct to a reduced calorie diet and increased physical activity for weight reduction and long-term maintenance have been established in pediatric patients aged 12 years and older with obesity. Use of WEGOVY for this indication is supported by a 68-week, double-blind,

placebo-controlled clinical trial in 201 pediatric patients aged 12 years and older with a BMI corresponding to ≥95th percentile for age and sex and from studies in adult patients with obesity *[see Clinical Studies (14.3)]*.

Adverse reactions with WEGOVY treatment in pediatric patients aged 12 years and older were generally similar to those reported in adults. Pediatric patients aged 12 years and older treated with WEGOVY had greater incidences of cholelithiasis, cholecystitis, hypotension, rash, and urticaria compared to adults treated with WEGOVY *[see Adverse Reactions (6.1)]*.

There are insufficient data in pediatric patients with type 2 diabetes treated with WEGOVY for obesity to determine if there is an increased risk of hypoglycemia with WEGOVY treatment similar to that reported in adults. Inform patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. In pediatric patients aged 12 years and older with type 2 diabetes, monitor blood glucose prior to starting WEGOVY and during WEGOVY treatment. When initiating WEGOVY in pediatric patients aged 12 years and older with type 2 diabetes, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.4)]*.

The safety and effectiveness of WEGOVY have not been established in pediatric patients less than 12 years of age.

8.5 Geriatric Use

In the WEGOVY clinical trials for weight reduction and long-term maintenance, 233 (9%) WEGOVY-treated patients were aged 65 to 75 years and 23 (1%) WEGOVY-treated patients were aged 75 years and older *[see Clinical Studies (14.2)]*. In a cardiovascular outcomes trial, 2656 (30%) WEGOVY-treated patients were aged 65 to 75 years and 703 (8%) WEGOVY-treated patients were aged 75 years and older *[see Clinical Studies (14.1)]*. No overall difference in effectiveness was observed between patients aged 65 years and older and younger adult patients. In the cardiovascular outcomes trial, patients aged 75 years and older reported more fractures of the hip and pelvis on WEGOVY than on placebo. Patients aged 75 years and older (WEGOVY-treated and placebo-treated) reported more serious adverse reactions overall compared to younger adult patients *[see Adverse Reactions (6.1)]*.

8.6 Renal Impairment

No dose adjustment of WEGOVY is recommended for patients with renal impairment. In a study in patients with renal impairment, including end-stage renal disease, no clinically relevant change in semaglutide pharmacokinetics was observed *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dose adjustment of WEGOVY is recommended for patients with hepatic impairment. In a study in patients with different degrees of hepatic impairment, no clinically relevant change in semaglutide pharmacokinetics was observed *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

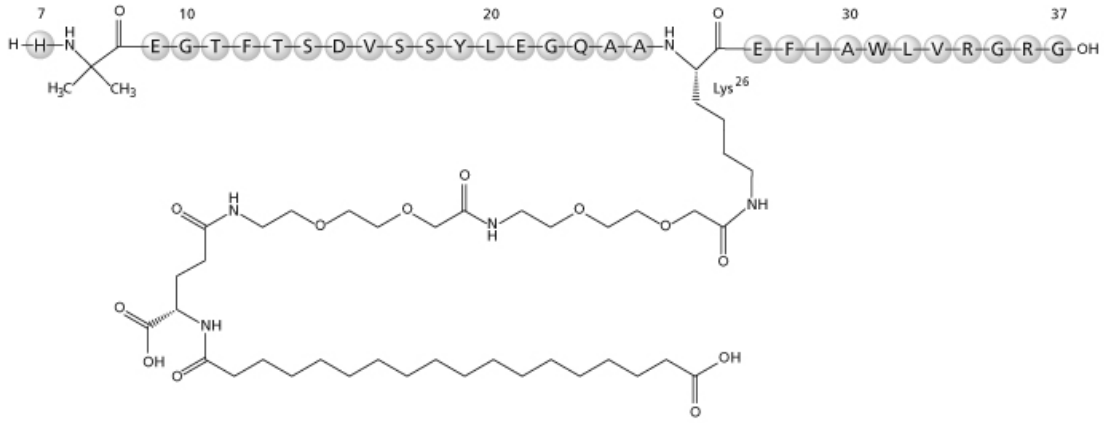
Overdoses have been reported with other GLP-1 receptor agonists. Effects have included severe nausea, severe vomiting, and severe hypoglycemia. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. In the event of an overdose of WEGOVY, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of WEGOVY of approximately 1 week.

11 DESCRIPTION

WEGOVY (semaglutide) injection, for subcutaneous use, contains semaglutide, a human GLP-1 receptor agonist (or GLP-1 analog). The peptide backbone is produced by yeast fermentation. The main protraction

mechanism of semaglutide is albumin binding, facilitated by modification of position 26 lysine with a hydrophilic spacer and a C18 fatty di-acid. Furthermore, semaglutide is modified in position 8 to provide stabilization against degradation by the enzyme dipeptidyl-peptidase 4 (DPP-4). A minor modification was made in position 34 to ensure the attachment of only one fatty di-acid. The molecular formula is $C_{187}H_{291}N_{45}O_{59}$ and the molecular weight is 4113.58 g/mol.

Figure 1. Structural Formula of semaglutide



WEGOVY is a sterile, aqueous, clear, colorless solution. Each 0.5 mL single-dose pen contains a solution of WEGOVY containing 0.25 mg, 0.5 mg or 1 mg of semaglutide; and each 0.75 mL single-dose pen contains a solution of WEGOVY containing 1.7 or 2.4 mg of semaglutide. Each 1 mL of WEGOVY contains the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; sodium chloride, 8.25 mg; and water for injection. WEGOVY has a pH of approximately 7.4. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.

GLP-1 is a physiological regulator of appetite and caloric intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation. Animal studies show that semaglutide distributed to and activated neurons in brain regions involved in regulation of food intake.

The exact mechanism of cardiovascular risk reduction has not been established.

12.2 Pharmacodynamics

Semaglutide lowers body weight with greater fat mass loss than lean mass loss. Semaglutide decreases calorie intake. The effects are likely mediated by affecting appetite.

Semaglutide stimulates insulin secretion and reduces glucagon secretion in a glucose-dependent manner. These effects can lead to a reduction of blood glucose.

Gastric Emptying

Semaglutide delays gastric emptying.

Cardiac Electrophysiology (QTc)

The effect of semaglutide on cardiac repolarization was tested in a thorough QTc trial. Semaglutide did not prolong QTc intervals at doses up to 1.5 mg at steady state.

12.3 Pharmacokinetics

Absorption

Absolute bioavailability of semaglutide is 89%. Maximum concentration of semaglutide is reached 1 to 3 days post dose.

Similar exposure was achieved with subcutaneous administration of semaglutide in the abdomen, thigh, or upper arm.

The average semaglutide steady state concentration following subcutaneous administration of WEGOVY was approximately 75 nmol/L in patients with either obesity (BMI greater than or equal to 30 kg/m^2) or overweight (BMI greater than or equal to 27 kg/m^2). The steady state exposure of WEGOVY increased proportionally with doses up to 2.4 mg once weekly.

Distribution

The mean volume of distribution of semaglutide following subcutaneous administration in patients with obesity or overweight is approximately 12.5 L. Semaglutide is extensively bound to plasma albumin (greater than 99%) which results in decreased renal clearance and protection from degradation.

Elimination

The apparent clearance of semaglutide in patients with obesity or overweight is approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 to 7 weeks after the last dose of 2.4 mg.

Metabolism

The primary route of elimination for semaglutide is metabolism following proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain.

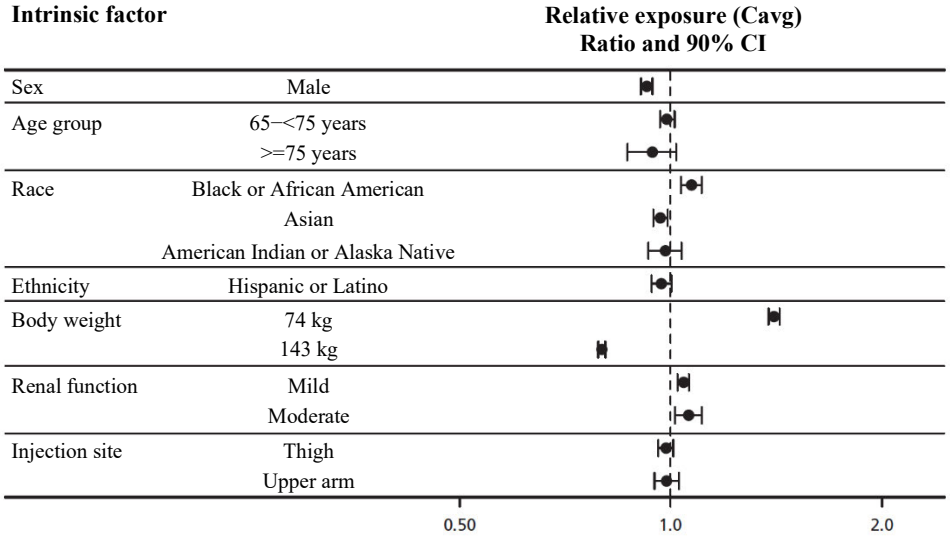
Excretion

The primary excretion routes of semaglutide-related material are via the urine and feces. Approximately 3% of the dose is excreted in the urine as intact semaglutide.

Specific Populations

The effects of intrinsic factors on the pharmacokinetics of semaglutide are shown in Figure 2.

Figure 2. Impact of intrinsic factors on semaglutide exposure



Data are steady-state dose-normalized average semaglutide exposures relative to a reference subject profile (non-Hispanic or Latino ethnicity, white female aged 18 to less than 65 years, with a body weight of 110 kg and normal renal function, who injected in the abdomen). Body weight categories (74 and 143 kg) represent the 5% and 95% percentiles in the dataset.

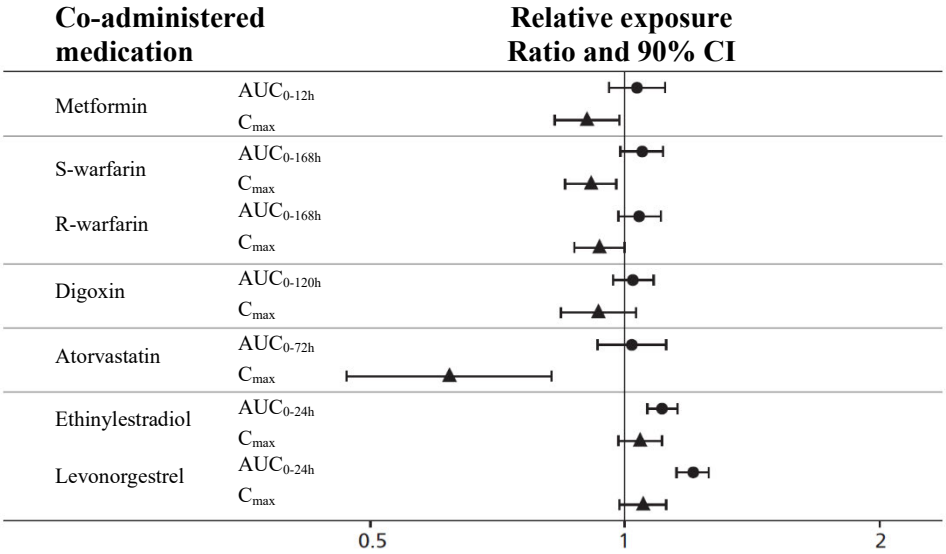
Patients with Renal Impairment
Renal impairment did not impact the exposure of semaglutide in a clinically relevant manner. The pharmacokinetics of semaglutide were evaluated following a single dose of 0.5 mg semaglutide in a study of patients with different degrees of renal impairment (mild, moderate, severe, or ESRD) compared with subjects with normal renal function. The pharmacokinetics were also assessed in subjects with overweight (BMI 27-29.9 kg/m^2) or obesity (BMI greater than or equal to 30 kg/m^2) and mild to moderate renal impairment, based on data from clinical trials.

Patients with Hepatic Impairment
Hepatic impairment did not impact the exposure of semaglutide. The pharmacokinetics of semaglutide were evaluated following a single dose of 0.5 mg semaglutide in a study of patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function.

Drug Interactions Studies
In vitro studies have shown very low potential for semaglutide to inhibit or induce CYP enzymes, or to inhibit drug transporters.

The delay of gastric emptying with semaglutide may influence the absorption of concomitantly administered oral medications *[see Drug Interactions (7.2)].* The potential effect of semaglutide on the absorption of co-administered oral medications was studied in trials at semaglutide 1 mg steady-state exposure. No clinically relevant drug-drug interactions with semaglutide (Figure 3) were observed based on the evaluated medications. In a separate study, no apparent effect on the rate of gastric emptying was observed with semaglutide 2.4 mg.

Figure 3. Impact of semaglutide 1 mg on the pharmacokinetics of co-administered medications



Relative exposure in terms of AUC and C_{max} for each medication when given with semaglutide compared to without semaglutide. Metformin and oral contraceptive drug (ethinylestradiol/levonorgestrel) were assessed at steady state. Warfarin (S-warfarin/R-warfarin), digoxin and atorvastatin were assessed after a single dose.
Abbreviations: AUC: area under the curve, C_{max}: maximum concentration, CI: confidence interval.

12.6 Immunogenicity
The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies

in the studies described below with the incidence of anti-drug antibodies in other studies, including those of semaglutide or of other semaglutide products.

During the 68-week treatment periods in Studies 2 and 3 *[see Clinical Studies (14.2)],* 50/1709 (3%) of WEGOVY-treated patients developed anti-semaglutide antibodies. Of these 50 WEGOVY-treated patients, 28 patients (2% of the total WEGOVY-treated study population) developed antibodies that cross-reacted with native GLP-1. No identified clinically significant effect of anti-semaglutide antibodies on pharmacokinetics for WEGOVY was observed. There is insufficient evidence to characterize the effects of anti-semaglutide antibodies on pharmacodynamics or effectiveness of semaglutide.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in CD-1 mice, subcutaneous doses of 0.3, 1 and 3 mg/kg/day (2-, 8-, and 22-fold the maximum recommended human dose [MRHD] of 2.4 mg/week, based on AUC) were administered to the males, and 0.1, 0.3 and 1 mg/kg/day (0.6-, 2-, and 5-fold MRHD) were administered to the females. A statistically significant increase in thyroid C-cell adenomas and a numerical increase in C-cell carcinomas were observed in males and females at all dose levels (greater than or equal to 0.6 times human exposure).

In a 2-year carcinogenicity study in Sprague Dawley rats, subcutaneous doses of 0.0025, 0.01, 0.025 and 0.1 mg/kg/day were administered (below quantification, 0.2-, 0.4-, and 2-fold the exposure at the MRHD). A statistically significant increase in thyroid C-cell adenomas was observed in males and females at all dose levels, and a statistically significant increase in thyroid C-cell carcinomas was observed in males at greater than or equal to 0.01 mg/kg/day, at clinically relevant exposures.

Human relevance of thyroid C-cell tumors in rats is unknown and could not be determined by clinical studies or nonclinical studies *[see Boxed Warning and Warnings and Precautions (5.1)]*. Semaglutide was not mutagenic or clastogenic in a standard battery of genotoxicity tests (bacterial mutagenicity [Ames] human lymphocyte chromosome aberration, rat bone marrow micronucleus).

In a combined fertility and embryo-fetal development study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (0.04-, 0.1-, and 0.4-fold the MRHD) were administered to male and female rats. Males were dosed for 4 weeks prior to mating, and females were dosed for 2 weeks prior to mating and throughout organogenesis until Gestation Day 17. No effects were observed on male fertility. In females, an increase in estrus cycle length was observed at all dose levels, together with a small reduction in numbers of corpora lutea at greater than or equal to 0.03 mg/kg/day. These effects were likely an adaptive response secondary to the pharmacological effect of semaglutide on food consumption and body weight.

14 CLINICAL STUDIES

14.1 Cardiovascular Outcomes Trial in Adult Patients with Cardiovascular Disease and Either Obesity or Overweight

Overview of Clinical Trial

Study 1 (NCT03574597) was a multi-national, multi-center, placebo-controlled, double-blind trial to determine the effect of WEGOVY relative to placebo on major adverse cardiovascular events (MACE) when added to current standard of care, which included management of CV risk factors and individualized healthy lifestyle counseling (including diet and physical activity). The primary endpoint, MACE, was the time to first occurrence of a three-part composite outcome which included cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

All patients were 45 years or older, with an initial BMI of 27 kg/m^2 or greater and established cardiovascular disease (prior myocardial infarction, prior stroke, or peripheral arterial disease). Patients with a history of type 1 or type 2 diabetes were excluded. Concomitant CV therapies could be adjusted, at the discretion of the

investigator, to ensure participants were treated according to the current standard of care for patients with established cardiovascular disease.

In this trial, 17,604 patients were randomized to WEGOVY or placebo. At baseline, the mean age was 62 years (range 45-93), 72% were male, 84% were White, 4% were Black or African American, and 8% were Asian, and 10% were Hispanic or Latino. Mean baseline body weight was 97 kg and mean BMI was 33 kg/m^2. At baseline, prior myocardial infarction was reported in 76% of randomized individuals, prior stroke in 23%, and peripheral arterial disease in 9%. Heart failure was reported in 24% of patients. At baseline, cardiovascular disease and risk factors were managed with lipid-lowering therapy (90%), platelet aggregation inhibitors (86%), angiotensin converting enzyme inhibitors or angiotensin II receptor blockers (74%), and beta blockers (70%). A total of 10% had moderate renal impairment (eGFR 30 to <60 mL/min/1.73m^2) and 0.4% had severe renal impairment eGFR <30 mL/min/1.73m^2.

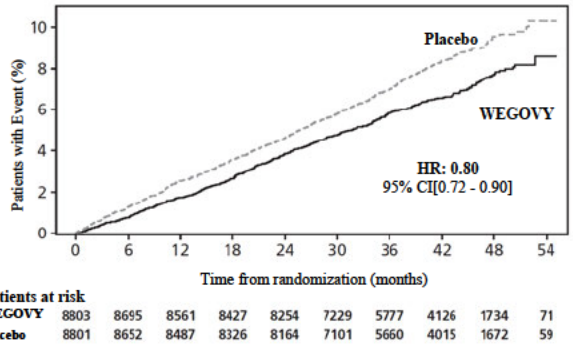
Results

In total, 96.9% of patients completed the trial, and vital status was available for 99.4% of patients. The median follow-up duration was 41.8 months. A total of 31% of WEGOVY-treated patients and 27% of placebo-treated patients permanently discontinued study drug.

For the primary analysis, a Cox proportional hazards model was used to test for superiority. Type 1 error was controlled across multiple tests.

WEGOVY significantly reduced the risk for first occurrence of MACE. The estimated hazard ratio (95% CI) was 0.80 (0.72, 0.90) (see Figure 4 and Table 5).

Figure 4. Cumulative Incidence Function: Time to First Occurrence of MACE in Study 1



Data from the in-trial period. Cumulative incidence estimates are based on time from randomization to first EAC-confirmed cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke with non-CV death modeled as competing risk using the Aalen-Johansen estimator. Patients without events of interest were censored at the end of their in-trial observation period. Time from randomization to first cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke was analyzed using a Cox proportional hazards model with treatment as categorical fixed factor. The hazard ratio and confidence interval are adjusted for the group sequential design using the likelihood ratio ordering.
HR: Hazard ratio; CI: confidence interval; CV: cardiovascular

The treatment effect for the primary composite endpoint, its components, and other relevant endpoints in Study 1 are shown in Table 5.

Table 5. Treatment Effect for MACE and Other Events in Study 1

	Patients with events n (%)		
	Placebo N = 8,801	**WEGOVY N = 8,803**	**Hazard Ratio (95% CI)**
Primary composite endpoint			
Composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke[1]	701 (8.0%)	569 (6.5%)	0.80 (0.72; 0.90)*[2]

Key secondary endpoints			
Cardiovascular death[3]	262 (3.0%)	223 (2.5%)	0.85 (0.71; 1.01)
All-cause death[4]	458 (5.2%)	375 (4.3%)	0.81 (0.71; 0.93)
Other secondary endpoints			
Fatal or non-fatal myocardial infarction[5]	334 (3.8%)	243 (2.8%)	0.72 (0.61; 0.85)
Fatal or non-fatal stroke[5]	178 (2.0%)	160 (1.8%)	0.89 (0.72; 1.11)

*p-value < 0.001, one-sided p-value
[1]Primary endpoint
[2]Adjusted for group sequential design using the likelihood ratio ordering.
[3]Cardiovascular death was the first confirmatory secondary endpoint in the testing hierarchy and superiority was not confirmed.
[4]Confirmatory secondary endpoint. Not statistically significant based on the prespecified testing hierarchy.
[5]Not included in the prespecified testing hierarchy for controlling type-I error.
NOTE: Time to first event was analyzed in a Cox proportional hazards model with treatment as factor. For patients with multiple events, only the first event contributed to the composite endpoint.

Table 6. Mean Changes in Anthropometry and Cardiometabolic Parameters at Week 104 in Study 1[1,2]

	PLACEBO		WEGOVY		
	Baseline	**Change from Baseline (LSMean)**	**Baseline**	**Change from Baseline (LSMean)**	**Difference from Placebo (LSMean)**
Body Weight (kg)	96.8	-0.9[3]	96.5	-9.4[3]	-8.5[3]
Waist Circumference (cm)	111.4	-1.0	111.3	-7.6	-6.5
Systolic Blood Pressure (mmHg)	131	-0.5	131	-3.8	-3.3
Diastolic Blood Pressure (mmHg)	79	-0.5	79	-1.0	-0.5
Heart Rate	69	0.7	69	3.8	3.1
HbA1c (%)	5.8	0.0	5.8	-0.3	-0.3
	Baseline	**% Change from Baseline (LSMean)**	**Baseline**	**% Change from Baseline (LSMean)**	**Relative difference from placebo (%) (LSMean)**
Total Cholesterol (mg/dL)[4]	156.0	-1.9	155.5	-4.6	-2.8
LDL Cholesterol (mg/dL)[4]	78.5	-3.1	78.5	-5.3	-2.2
HDL Cholesterol (mg/dL)[4]	44.2	0.6	44.1	4.9	4.2
Triglycerides (mg/dL)[4]	139.5	-3.2	138.6	-18.3	-15.6

[1]Parameters listed in the table were not included in the pre-specified hierarchical testing.
[2]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.
[3]For body weight the 'change from baseline' and 'difference to placebo' the unit is percentage change from baseline.
[4]Baseline value is the geometric mean.

The reduction of MACE with WEGOVY was not impacted by age, sex, race, ethnicity, BMI at baseline, or level of renal function impairment.

14.2 Weight Reduction and Long-term Maintenance Studies in Adults with Obesity or Overweight

Overview of Clinical Studies in Adults

The safety and efficacy of WEGOVY for weight reduction and long-term maintenance of body weight in conjunction with a reduced calorie diet and increased physical activity were studied in three 68-week, randomized, double-blind, placebo-controlled trials; one 68-week, randomized, double-blind, placebo withdrawal trial; and one 68-week, randomized, double-blind trial that investigated 2 different doses of WEGOVY versus placebo. In Studies 2 (NCT#03548935), 3 (NCT#03552757), and 4 (NCT#03611582), WEGOVY or matching placebo was escalated to 2.4 mg subcutaneous weekly during a 16-week period

followed by 52 weeks on maintenance dose. In Study 5 (NCT#03548987), WEGOVY was escalated during a 20-week run-in period, and patients who reached a WEGOVY 2.4 mg subcutaneous weekly dosage after the run-in period were randomized to either continued treatment with WEGOVY or placebo for 48 weeks. In Study 6 (NCT#03811574), WEGOVY was escalated to 1.7 mg or 2.4 mg subcutaneous weekly dosages or placebo over 12 to 16 weeks followed by 52 weeks on either maintenance dose.

In Studies 2, 3 and 5, all patients received instruction for a reduced calorie diet (approximately 500 kcal/day deficit) and increased physical activity counseling (recommended to a minimum of 150 min/week) that began with the first dose of study medication or placebo and continued throughout the trial. In Study 4, patients received an initial 8-week low-calorie diet (total energy intake 1,000 to 1,200 kcal/day) followed by 60 weeks of a reduced calorie diet(1200-1800 kcal/day) and increased physical activity (100 mins/week with gradual increase to 200 mins/week).

Study 2 was a 68-week trial that enrolled 1,961 patients with obesity (BMI greater than or equal to 30 kg/m^2) or with overweight (BMI 27-29.9 kg/m^2) and at least one weight-related comorbid condition, such as treated or untreated dyslipidemia or hypertension; patients with type 2 diabetes mellitus were excluded. Patients were randomized in a 2:1 ratio to either WEGOVY or placebo. At baseline, mean age was 46 years (range 18-86), 74% were female, 75% were White, 13% were Asian and 6% were Black or African American. A total of 12% were Hispanic or Latino ethnicity. Mean baseline body weight was 105.3 kg and mean BMI was 37.9 kg/m^2.

Study 3 was a 68-week trial that enrolled 807 patients with type 2 diabetes and BMI greater than or equal to 27 kg/m^2. Patients included in the trial had HbA_{1c} 7-10% and were treated with either: diet and exercise alone or 1 to 3 oral anti-diabetic drugs (metformin, sulfonylurea, glitazone or sodium-glucose co-transporter 2 inhibitor). Patients were randomized in a 1:1 ratio to receive either WEGOVY or placebo. At baseline, the mean age was 55 years (range 19-84), 51% were female, 62% were White, 26% were Asian and 8% were Black or African American. A total of 13% were Hispanic or Latino ethnicity. Mean baseline body weight was 99.8 kg and mean BMI was 35.7 kg/m^2.

Study 4 was a 68-week trial that enrolled 611 patients with obesity (BMI greater than or equal to 30 kg/m^2) or with overweight (BMI 27-29.9 kg/m^2) and at least one weight-related comorbid condition such as treated or untreated dyslipidemia or hypertension; patients with type 2 diabetes mellitus were excluded. The patients were randomized in a 2:1 ratio to receive either WEGOVY or placebo. At baseline, the mean age was 46 years, 81% were female, 76% were White, 19% were Black or African American and 2% were Asian. A total of 20% were Hispanic or Latino ethnicity. Mean baseline body weight was 105.8 kg and mean BMI was 38.0 kg/m^2.

Study 5 was a 68-week trial that enrolled 902 patients with obesity (BMI greater than or equal to 30 kg/m^2) or with overweight (BMI 27-29.9 kg/m^2) and at least one weight-related comorbid condition such as treated or untreated dyslipidemia or hypertension; patients with type 2 diabetes mellitus were excluded. Mean body weight at baseline for the 902 patients was 106.8 kg and mean BMI was 38.3 kg/m^2. All patients received WEGOVY during the run-in period of 20 weeks that included 16 weeks of dose escalation. Trial product was permanently discontinued before randomization in 99 of 902 patients (11%); the most common reason was adverse reactions (n=48, 5.3%); 803 patients reached WEGOVY 2.4 mg and were then randomized in a 2:1 ratio to either continue on WEGOVY or receive placebo. Among the 803 randomized patients, the mean age was 46 years, 79% were female, 84% were White, 13% were Black or African American, and 2% Asian. A total of 8% were Hispanic or Latino ethnicity. Mean body weight at randomization (week 20) was 96.1 kg and mean BMI at randomization (week 20) was 34.4 kg/m^2.

Study 6 was a 68-week trial that enrolled 401 East-Asian patients (Japan and South Korea) with BMI greater than or equal to 35 kg/m^2 and at least one weight-related comorbid condition or with BMI 27-34.9 kg/m^2 and at least two weight-related comorbid conditions. The patients were randomized 2:1:1 to receive WEGOVY 2.4 mg, WEGOVY 1.7 mg, or placebo. At baseline, the mean age was 51 years, 63% were male, and all patients

were Asian. Mean baseline body weight was 87.5 kg and mean BMI was 31.9 kg/m^2. At baseline, 24.7% of patients had type 2 diabetes mellitus.

Results

The proportions of patients who discontinued study drug in Studies 2, 3, and 4 was 16.0% for the WEGOVY-treated group and 19.1% for the placebo-treated group, and 6.8% of patients treated with WEGOVY and 3.2% of patients treated with placebo discontinued treatment due to an adverse reaction *[see Adverse Reactions (6.1)]*. In Study 5, the proportions of patients who discontinued study drug were 5.8% and 11.6% for WEGOVY and placebo, respectively. In Study 6, the proportions of patients who discontinued study drug were 7.9%, 6.5%, and 3.0% for WEGOVY 1.7 mg, WEGOVY 2.4 mg, and placebo, respectively.

For Studies 2, 3 and 4, the primary efficacy parameters were mean percent change in body weight and the percentages of patients achieving greater than or equal to 5% weight loss from baseline to week 68.

After 68 weeks, treatment with WEGOVY resulted in a statistically significant reduction in body weight compared with placebo. Greater proportions of patients treated with WEGOVY achieved 5%, 10% and 15% weight loss than those treated with placebo as shown in Table 7.

Table 7. Changes in Body Weight at Week 68 in Studies 2, 3, and 4

	Study 2 (Obesity or overweight with comorbidity)		**Study 3 (Type 2 diabetes with obesity or overweight)**		**Study 4 (Obesity or overweight with comorbidity undergoing intensive lifestyle therapy)**	
Intention-to-Treat[1]	**PLACEBO N = 655**	**WEGOVY N = 1306**	**PLACEBO N = 403**	**WEGOVY N = 404**	**PLACEBO N = 204**	**WEGOVY N = 407**
Body Weight						
Baseline mean (kg)	105.2	105.4	100.5	99.9	103.7	106.9
% change from baseline (LSMean)	-2.4	-14.9	-3.4	-9.6	-5.7	-16.0
% difference from placebo (LSMean) (95% CI)		-12.4 (-13.3; -11.6)*		-6.2 (-7.3; -5.2)*		-10.3 (-11.8; -8.7)*
% of Patients losing greater than or equal to 5% body weight	31.1	83.5	30.2	67.4	47.8	84.8
% difference from placebo (LSMean) (95% CI)		52.4 (48.1; 56.7)*		37.2 (30.7; 43.8)*		37.0 (28.9; 45.2)*
% of Patients losing greater than or equal to 10% body weight	12.0	66.1	10.2	44.5	27.1	73.0
% difference from placebo (LSMean) (95% CI)		54.1 (50.4; 57.9)*		34.3 (28.4; 40.2)*		45.9 (38.0; 53.7)*
% of Patients losing greater than or equal to 15% body weight	4.8	47.9	4.3	25.1	13.2	53.4
% difference from placebo (LSMean) (95% CI)		43.1 (39.8; 46.3)*		20.7 (15.7; 25.8)*		40.2 (33.1; 47.3)*

LSMean = least squares mean; CI = confidence interval

[1]The intent-to-treat population includes all randomized patients. In Study 2, at week 68, the body weight was missing for 7.2% and 11.9% of patients randomized to WEGOVY and placebo, respectively. In Study 3, at week 68, the body weight was missing for 4.0% and 6.7% of patients randomized to WEGOVY and placebo, respectively. In Study 4, at week 68, the body weight was missing for 8.4% and 7.4% of patients randomized to WEGOVY and placebo, respectively. Missing data were imputed from retrieved subjects of the same randomized treatment arm (RD-MI).

* $p<0.0001$ (unadjusted 2-sided) for superiority.

For Study 5, the primary efficacy parameter was mean percent change in body weight from randomization (week 20) to week 68.

From randomization (week 20) to week 68, treatment with WEGOVY resulted in a statistically significant reduction in body weight compared with placebo (Table 8). Because patients who discontinued WEGOVY during titration and those who did not reach the 2.4 mg weekly dose were not eligible for the randomized treatment period, the results may not reflect the experience of patients in the general population who are first starting WEGOVY.

Table 8. Changes in Body Weight at Week 68 in Study 5 (Obesity or overweight with comorbidity after 20 week run-in)

	WEGOVY N = 803[1]	
Body Weight (only randomized patients)		
Mean at week 0 (kg)	107.2	
	PLACEBO N = 268	**WEGOVY N = 535**
Body Weight		
Mean at week 20 (SD) (kg)	95.4 (22.7)	96.5 (22.5)
% change from week 20 at week 68 (LSMean)	6.9	-7.9
% difference from placebo (LSMean) (95% CI)		-14.8 (-16.0; -13.5)*

LSMean = least squares mean; CI = confidence interval
[1]902 patients were enrolled at week 0 with a mean baseline body weight of 106.8 kg. The intent-to-treat population includes all randomized patients. At week 68, the body weight was missing for 2.8% and 6.7% of patients randomized to WEGOVY and placebo, respectively. Missing data were imputed from retrieved subjects of the same randomized treatment arm (RD-MI).
*$p<0.001$ (unadjusted 2-sided) for superiority, controlled for multiplicity.

For Study 6, the primary efficacy parameters were mean percent change in body weight and the percentage of patients achieving greater than or equal to 5% weight loss from baseline to week 68.

After 68 weeks, treatment with WEGOVY 1.7 mg and 2.4 mg resulted in a statistically significant reduction in body weight compared with placebo. Greater proportions of patients treated with WEGOVY achieved 5%, 10%, and 15% weight loss than those treated with placebo as shown in Table 9.

Table 9. Changes in Body Weight at Week 68 in Study 6 in East-Asian Patients (WEGOVY 1.7 mg)

	Study 6 (BMI ≥35 kg/m^2 with at least one comorbidity or BMI 27-34.9 kg/m^2 with at least two comorbidities)		
Intention-to-treat[1]	**PLACEBO N = 101**	**WEGOVY 1.7 mg N = 101**	**WEGOVY 2.4 mg N = 199**
Body Weight			
Baseline mean (kg)	90.2	86.1	86.9
% change from baseline (LSMean)	-2.1	-9.6	-13.2
% difference from placebo (LSMean) (95% CI)		-7.5 (-9.6; -5.4)*	-11.1 (-12.9; -9.2)*
% of Patients losing greater than or equal to 5% body weight	19.4	72.8	84.0
% difference from placebo (LSMean) (95% CI)		53.3 (41.0; 65.6)*	64.5 (54.8; 74.3)*
% of Patients losing greater than or equal to 10% body weight	4.5	39.1	59.9
% difference from placebo (LSMean) (95% CI)		34.5 (23.9; 45.1)*	55.4 (47.3; 63.6)*
% of Patients losing greater than or equal to 15% body weight	2.6	20.8	38.2

% difference from placebo (LSMean) (95% CI)		18.2 (9.8; 26.7)*	35.6 (27.9; 43.3)*

LSMean = least squares mean; CI = confidence interval

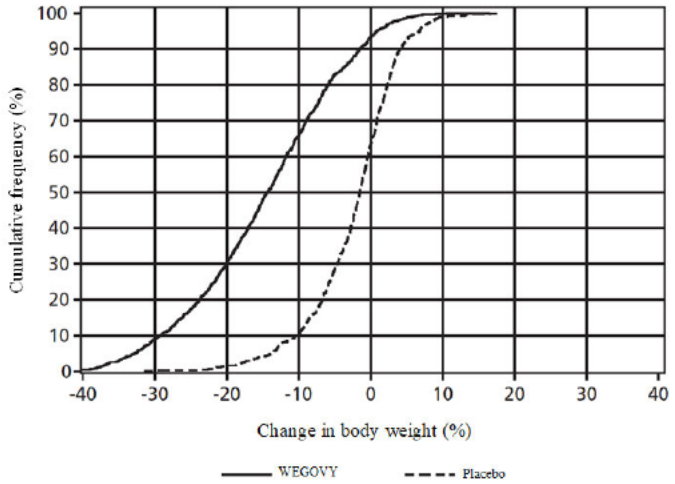
[1]The intent-to-treat population includes all randomized patients. At baseline, 24.7% of patients had type 2 diabetes mellitus. At week 68, the body weight was missing for 3%, 3%, and 1% of patients randomized to WEGOVY 1.7 mg, WEGOVY 2.4 mg, and placebo, respectively. Missing data were imputed from retrieved subjects of the same randomized treatment arm (RD-MI).

*p<0.0001 (unadjusted 2-sided) for superiority.

A reduction in body weight was observed with WEGOVY irrespective of age, sex, race, ethnicity, BMI at baseline, body weight (kg) at baseline, and level of renal function impairment.

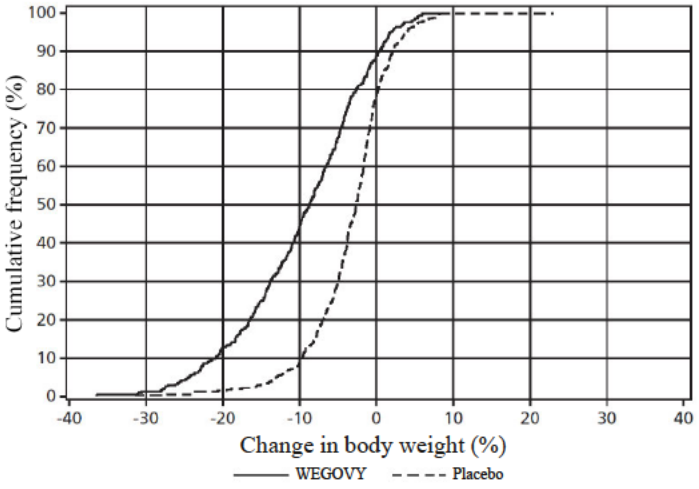
The cumulative frequency distributions of change in body weight are shown in Figure 5 and Figure 6 for Studies 2 and 3. One way to interpret this figure is to select a change in body weight of interest on the horizontal axis and note the corresponding proportions of patients (vertical axis) in each treatment group who achieved at least that degree of weight loss. For example, note that the vertical line arising from -10% in Study 2 intersects the WEGOVY and placebo curves at approximately 66%, and 12%, respectively, which correspond to the values shown in Table 7.

Figure 5. Change in body weight (%) from baseline to week 68 (Study 2)



Observed data from in-trial period including imputed data for missing observations (RD-MI).

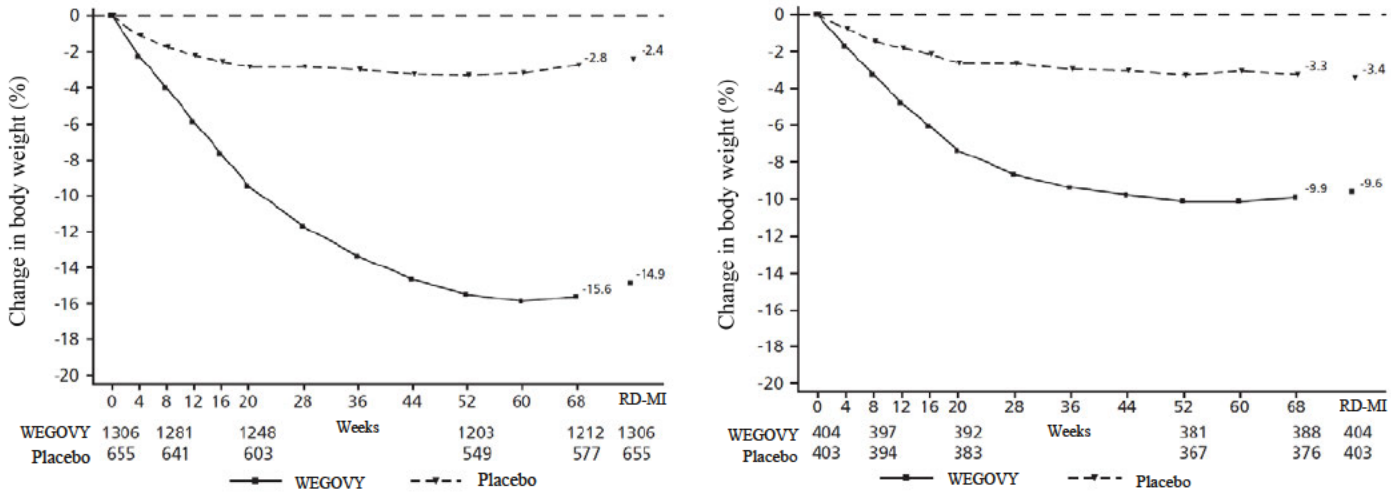
Figure 6. Change in body weight (%) from baseline to week 68 (Study 3)



Observed data from in-trial period including imputed data for missing observations (RD-MI).

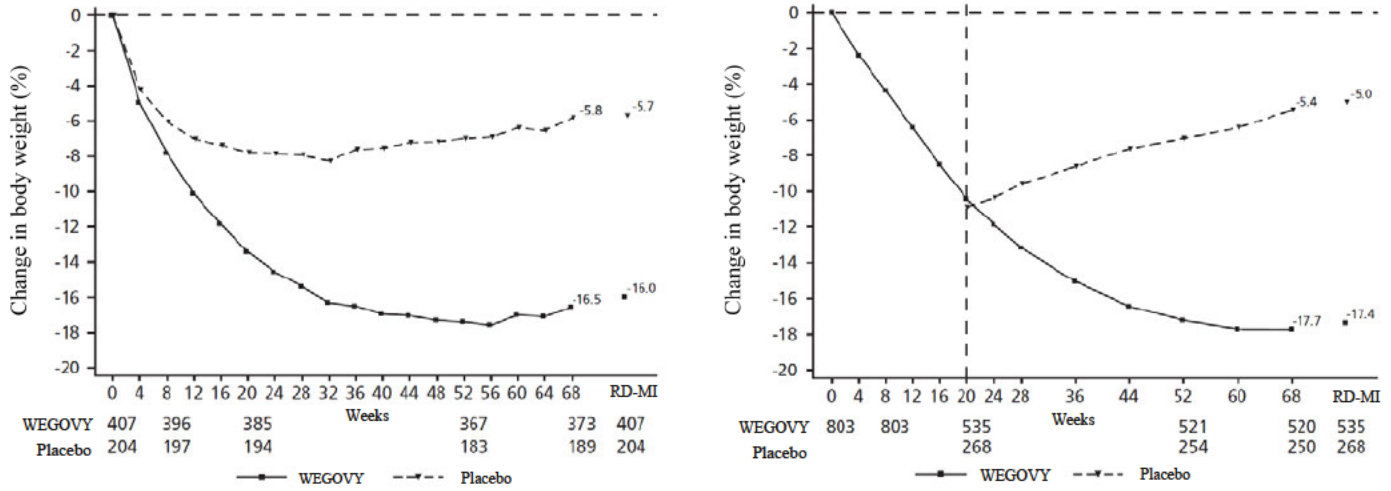
The time courses of weight loss with WEGOVY and placebo from baseline through week 68 are depicted in Figure 7, Figure 8 and Figure 9.

Figure 7. Change from baseline (%) in body weight (Study 2 on left and Study 3 on right)



Observed values for patients completing each scheduled visit, and estimates with multiple imputations from retrieved dropouts (RD-MI)

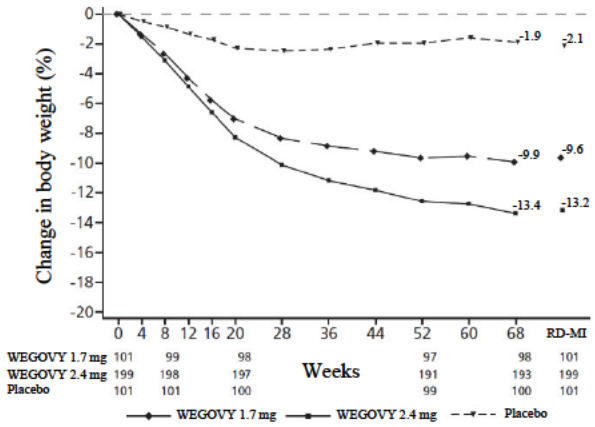
Figure 8. Change from baseline (%) in body weight (Study 4 on left and Study 5[a] on right)



Observed values for patients completing each scheduled visit, and estimates with multiple imputations from retrieved dropouts (RD-MI)

[a]Change from week 0 was not a primary endpoint in study 4. Dotted line indicates time of randomization. Randomized patients (shown) do not include 99 patients that discontinued during the 20 week run-in period.

Figure 9. Change in body weight (%) from baseline to week 68 (Study 6 in East-Asian Patients)



Observed values for patients completing each scheduled visit and estimates with multiple imputations from retrieved dropouts (RD-MI). At baseline, 24.7% of patients had type 2 diabetes mellitus.

Effect of WEGOVY on Anthropometry and Cardiometabolic Parameters in Adults

Changes in waist circumference and cardiometabolic parameters with WEGOVY are shown in Table 10 for Studies 2, 3, and 4; in Table 11 for Study 5; and in Table 12 for Study 6.

Table 10. Changes in Anthropometry and Cardiometabolic Parameters at Week 68 in Studies 2, 3, and 4

	Study 2 (Obesity or overweight with comorbidity)		Study 3 (Type 2 diabetes with obesity or overweight)		Study 4 (Obesity or overweight with comorbidity undergoing intensive lifestyle therapy)	
Intention-to-Treat	PLACEBO N = 655	WEGOVY N = 1306	PLACEBO N = 403	WEGOVY N = 404	PLACEBO N = 204	WEGOVY N = 407
Waist Circumference (cm)						
Baseline	114.8	114.6	115.5	114.5	111.8	113.6
Changes from baseline (LSMean[1])	-4.1	-13.5	-4.5	-9.4	-6.3	-14.6
Difference from placebo (LSMean)		-9.4		-4.9		-8.3
Systolic Blood Pressure (mmHg)						
Baseline	127	126	130	130	124	124
Changes from baseline (LSMean[1])	-1.1	-6.2	-0.5	-3.9	-1.6	-5.6
Difference from placebo (LSMean)		-5.1		-3.4		-3.9
Diastolic Blood Pressure (mmHg)[2]						
Baseline	80	80	80	80	81	80
Changes from baseline (LSMean[1])	-0.4	-2.8	-0.9	-1.6	-0.8	-3.0
Difference from placebo (LSMean)		-2.4		-0.7		-2.2
Heart Rate[2,3]						
Baseline	72	72	76	75	71	71
Changes from baseline (LSMean)	-0.7	3.5	-0.2	2.5	2.1	3.1
Difference from placebo (LSMean)		4.3		2.7		1.0

	Study 2 (Obesity or overweight with comorbidity)		Study 3 (Type 2 diabetes with obesity or overweight)		Study 4 (Obesity or overweight with comorbidity undergoing intensive lifestyle therapy)	
Intention-to-Treat	PLACEBO N = 655	WEGOVY N = 1306	PLACEBO N = 403	WEGOVY N = 404	PLACEBO N = 204	WEGOVY N = 407
HbA1c (%)[2]						
Baseline	5.7	5.7	8.1	8.1	5.8	5.7
Changes from baseline (LSMean[1])	-0.2	-0.4	-0.4	-1.6	-0.3	-0.5
Difference from placebo (LSMean)		-0.3		-1.2		-0.2
Total Cholesterol (mg/dL)[2,4]						
Baseline	192.1	189.6	170.8	170.8	188.7	185.4
Percent Change from baseline (LSMean[1])	0.1	-3.3	-0.5	-1.4	2.1	-3.9
Relative difference from placebo (LSMean)		-3.3		-0.9		-5.8
LDL Cholesterol (mg/dL)[2,4]						
Baseline	112.5	110.3	90.1	90.1	111.8	107.7
Percent Change from baseline (LSMean[1])	1.3	-2.5	0.1	0.5	2.6	-4.7
Relative difference from placebo (LSMean)		-3.8		0.4		-7.1
HDL (mg/dL)[2,4]						
Baseline	49.5	49.4	43.8	44.7	50.9	51.6
Percent Change from baseline (LSMean[1])	1.4	5.2	4.1	6.9	5.0	6.5
Relative difference from placebo (LSMean)		3.8		2.7		1.5
Triglycerides (mg/dL)[2,4]						
Baseline	127.9	126.2	159.5	154.9	110.9	107.9
Percent Change from baseline (LSMean[1])	-7.3	-21.9	-9.4	-22.0	-6.5	-22.5
Relative difference from placebo (LSMean)		-15.8		-13.9		-17.0

Missing data were imputed from retrieved subjects of the same randomized treatment arm (RD-MI)

[1]Model based estimates based on an analysis of covariance model including treatment (and stratification factors for Study 3 only) as a factor and baseline value as a covariate

[2]Not included in the pre-specified hierarchical testing (except HbA_{1c} for Study 3)

[3]Model based estimates based on a mixed model for repeated measures including treatment (and stratification factors for Study 3 only) as a factor and baseline values as a covariate

[4]Baseline value is the geometric mean

Table 11. Mean Changes in Anthropometry and Cardiometabolic Parameters in Study 5 (Obesity or overweight with comorbidity after 20 week run-in)[1]

	PLACEBO N = 268		WEGOVY N = 535		
	Randomization (week 20)	**Change from Randomization (week 20) to week 68 (LSMean[1])**	**Randomization (week 20)**	**Change from Randomization (week 20) to week 68 (LSMean[1])**	**Difference from placebo (LSMean)**
Waist Circumference (cm)	104.7	3.3	105.5	-6.4	-9.7
Systolic Blood Pressure (mmHg)	121	4.4	121	0.5	-3.9
Diastolic Blood Pressure (mmHg)[2]	78	0.9	78	0.3	-0.5
Heart Rate[2,3]	76	-5.3	76	-2.0	3.3
HbA1c (%)[2]	5.4	0.1	5.4	-0.1	-0.2
	Randomization (week 20)	**% Change from Randomization (week 20) (LSMean[1])**	**Randomization (week 20)**	**% Change from Randomization (week 20) (LSMean[1])**	**Relative difference from placebo (LSMean)**
Total Cholesterol (mg/dL)[2,4]	175.1	11.4	175.9	4.9	-5.8
LDL Cholesterol (mg/dL)[2,4]	109.1	7.6	108.7	1.1	-6.1
HDL Cholesterol (mg/dL)[2,4]	43.6	17.8	44.5	18.2	0.3
Triglycerides (mg/dL)[2,4]	95.3	14.8	98.1	-5.6	-17.8

Missing data were imputed from retrieved subjects of the same randomized treatment arm (RD-MI)
[1]Model based estimates based on an analysis of covariance model including treatment as a factor and baseline value as a covariate
[2]Not included in the pre-specified hierarchical testing
[3]Model based estimates based on a mixed model for repeated measures including treatment as a factor and baseline values as a covariate
[4]Baseline value is the geometric mean

Table 12. Mean Changes in Anthropometry and Cardiometabolic Parameters at Week 68 in Study 6 in East-Asian Patients (WEGOVY 1.7 mg)

	Study 6 (BMI ≥35 kg/m^2 with at least one comorbidity or BMI 27-34.9 kg/m^2 with at least two comorbidities)		
Intention-to-treat	**PLACEBO N = 101**	**WEGOVY 1.7 mg N = 101**	**WEGOVY 2.4 mg N = 199**
Waist circumference (cm)			
Baseline	103.8	101.4	103.8
Change from baseline (LSMean[1])	-1.8	-7.7	-11.0
Difference from placebo (LSMean)		-5.9	-9.3
Systolic blood pressure (mmHg)[2]			
Baseline	133	135	133
Change from baseline (LSMean[1])	-5.3	-10.8	-10.8
Difference from placebo (LSMean)		-5.4	-5.5
Diastolic blood pressure (mmHg)[2]			
Baseline	86	85	83
Change from baseline (LSMean[1])	-2.2	-4.6	-5.3
Difference from placebo (LSMean)		-2.4	-3.1
Heart Rate[2, 3]			
Baseline	73	73	73
Change from baseline (LSMean)	2.4	4.4	6.3
Difference from placebo (LSMean)		2.0	3.9
HbA_{1c} (%)[2]			
Baseline	6.4	6.4	6.4
Change from baseline (LSMean[1])	0.0	-0.9	-0.9
Difference from placebo (LSMean)		-0.9	-0.9
Total Cholesterol (mg/dL)[2,4]			
Baseline	203.1	203.3	197.2
Percent change from baseline (LSMean[1])	0.8	-6.6	-8.7

Relative difference from placebo (LSMean)		-7.3	-9.4
LDL Cholesterol (mg/dL)[2,4]			
Baseline	123.3	120.1	116.5
Percent change from baseline (LSMean[1])	-3.8	-10.1	-14.6
Relative difference from placebo (LSMean)		-6.5	-11.2
HDL Cholesterol (mg/dL)[2,4]			
Baseline	48.7	50.2	50.8
Percent change from baseline (LSMean[1])	5.9	6.7	9.2
Relative difference from placebo (LSMean)		0.7	3.1
Triglyceride (mg/dL)[2,4]			
Baseline	134.2	138.8	127.1
Percent change from baseline (LSMean[1])	5.5	-19.5	-21.2
Relative difference from placebo (LSMean)		-23.7	-25.3

Missing data were imputed from retrieved subjects of the same randomized treatment arm (RD-MI). At baseline, 24.7% of patients had type 2 diabetes mellitus.

[1]Model based estimates based on an analysis of covariance model including treatment and type 2 diabetes status as factors and baseline value as a covariate

[2]Not included in the pre-specified hierarchical testing

[3]Model based estimates based on a mixed model for repeated measures including treatment and type 2 diabetes status as factors and baseline values as a covariate

[4]Baseline value is the geometric mean

14.3 Weight Reduction and Long-Term Maintenance Study in Pediatric Patients Aged 12 Years and Older with Obesity

Overview of Clinical Trial in Pediatric Patients

WEGOVY was evaluated in a 68-week, double-blind, randomized, parallel group, placebo-controlled, multi-center trial in 201 pubertal pediatric patients aged 12 years and older with BMI corresponding to ≥95th percentile standardized for age and sex (Study 7) (NCT#04102189). After a 12-week lifestyle run-in period (including dietary recommendations and physical activity counseling), patients were randomized 2:1 to WEGOVY once weekly or placebo once weekly. WEGOVY or matching placebo was escalated to 2.4 mg or maximally tolerated dose during a 16-week period followed by 52 weeks on maintenance dose. Of WEGOVY-treated patients who completed the trial, 86.7% were on the 2.4 mg dose at the end of the trial; for 5% of patients, 1.7 mg was the maximum tolerated dose.

The mean age was 15 years; 38% of patients were male; 79% were White, 8% were Black or African American, 2% were Asian, and 11% were of other or unknown race; and 11% were of Hispanic or Latino ethnicity. The mean baseline body weight was 108 kg, and mean BMI was 37 kg/m^2.

Results

The proportions of patients who discontinued study drug were 10% for the WEGOVY-treated group and 10% for the placebo-treated group.

The primary endpoint was percent change in BMI from baseline to week 68. After 68 weeks, treatment with WEGOVY resulted in a statistically significant reduction in percent BMI compared with placebo. Greater proportions of patients treated with WEGOVY achieved ≥5% reduction in baseline BMI than those treated with placebo as shown in Table 13.

Table 13. Changes in Weight and BMI at Week 68 in Pediatric Patients with Obesity Aged 12 Years and Older in Study 7

Intention-to-Treat[a]	**PLACEBO N = 67**	**WEGOVY N = 134**
BMI		
Baseline mean (kg/m^2)	35.7	37.7
% change from baseline in BMI (LSMean)	0.6	-16.1
% difference from placebo		-16.7

Intention-to-Treat[a]	PLACEBO N = 67	WEGOVY N = 134
(LSMean) (95% CI)		(-20.3; -13.2)*
% of Patients with greater than or equal to 5% reduction in baseline BMI[b]	19.7	77.1
% difference from placebo (LSMean)		57.4
% of Patients with greater than or equal to 10% reduction in baseline BMI[b]	7.7	65.1
% difference from placebo (LSMean)		57.5
% of Patients with greater than or equal to 15% reduction in baseline BMI[b]	4.0	57.8
% difference from placebo (LSMean)		53.9
Body Weight[b]		
Baseline mean (kg)	102.6	109.9
% change from baseline (LSMean)[a]	2.7	-14.7
% difference from placebo (LSMean)		-17.4

LSMean = least squares mean; CI = confidence interval

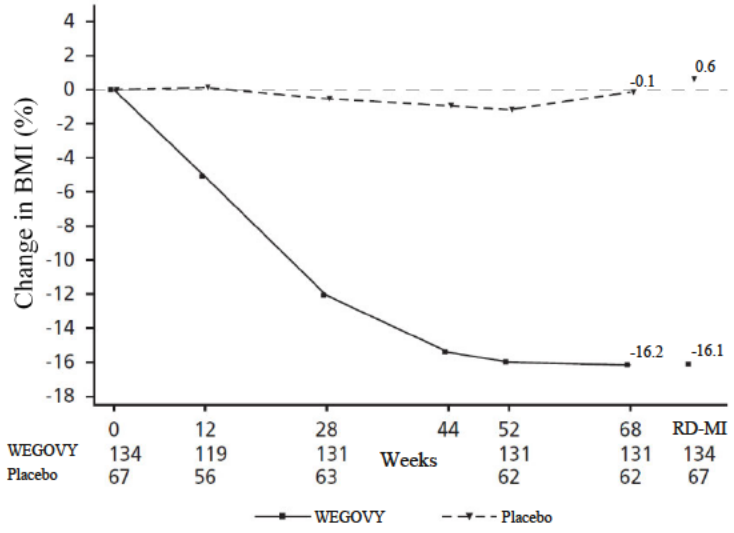
[a]The intention-to-treat population includes all randomized patients. Missing data were imputed using available data according to value and timing of last available observation on treatment and endpoint's baseline value from retrieved subjects (RD-MI). At week 68, the BMI was missing for 2.2% and 7.5% of patients randomized to WEGOVY and placebo, respectively.

[b]Parameters not included in the pre-specified hierarchical testing.

* $p<0.0001$ (unadjusted 2-sided) for superiority.

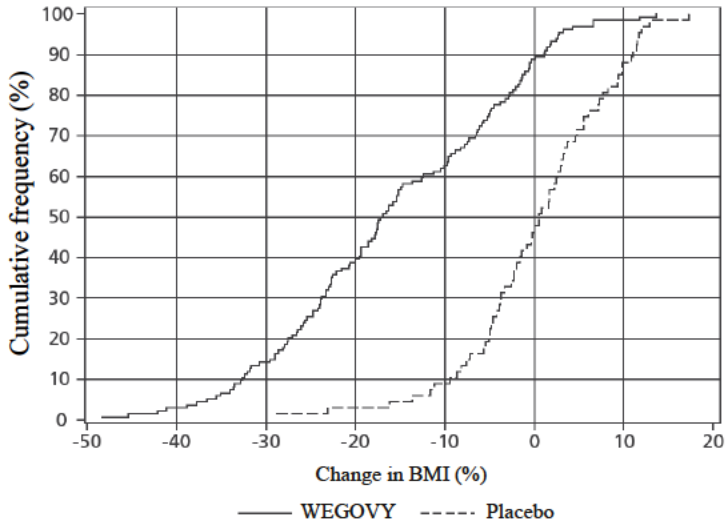
The time course of change in BMI with WEGOVY and placebo from baseline through week 68 is depicted in Figure 10. The cumulative frequency distribution of change in BMI is shown in Figure 11.

Figure 10. Change from Baseline (%) in BMI in Pediatric Patients with Obesity Aged 12 Years and Older in Study 7



Observed values for patients completing each scheduled visit, and estimates with multiple imputations from retrieved dropouts (RD-MI)

Figure 11. Change in BMI (%) from Baseline to Week 68 in Pediatric Patients with Obesity Aged 12 Years and Older in Study 7



Observed data from in-trial period including imputed data for missing observations (RD-MI)

Effect of WEGOVY on Anthropometry and Cardiometabolic Parameters in Pediatric Patients with Obesity Aged 12 Years and Older

Changes in waist circumference and cardiometabolic parameters with WEGOVY are shown in Table 14 for the study in pediatric patients aged 12 years and older.

Table 14. Mean Changes in Anthropometry and Cardiometabolic Parameters in Pediatric Patients with Obesity Aged 12 Years and Older in Study 7[1]

	PLACEBO N = 67		WEGOVY N = 134		
	Baseline	**Change from Baseline (LSMean)**	**Baseline**	**Change from Baseline (LSMean)**	**Difference from placebo (LSMean)**
Waist Circumference (cm)[2]	107.3	-0.6	111.9	-12.7	-12.1
Systolic Blood Pressure (mmHg)[2]	120	-0.8	120	-2.7	-1.9
Diastolic Blood Pressure (mmHg)[2]	73	-0.8	73	-1.4	-0.6
Heart Rate[3]	76	-2.3	79	1.2	3.5
HbA1c (%)[2,4]	5.4	-0.1	5.5	-0.4	-0.2
	Baseline	**% Change from Baseline (LSMean)**	**Baseline**	**% Change from Baseline (LSMean)**	**Relative difference from placebo (LSMean)**
Total Cholesterol (mg/dL)[2,5]	160.1	-1.3	159.4	-8.3	-7.1
LDL Cholesterol (mg/dL)[2,5]	91.7	-3.6	89.8	-9.9	-6.6
HDL Cholesterol (mg/dL)[2,5]	43.3	3.2	43.7	8.0	4.7
Triglycerides (mg/dL)[2,5]	108.0	2.6	111.3	-28.4	-30.2

[1]Parameters listed in the table were not included in the pre-specified hierarchical testing.
[2]Missing data were imputed using available data according to value and timing of last available observation on treatment and endpoint's baseline value from retrieved subjects (RD-MI). Model based estimates based on an analysis of covariance model including treatment and stratification groups (gender, Tanner stage group) and the interaction between stratification groups as factors and baseline value as a covariate.
[3]Model based estimates based on a mixed model for repeated measures including treatment as a factor and baseline value as a covariate all nested within visit.
[4]For patients without type 2 diabetes at randomization (N=129 for WEGOVY-treated patients and N=64 for placebo-treated patients).
[5]Baseline value is the geometric mean.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

WEGOVY injection is a clear, colorless solution in a pre-filled, disposable, single-dose pen-injector with an integrated needle. It is supplied in cartons containing 4 pen-injectors in the following packaging configurations:

Total Strength per Total Volume	NDC
0.25 mg/0.5 mL	0169-4525-14
0.5 mg/0.5 mL	0169-4505-14
1 mg/0.5 mL	0169-4501-14
1.7 mg/0.75 mL	0169-4517-14
2.4 mg/0.75 mL	0169-4524-14

Recommended Storage

Store the WEGOVY single-dose pen in the refrigerator from 2°C to 8°C (36°F to 46°F). If needed, prior to cap removal, the pen can be kept from 8°C to 30°C (46°F to 86°F) up to 28 days. Do not freeze. Protect WEGOVY from light. WEGOVY must be kept in the original carton until time of administration. Discard the WEGOVY pen after use.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Risk of Thyroid C-cell Tumors

Inform patients that semaglutide causes thyroid C-cell tumors in rodents and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) to their physician *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Acute Pancreatitis

Inform patients of the potential risk for acute pancreatitis. Instruct patients to discontinue WEGOVY promptly and contact their physician if pancreatitis is suspected (severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting) *[see Warnings and Precautions (5.2)]*.

Acute Gallbladder Disease

Inform patients of the risk of acute gallbladder disease. Advise patients that substantial or rapid weight loss can increase the risk of gallbladder disease, but that gallbladder disease may also occur in the absence of substantial or rapid weight loss. Instruct patients to contact their healthcare provider for appropriate clinical follow-up if gallbladder disease is suspected *[see Warnings and Precautions (5.3)].*

Hypoglycemia

Inform patients of the risk of hypoglycemia and educate patients on the signs and symptoms of hypoglycemia. Advise patients with diabetes mellitus on glycemic lowering therapy that they may have an increased risk of hypoglycemia when using WEGOVY and to report signs and/or symptoms of hypoglycemia to their healthcare provider *[see Warnings and Precautions (5.4)]*.

Dehydration and Renal Impairment

Advise patients treated with WEGOVY of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs *[see Warnings and Precautions (5.5)]*.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of semaglutide, the active ingredient in WEGOVY. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking WEGOVY and seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.6)]*.

Diabetic Retinopathy Complications in Patients with Type 2 Diabetes
Inform patients with type 2 diabetes to contact their physician if changes in vision are experienced during treatment with WEGOVY *[see Warnings and Precautions (5.7)]*.

Heart Rate Increase
Instruct patients to inform their healthcare providers of palpitations or feelings of a racing heartbeat while at rest during WEGOVY treatment *[see Warnings and Precautions (5.8)]*.

Suicidal Behavior and Ideation
Advise patients to report emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Inform patients that if they experience suicidal thoughts or behaviors, they should stop taking WEGOVY *[see Warnings and Precautions (5.9)]*.

Pregnancy
WEGOVY may cause fetal harm. Advise patients to inform their healthcare provider of a known or suspected pregnancy. Advise patients who are exposed to WEGOVY during pregnancy to contact Novo Nordisk at 1-877-390-2760 or www.wegovypregnancyregistry.com *[see Use in Specific Populations (8.1)]*.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd
Denmark

For additional information about WEGOVY contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
1-833-934-6891

Version: 4

PATENT INFORMATION: http://www.novonordisk-us.com/products/product-patents.html

Medication Guide

WEGOVY® (wee-GOH-vee)

(semaglutide) injection, for subcutaneous use

Read this Medication Guide and Instructions for Use before you start using WEGOVY and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about WEGOVY?

WEGOVY may cause serious side effects, including:

- **Possible thyroid tumors, including cancer**. Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rodents, WEGOVY and medicines that work like WEGOVY caused thyroid tumors, including thyroid cancer. It is not known if WEGOVY will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.
- Do not use WEGOVY if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

What is WEGOVY?

- WEGOVY is an injectable prescription medicine used with a reduced calorie diet and increased physical activity:
  - to reduce the risk of major cardiovascular events such as death, heart attack, or stroke in adults with known heart disease and with either obesity or overweight.
  - that may help adults and children aged 12 years and older with obesity, or some adults with overweight who also have weight-related medical problems, to help them lose excess body weight and keep the weight off.
- WEGOVY contains semaglutide and should not be used with other semaglutide-containing products or other GLP-1 receptor agonist medicines.
- It is not known if WEGOVY is safe and effective for use in children under 12 years of age.

Do not use WEGOVY if:

- you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- you have had a serious allergic reaction to semaglutide or any of the ingredients in WEGOVY. See the end of this Medication Guide for a complete list of ingredients in WEGOVY. Symptoms of a serious allergic reaction include:
  - swelling of your face, lips, tongue or throat
  - problems breathing or swallowing
  - severe rash or itching
  - fainting or feeling dizzy
  - very rapid heartbeat

Before using WEGOVY, tell your healthcare provider if you have any other medical conditions, including if you:

- have or have had problems with your pancreas or kidneys.
- have type 2 diabetes and a history of diabetic retinopathy.
- have or have had depression or suicidal thoughts, or mental health issues.
- are pregnant or plan to become pregnant. WEGOVY may harm your unborn baby. You should stop using WEGOVY 2 months before you plan to become pregnant.
  - **Pregnancy Exposure Registry:** There is a pregnancy exposure registry for women who use WEGOVY during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry or you may contact Novo Nordisk at 1-877-390-2760.
- are breastfeeding or plan to breastfeed. It is not known if WEGOVY passes into your breast milk. You should talk with your healthcare provider about the best way to feed your baby while using WEGOVY.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. WEGOVY may affect the way some medicines work and some medicines may affect the way WEGOVY works. Tell your healthcare provider if you are taking other medicines to treat diabetes,

including sulfonylureas or insulin. WEGOVY slows stomach emptying and can affect medicines that need to pass through the stomach quickly.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use WEGOVY?

- Read the **Instructions for Use** that comes with WEGOVY.
- Use WEGOVY exactly as your healthcare provider tells you to.
- **Your healthcare provider should show you how to use WEGOVY before you use it for the first time.**
- WEGOVY is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm. **Do not** inject WEGOVY into a muscle (intramuscularly) or vein (intravenously).
- Change (rotate) your injection site with each injection. **Do not** use the same site for each injection.
- **Use WEGOVY 1 time each week, on the same day each week, at any time of the day.**
- Start WEGOVY with 0.25 mg per week in your first month. In your second month, increase your weekly dose to 0.5 mg. In the third month, increase your weekly dose to 1 mg. In the fourth month, increase your weekly dose to 1.7 mg. In the fifth month onwards, your healthcare provider may either maintain your dose at 1.7 mg weekly or increase your weekly dose to 2.4 mg.
- If you need to change the day of the week, you may do so as long as your last dose of WEGOVY was given **2** or more days before.
- If you miss a dose of WEGOVY and the next scheduled dose is more than 2 days away (48 hours), take the missed dose as soon as possible. If you miss a dose of WEGOVY and the next schedule dose is less than 2 days away (48 hours), do not administer the dose. Take your next dose on the regularly scheduled day.
- If you miss doses of WEGOVY for more than 2 weeks, take your next dose on the regularly scheduled day or call your healthcare provider to talk about how to restart your treatment.
- You can take WEGOVY with or without food.
- If you take too much WEGOVY, you may have severe nausea, severe vomiting and severe low blood sugar. Call your healthcare provider or go to the nearest hospital emergency room right away if you experience any of these symptoms.

What are the possible side effects of WEGOVY?

WEGOVY may cause serious side effects, including:

- **See "What is the most important information I should know about WEGOVY?"**
- **inflammation of your pancreas (pancreatitis).** Stop using WEGOVY and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- **gallbladder problems.** WEGOVY may cause gallbladder problems including gallstones. Some gallbladder problems need surgery. Call your healthcare provider if you have any of the following symptoms:
    - pain in your upper stomach (abdomen)
    - fever
    - yellowing of skin or eyes (jaundice)
    - clay-colored stools
- **increased risk of low blood sugar (hypoglycemia), especially those who also take medicines to treat diabetes mellitus such as insulin or sulfonylureas.** Low blood sugar in patients with diabetes who receive WEGOVY can be a serious side effect. Talk to your healthcare provider about how to recognize and treat low blood sugar. You should check your blood sugar before you start taking WEGOVY and while you take WEGOVY. Signs and symptoms of low blood sugar may include:
    - dizziness or light-headedness
    - blurred vision
    - anxiety
    - irritability or mood changes
    - fast heartbeat
    - sweating
    - slurred speech
    - hunger
    - confusion or drowsiness
    - feeling jittery
    - shakiness
    - weakness
    - headache

- **kidney problems (kidney failure).** In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse. It is important for you to drink fluids to help reduce your chance of dehydration.
- **serious allergic reactions.** Stop using WEGOVY and get medical help right away, if you have any symptoms of a serious allergic reaction including:
  - swelling of your face, lips, tongue or throat
  - severe rash or itching
  - very rapid heartbeat
  - problems breathing or swallowing
  - fainting or feeling dizzy
- **change in vision in people with type 2 diabetes.** Tell your healthcare provider if you have changes in vision during treatment with WEGOVY.
- **increased heart rate.** WEGOVY can increase your heart rate while you are at rest. Your healthcare provider should check your heart rate while you take WEGOVY. Tell your healthcare provider if you feel your heart racing or pounding in your chest and it lasts for several minutes.
- **depression or thoughts of suicide.** You should pay attention to any mental changes, especially sudden changes in your mood, behaviors, thoughts, or feelings. Call your healthcare provider right away if you have any mental changes that are new, worse, or worry you.

The most common side effects of WEGOVY in adults or children aged 12 years and older may include:

- nausea
- diarrhea
- vomiting
- constipation
- stomach (abdomen) pain
- headache
- tiredness (fatigue)
- upset stomach
- dizziness
- feeling bloated
- belching
- low blood sugar in people with type 2 diabetes
- gas
- stomach flu
- heartburn
- runny nose or sore throat

Talk to your healthcare provider about any side effect that bothers you or does not go away. These are not all the possible side effects of WEGOVY.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of WEGOVY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use WEGOVY for a condition for which it was not prescribed. Do not give WEGOVY to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about WEGOVY that is written for health professionals.

What are the ingredients in WEGOVY?

Active Ingredient: semaglutide

Inactive Ingredients: disodium phosphate dihydrate, 1.42 mg; sodium chloride, 8.25 mg; water for injection; and hydrochloric acid or sodium hydroxide may be added to adjust pH.

Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

WEGOVY® is a registered trademark of Novo Nordisk A/S.

PATENT Information: http://novonordisk-us.com/products/product-patents.html

For more information, go to startWegovy.com or call 1-833-Wegovy-1.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 03/2024

Instructions for Use
WEGOVY®
(semaglutide) injection
WEGOVY comes in five strengths:

0.25 mg / 0.5 mL	0.5 mg / 0.5 mL	1 mg / 0.5 mL	1.7 mg / 0.75 mL	2.4 mg / 0.75 mL

Before you use your WEGOVY pen for the first time, talk to your healthcare provider or your caregiver about how to prepare and inject WEGOVY correctly.

Pull out to get started

Important information

Read this Instructions for Use before you start using WEGOVY. This information does not replace talking to your healthcare provider about your medical condition or treatment.

· **Your WEGOVY pen is for 1 time use only**. The WEGOVY pen is for subcutaneous (under the skin) use only.
· **The dose of WEGOVY is already set on your pen.**
· **The needle is covered by the needle cover and the needle will not be seen.**
· Do not remove the pen cap until you are ready to inject.
· Do not touch or push on the needle cover. You could get a needle stick injury.
· Your WEGOVY injection will start when the needle cover is pressed firmly against your skin.
· **Do not** remove the pen from your skin before the yellow bar in the pen window has stopped moving. The medicine may appear on the skin or squirt from the needle and you may not get your full dose of WEGOVY if:

- the pen is removed too early **or**
- you have not pressed the pen firmly against the skin for the entire injection.

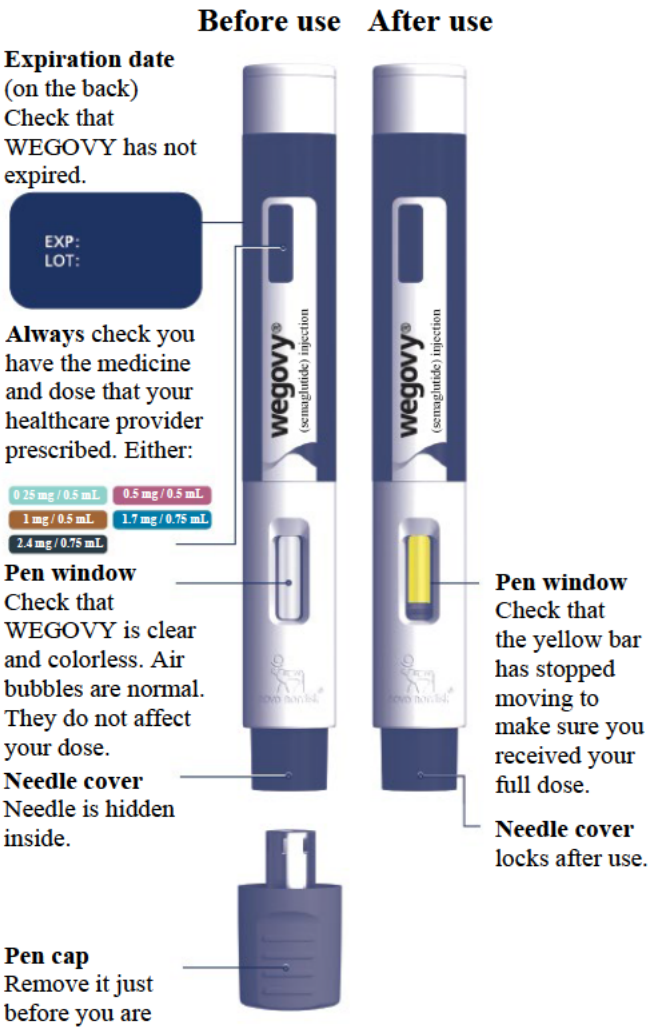
· If the yellow bar does not start moving or stops during the injection, contact your healthcare provider or Novo Nordisk at startWegovy.com or call Novo Nordisk Inc. at 1-833-934-6891.
· The needle cover will lock when the pen is removed from your skin. **You cannot stop the injection and restart it later.**
· People who are blind or have vision problems should not use the WEGOVY pen without help from a person trained to use the WEGOVY pen.

How do I store WEGOVY?

· Store the WEGOVY pen in the refrigerator between 36°F to 46°F (2°C to 8°C).
· If needed, before removing the pen cap, WEGOVY can be stored from 46°F to 86°F (8°C to 30°C) in the original carton for up to 28 days.
· Keep WEGOVY in the original carton to protect it from light.
· **Do not freeze**.
· Throw away the pen if WEGOVY has been frozen, has been exposed to light or temperatures above 86°F(30°C), or has been out of the refrigerator for 28 days or longer.

Keep WEGOVY and all medicines out of the reach of children.

WEGOVY pen parts



How to use your WEGOVY pen

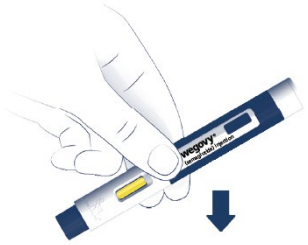
Do not use your WEGOVY pen without receiving training from your healthcare provider. Make sure that you or your caregiver know how to give an injection with the pen before you start your treatment.

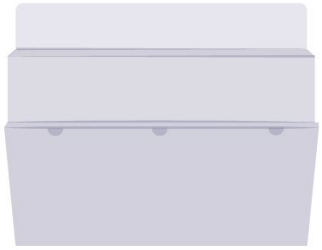
Read and follow the instructions so that you use your WEGOVY pen correctly:

Preparation

Step 1. Prepare for your injection.

- **Supplies you will need to give your WEGOVY injection:**
  - WEGOVY pen
  - 1 alcohol swab or soap and water
  - 1 gauze pad or cotton ball
  - 1 sharps disposable container for used WEGOVY pens





- **Wash your hands.**
- **Check your WEGOVY pen.**
  Do not use your WEGOVY pen if:
  - The pen appears to have been used or any part of the pen appears broken, for example if it has been dropped.
  - The WEGOVY medicine is not clear and colorless through the pen window.
  - The expiration date (EXP) has passed.

Contact Novo Nordisk at 1-833-934-6891 if your WEGOVY pen fails any of these checks.

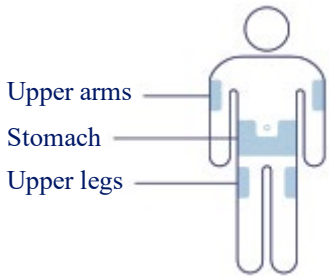
Step 2. Choose your injection site.

• Your healthcare provider can help you choose the injection site that is best for you
  - You may inject into your upper leg (front of the thighs), lower stomach (keep 2 inches away from your belly button) or upper arm.

• Do not inject into an area where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

• You may inject in the same body area each week, but make sure it is not in the same spot each time.

Clean the injection site with an alcohol swab or soap and water. Do not touch the injection site after cleaning. Allow the skin to dry before injecting.



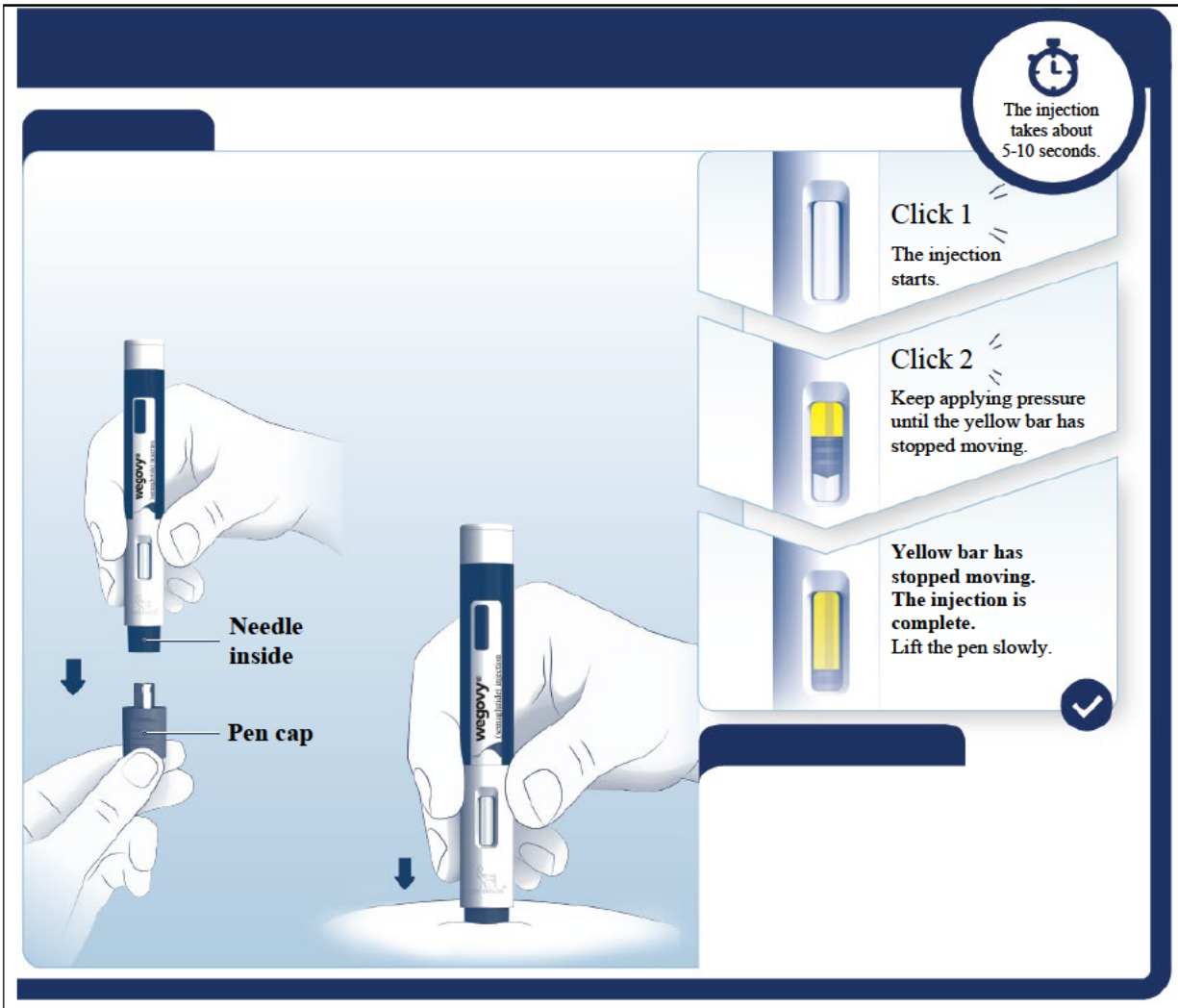
Injection

Step 3. Remove pen cap.

• Pull the pen cap straight off your pen.

Step 4. Inject WEGOVY.

- **Push the pen firmly against your skin and keep applying pressure until the yellow bar has stopped moving.**
  If the yellow bar does not start moving, press the pen more firmly against your skin.
- **You will hear 2 clicks during the injection.**
  - Click 1: the injection has started.
  - Click 2: the injection is ongoing.
- **If you have problems with the injection, refer to the "Troubleshooting" section.**



Throw away pen

Step 5. Throw away (dispose of) pen.

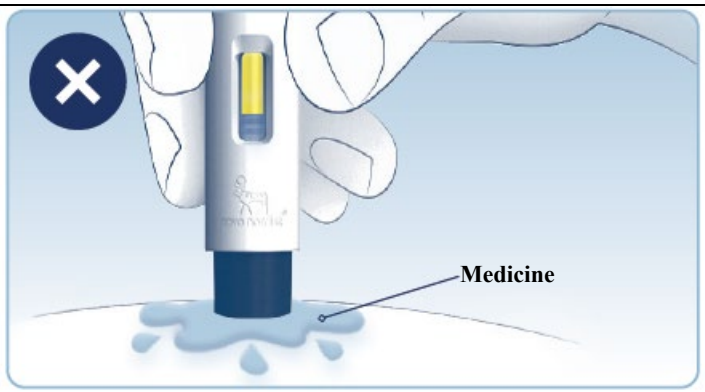
Safely dispose of the WEGOVY pen right away after each use. See **"How do I throw away (dispose of) WEGOVY pens?"**

• What if blood appears after injection?

If blood appears at the injection site, press the site lightly with a gauze pad or cotton ball.

Troubleshooting

- **If you have problems injecting, change to a more firm injection site, such as upper leg, or upper arm or consider standing up while injecting into the lower stomach.**
- **If medicine appears on the skin or squirts from the needle, make sure the next time you inject to keep applying pressure until the yellow bar has stopped moving. Then you can lift the pen slowly from your skin.**



How do I throw away (dispose of) WEGOVY pens?

Put the used WEGOVY pen in an FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of)** the pen in your household trash.

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- able to be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific sharps disposal in the state that you live in, go to the FDA's website at http://www.fda.gov/safesharpsdisposal.

- Do not reuse the pen.
- Do not recycle the pen or sharps disposal container, or throw them into household trash.

Important: Keep your WEGOVY pen, sharps disposal container and all medicines out of the reach of children.

How do I care for my pen?

Protect your pen

- Do not drop your pen or knock it against hard surfaces.
- Do not expose your pen to any liquids.
- If you think that your pen may be damaged, do not try to fix it. Use a new one.
- Keep the pen cap on until you are ready to inject. Your pen will no longer be sterile if you store an unused pen without the cap, if you pull the pen cap off and put it on again, or if the pen cap is missing. This could lead to an infection.

If you have any questions about WEGOVY, go to startWegovy.com or call Novo Nordisk Inc. at 1-833-Wegovy-1

Manufactured by:
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsvaerd, Denmark

For information about WEGOVY, go to startWegovy.com or contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
1-833-Wegovy-1

Version: 2

PATENT Information: http://novonordisk-us.com/products/product-patents.html

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: August 2022

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215256Orig1s011

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505b1 NDA Efficacy Supplement
Application Number	215256
Priority or Standard	Priority
Submit Date	September 8, 2023
Received Date	September 8, 2023
PDUFA Goal Date	March 8, 2024
Division/Office	DDLO/OCHEN
Reviewer Name	Julie Golden
Review Completion Date	March 7, 2024
Established/Proper Name	Semaglutide
Trade Name	Wegovy
Applicant	Novo Nordisk, Inc.
Dosage Form	Subcutaneous injection
Applicant Proposed Dosing Regimen	The maintenance dosage of WEGOVY in adults [after dose escalation] is either 2.4 mg (recommended) or 1.7 mg once-weekly. Consider treatment response and tolerability when selecting the maintenance dosage.
Applicant Proposed Indication/Population	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	WEGOVY is indicated in combination with a reduced calorie diet and increased physical activity to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight.

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Wegovy (semaglutide) is a glucagon-like peptide-1 (GLP-1) receptor agonist (RA) that is currently approved as a once-weekly subcutaneous (SC) injection as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of

- 30 kg/m^2 or greater (obesity), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition.

The maintenance dosing regimen is 2.4 mg (recommended) or 1.7 mg once weekly. To reduce the likelihood of gastrointestinal symptoms, a dose-escalation regimen is recommended, with a starting dose of 0.25 mg once weekly for 4 weeks and then dose increases every 4 weeks to 0.5, 1.0, 1.7, and 2.4 mg/week.

Semaglutide SC injection at doses up to 2 mg once weekly is currently approved in the US for treatment of type 2 diabetes (T2D) and for cardiovascular (CV) risk reduction in people with T2D and established cardiovascular disease (NDA 209637, Ozempic). Oral semaglutide is also approved in the US at daily doses up to 14 mg for treatment of T2D (NDA 213051, Rybelsus).

1.2. Conclusions on the Substantial Evidence of Effectiveness

This submission met the criteria for substantial evidence of effectiveness for cardiovascular (CV) risk reduction based on 1 adequate and well-controlled, large, multicenter CV outcomes trial with highly persuasive results on severe morbidity and mortality, considered to be the scientific equivalent of 2 clinical investigations. SELECT (trial ID: EX9536-4388) was a multinational, randomized, placebo-controlled trial to evaluate the effect of semaglutide on CV outcomes in 17604 subjects with either overweight or obesity and without T2D, and is the first trial to demonstrate that a drug for weight reduction is effective in reducing major adverse CV events (MACE) in this population.

Eligible subjects were randomized to semaglutide (8803 subjects) or placebo (8801 subjects); 96.9% of subjects completed the trial, and in 99.6%, vital status was available. A total of 1270 first MACE were confirmed by the external adjudication committee (EAC), corresponding to 6.5% of subjects and 2.0 events of MACE per 100 patient-years of observation (PYO) for semaglutide versus 8.0% of subjects and 2.5 events per 100 PYO for placebo. The hazard ratio (HR) (95% confidence interval (CI)) of time to first MACE was 0.80 (0.72, 0.90), $p<0.0001$. All

components of MACE trended in favor of semaglutide. Sensitivity analyses that accounted for missing data, various scenarios with COVID-19, and the potential for CV death misclassification, were all consistent with the primary endpoint.

Although the confirmatory secondary endpoint, CV death, did not meet statistical significance, the point estimate was favorable [HR 0.85 (0.71, 1.01)], and the all-cause mortality endpoint was nominally significant [HR 0.81 (0.71, 0.93)].

Endpoints such as weight, blood pressure, lipids, and glycemia were consistent with changes seen in phase 3 chronic weight management studies and support the cardiometabolic benefits of semaglutide.

The highly consistent phase 3 chronic weight management study data for weight and related cardiometabolic endpoints are considered supportive evidence. An additional compelling piece of data is the effect of semaglutide on MACE in patients with T2D. In the SUSTAIN 6 trial reviewed under NDA 209637,[1] Ozempic (semaglutide in T2D) reduced the risk of MACE [HR 0.74 (0.58, 0.95), nominal p-value = 0.017 for superiority] compared to standard of care. Further support is provided by numerical, but not statistically significant, reductions in risk of MACE with the orally administered version of semaglutide for T2D, Rybelsus, reviewed under NDA 213182 (PIONEER 6).

This review serves as the primary clinical review, Cross-Discipline Team Leader (CDTL) review, and the Decisional Memo. It summarizes the major issues related to approvability and labeling of the NDA. All review disciplines recommend approval. For additional details regarding methods and results, refer to the individual discipline reviews and consults reviews referenced in this document.

1.3. Benefit-Risk Assessment

See next page.

[1] See Dr. Andreea Ondina Lungu's review under NDA 209637, dated January 14, 2020. DARRTS Ref ID 4546095

Benefit-Risk Integrated Assessment

Obesity is a chronic, relapsing disease characterized by excess body fat, and caused by an interaction of genetic, environmental, and other factors. In adults, obesity and overweight are defined by body mass index (BMI), with cut-offs generally selected based on epidemiological data demonstrating a positive relationship to cardiovascular (CV) morbidity and mortality with increasing body weight. Between 2017 and March 2020, the prevalence of obesity (BMI ≥ 30 kg/m^2) in U.S. adults was 41.9% and the prevalence of severe obesity (BMI ≥ 40 kg/m^2) was 9.2%.

Although weight loss in patients with overweight and obesity improves CV risk factors such as hypertension, dyslipidemia, and hyperglycemia, and it has been assumed that such changes would confer a CV benefit over time, until the SELECT trial (trial ID EX9536-4388, the subject of this efficacy supplement), no weight loss drug had ever been demonstrated to reduce CV risk.

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that is currently approved in the U.S. as a subcutaneous injection at doses up to 2.4 mg weekly for chronic weight management in overweight and obesity, and as a subcutaneous injection at doses up to 2 mg weekly and as an oral tablet at doses up to 14 mg daily for the treatment of type 2 diabetes (T2D). In addition to the glycemic control indication, the subcutaneous injection product is also approved to reduce the risk of major adverse cardiovascular events in patients with T2D and established CV disease.

SELECT is the first trial to demonstrate that a drug used for weight reduction (semaglutide [Wegovy]) is effective in reducing major adverse CV events (MACE) in a population of subjects with obesity and overweight but without type 2 diabetes (T2D). The results of the SELECT trial meet the statutory requirement for substantial evidence of effectiveness for cardiovascular risk reduction in this population. This determination is based on a single adequate and well-controlled clinical trial, given the size of the trial and its clinically meaningful and statistically persuasive effect on MACE, as described in FDA guidance. Substantial evidence of effectiveness is further supported by favorable findings for each of the components of the composite primary endpoint, consistency in subgroups, similar results when evaluating for missing data in sensitivity analyses, and although not formally statistically significant per the prespecified plan to control the type 1 error rate, a reduction in all-cause mortality with good vital status collection. Furthermore, the highly consistent weight and related cardiometabolic endpoint results in SELECT compared with those in the chronic weight management trials in subjects with overweight and obesity, as well as similar effects of semaglutide on MACE in a population of patients with T2D strongly support the finding of CV benefit in this population.

The effect on the primary MACE endpoint appears consistent across important demographic and clinical subgroups, but there are some

uncertainties. The trial's racial diversity was not reflective of the U.S. population, and only 28% of the study population was female. However, strengths of the study are its size and duration. Despite many subjects starting and stopping drug or taking lower doses for reasons of tolerability, the result was robust and clinically meaningful.

In general, the safety profile of semaglutide as evaluated in SELECT is consistent with known safety issues with semaglutide in other clinical settings and trials. Systematically collected events included all serious adverse events (SAEs) as well as selected predefined categories of adverse events (AEs), regardless of seriousness (e.g., AEs leading to discontinuation, COVID-19 AEs). The most commonly reported SAEs were CV-related, although most CV events were less frequently reported in semaglutide-treated subjects than in placebo-treated subjects, consistent with the primary efficacy endpoint result.

Gastrointestinal (GI) disorders are common and well-described side effects of semaglutide and other GLP-1 RAs; in SELECT, GI SAEs were reported slightly more frequently in semaglutide- than placebo-treated subjects (3.9% vs. 3.7%, respectively). The most common SAEs in the GI disorders system organ class were due to abdominal wall hernias, with 65 semaglutide-treated subjects (0.7%) vs. 46 placebo-treated subjects (0.5%). Most events were inguinal hernias. Small imbalances were noted for diarrhea, gastrointestinal hemorrhage, vomiting, colitis, and gastroparesis. One event of significant aspiration pneumonia during a medical procedure appears to have likely been related to semaglutide-induced gastroparesis. [redacted] (b) (5)

A small numerical imbalance in psychiatric SAEs was noted (semaglutide 0.7% vs. placebo 0.6%) but is of unclear significance, as most of the events were distributed among terms. Depression SAEs and suicide and self-injury SAEs were similar between treatment groups. More subjects on semaglutide discontinued treatment because of psychiatric disorders, including mood disorders, sleep disorders, and anxiety disorders. The external adjudication committee (EAC) classified 5 deaths in semaglutide-treated subjects and 3 deaths in placebo-treated subjects as completed suicides. [redacted] (b) (5).

Serious hypoglycemia was reported rarely, and in association with other contributing factors, including history of bariatric surgery.

Other SAEs reported included syncope and certain fractures in women and elderly patients.

The proportion of subjects with AEs leading to discontinuation of trial product was higher with semaglutide than with placebo (16.6% vs 8.2%), primarily due to GI disorders (e.g., nausea, vomiting, diarrhea, constipation, dyspepsia, and gastroesophageal reflux disease), nervous system

disorders (e.g., dizziness and headache), and metabolism and general disorders (e.g., decreased appetite, weight decreased, asthenia, and fatigue).

In summary, the benefit-risk for semaglutide once-weekly for use in reduction of MACE in a population of individuals with overweight and obesity and established CV disease is favorable. The CV benefit is statistically significant and clinically meaningful and safety concerns can be adequately addressed through labeling.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Obesity and overweight impact millions of Americans. • Obesity is a chronic, relapsing disease that is difficult to treat. • Obesity increases the risk of adverse chronic health outcomes, including hypertension, dyslipidemia, type 2 diabetes (T2D), coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and some cancers. • Prior to this trial, the cardiovascular benefit of pharmacologically induced weight loss had not been clinically demonstrated.	Overweight and obesity are associated with increased cardiovascular (CV) risk. Weight loss of 5-10% in patients with overweight and obesity is generally accepted as beneficial on cardiometabolic health biomarkers. Patients with obesity and patients with overweight and CV risk factors are generally considered appropriate for drug treatment.
Current Treatment Options	• There is currently no FDA-approved treatment for CV risk reduction in a population of adults with overweight and obesity and without T2D	Semaglutide as a treatment for CV risk reduction in patients with obesity and overweight but without T2D addresses an unmet medical need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The hazard ratio (HR) (95% confidence interval (CI)) of time to first MACE for semaglutide vs. placebo was 0.80 (0.72, 0.90), p<0.0001. • All components of MACE trended in favor of semaglutide. • Although the confirmatory secondary endpoint, CV death, did not meet statistical significance, the point estimate was favorable [HR 0.85 (0.71, 1.01)], and the all-cause mortality endpoint was nominally significant [HR 0.81 (0.71, 0.93)]. • The heart failure (HF) endpoint was not statistically significant, although the composite was nominally significant. • Endpoints such as weight, blood pressure, lipids, and glycemia were consistent with changes seen in phase 3 chronic weight management studies and support the cardiometabolic benefits of semaglutide. • The CV benefit appears consistent across important demographic and clinical subgroups, but there are some uncertainties. The trial's racial diversity was not reflective of the U.S. population and only 28% of the study population was female.	SELECT demonstrated substantial evidence of effectiveness for reduction in the incidence of MACE in patients with overweight or obesity and CV disease. Strengths of the study are its size and duration. MACE results were consistent and robust across sensitivity analyses. (b) (4)
Risk and Risk Management	• In general, the safety profile of semaglutide as evaluated in SELECT is consistent with known safety issues with semaglutide in other clinical settings and trials. • GI SAEs were the most frequently reported with an unfavorable imbalance in the semaglutide arm vs. the placebo arm. • The proportion of subjects with AEs leading to discontinuation of trial product was higher with semaglutide than with placebo (16.6% vs 8.2%), primarily due to GI disorders (e.g., nausea, vomiting, diarrhea, constipation, dyspepsia, and gastroesophageal	Risks with semaglutide are acceptable given its demonstrated CV benefits. Risks can be addressed with labeling. (b) (5)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	reflux disease), nervous system disorders (e.g., dizziness and headache), and metabolism and general disorders (e.g., decreased appetite, weight decreased, asthenia, and fatigue). • GI disorders, gallbladder disorders, suicidal ideation and behaviors, hypoglycemia, syncope, and increased heart rate are currently addressed in labeling. • New safety items observed in SELECT included fractures in women and older patients, dysesthesia, and gastroparesis potentially increasing the risk of aspiration pneumonia with anesthesia.	

1.4. Patient Experience Data

Patient experience data were collected in the form of patient reported questionnaires as exploratory efficacy endpoints; see below.

Patient Experience Data Relevant to this Application

☒	The patient experience data that were submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	Sec 6.1.2 Study Results, Other Exploratory Efficacy Outcomes
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Obesity is a chronic, relapsing disease characterized by excess body fat. The pathophysiology of obesity involves the interaction of genetic, environmental, behavioral, and other factors. In adults, obesity and overweight are defined by body mass index (BMI), with cut-offs generally selected based on epidemiological data demonstrating a positive relationship to cardiovascular (CV) morbidity and mortality with increasing body weight.[2] As currently defined in the draft FDA guidance for developing drugs for chronic weight management, the population considered appropriate for treatment with a drug is typically defined as ≥ 30 kg/m^2 (obesity), or ≥ 27 kg/m^2 (overweight) with a weight-related comorbidity.[3]

Between 2017 and March 2020, the prevalence of obesity in U.S. adults was 41.9% and the prevalence of severe obesity (BMI ≥ 40 kg/m^2) was 9.2%.[4]

According to the 2013 American Heart Association / American College of Cardiology guidelines on the management of overweight and obesity, obesity raises the risk of morbidity from, and is also associated with increased risk of, all-cause and cardiovascular (CV) disease mortality.[5] Although some, but not all, observational studies suggest that modest degrees of intentional weight loss in individuals with overweight and obesity can reduce the incidence of some cancers, cardiovascular disease, and all-cause mortality, weight loss (at least at the magnitude seen in trials of most other weight management drugs) has not been established as a surrogate for CV benefit. For example, the Look AHEAD (Action for Health in Diabetes) trial[6] was a randomized controlled trial in over 5000 patients with T2D comparing an intensive lifestyle intervention (including weight loss) to standard-of-care for a follow-up of 10 years. The trial was stopped early (9.6 years) for futility of the composite primary outcome (first occurrence of CV death, non-fatal MI, non-fatal stroke, or hospitalized angina); HR 0.95 (95% CI 0.83, 1.09). In

[2] Jensen MD, et al. Executive summary: Guidelines (2013) for the management of overweight and obesity in adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Obesity 2014. 22(S2): S5-39.
[3] FDA Draft Guidance for Industry: Developing Products for Weight Management. February 2007.
[4] Stierman B, et al. National Health and Nutrition Examination Survey 2017–March 2020 prepandemic data files—Development of files and prevalence estimates for selected health outcomes. National Health Statistics Reports; no 158. Hyattsville, MD: National Center for Health Statistics. 2021 https://www.cdc.gov/obesity/data/adult.html. Accessed February 5, 2024.
[5] Jensen MD, et al. Executive summary: Guidelines (2013) for the management of overweight and obesity in adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Obesity 2014. 22(S2): S5-39.
[6] The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013; 369: 145-54.

Look AHEAD, weight loss was greater in the intervention group (8.6% at 1 year, 6.0% at study end) as compared to the control group (0.7% at 1 year, 3.5% at study end).

Although weight loss in patients with overweight and obesity improves CV risk factors such as hypertension, dyslipidemia, and hyperglycemia, and it has been assumed that such changes would confer a CV benefit over time, until the SELECT trial, no weight loss drug had ever been demonstrated to reduce CV risk.

2.2. Analysis of Current Treatment Options

Aside from semaglutide, as of this writing there are 5 other drugs approved in the U.S. for chronic weight management in the treatment of obesity: orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, and tirzepatide. However, there are no weight loss drugs that are currently approved to reduce the risk of CV events. In fact, weight loss drugs[7] that have been previously studied in completed CV outcomes trials have shown either neutral CV effects[8] or CV harm.[9]

Although semaglutide for T2D (Ozempic) has been approved to reduce the risk of major adverse CV events (CV death, non-fatal myocardial infarction or non-fatal stroke) in adults with T2D and established CV disease, a CV indication was not also included in the Wegovy label because the populations are considered distinct. (b) (4)

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Semaglutide (Wegovy, NDA 215256) was approved in the U.S. on June 4, 2021, for chronic weight management in adults with obesity. It was subsequently approved for adolescents on December 23, 2023. The maintenance dosage of Wegovy is 2.4 mg administered weekly as a SC injection. If patients do not tolerate the 2.4 mg dose, the maintenance dosage may be reduced to 1.7 mg once weekly.[11]

[7] Lorcaserin and sibutramine have both been withdrawn from the US market.
[8] Bohula EA, et al. Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients. N Engl J Med 2018; 379:1107-17.
[9] James WPT, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 2010; 363:905-17.

(b) (4)

Semaglutide is also marketed in the U.S. as Ozempic (NDA 209637) at doses of 0.5, 1, and 2 mg once weekly SC, and Rybelsus (NDA 213051) at doses of 7 and 14 mg once daily PO, for glycemic control in patients with T2D.

Ozempic also has an indication to reduce MACE in patients with T2D and established CV disease.

3.2. Summary of Presubmission/Submission Regulatory Activity

- A Type C meeting was held on March 12, 2018, to discuss the design of SELECT (IND 126360, meeting minutes dated April 10, 2018.[12]
    - FDA encouraged use of 3-point MACE as the primary endpoint, as expanded 5-point MACE can include more subjective endpoints (coronary revascularization) or those of questionable clinical significance (unstable angina).
    - The sponsor committed to follow all patients and collect all data points and noted that multiple attempts would be made to contact patients lost to follow-up. The sponsor stated their intent to collect vital status on all subjects who were lost to follow-up.
    - There was some discussion of other benefits of medication-assisted weight loss aside from those that are MACE-related. FDA considered the SELECT trial as an opportunity to better characterize the benefits and risks of long-term weight loss with semaglutide treatment. The applicant was encouraged to move heart failure events up in the testing hierarchy.
    - FDA agreed to the sponsor's proposal of safety data collection in the trial and that the sponsor could consider eliminating the C-SSRS and PHQ-9 questionnaires.

- On June 4, 2021, NDA 215256 (Wegovy for chronic weight management) was approved. The approval letter included the postmarketing requirement (PMR 4081-6):
    - *Complete the ongoing randomized, double-blind, parallel-group, placebo-controlled trial in approximately 17,500 patients with established CV disease and overweight or obesity (randomized 1:1 to semaglutide 2.4 mg and placebo) to evaluate the long-term effects of semaglutide 2.4 mg on pancreatitis, gallbladder disorders, renal safety, serious hepatic events, malignant neoplasms, serious hypoglycemia, and serious gastrointestinal disorders.*

- On February 4, 2022, Type C written responses were provided[13] regarding the submission of the SELECT trial and included discussion on the information that would be needed for the

[11] Approval of Wegovy 1.7 mg dose in NDA 215256 S-007
[12] DARRTS Reference ID: 4246542
[13] DARRTS Reference ID: 4932860

supplement. Some of the items raised include:

- FDA agreed that pooled safety data and Module 2 documents were not required; however, the clinical trial report (CTR) should include an assessment of benefit-risk, analyses of all endpoints (including exploratory), subgroup analyses for safety and efficacy, immunogenicity/allergy assessment, a dose assessment (including titration doses) for efficacy and safety, and an evaluation of safety in special groups and situations: intrinsic factors, extrinsic factors, drug interactions, pregnancy/lactation, and withdrawal/rebound.
- An analysis of suicidal ideation and behaviors using the SMQ 'Suicide/self-injury' was requested.

- The applicant's request for Fast Track Designation was denied on August 5, 2022.

- A teleconference between the applicant and the Division was held to present the topline results from the SELECT trial on August 17, 2023.

3.3. Foreign Regulatory Actions and Marketing History

According to the most recently submitted annual report, Wegovy has been approved in over 40 countries and has launched in 3 (the US, Denmark, and Norway). Ozempic has been approved in over 80 countries and launched in over 60; Rybelsus has been approved in over 60 countries and launched in over 40.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI conducted inspections of 3 clinical investigator (CI) sites and the contract research organization (CRO). Dr. Ling Yang noted in her review[14] that the data generated by these CI sites and the primary endpoint data adjudicated by the CRO are verifiable. The clinical trial appears to have been conducted adequately and the clinical data submitted by the sponsor appear acceptable in support of the new indication. See Dr. Yang's review for more details.

4.2. Product Quality

No new chemistry information was provided with this supplement.

[14] Yang L, Clinical Inspection Summary, dated January 31, 2024. DARRTS Reference ID: 5320463

4.3. Clinical Microbiology

No new microbiology information was provided with this supplement.

4.4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was provided with this supplement.

4.5. Clinical Pharmacology

No new clinical pharmacology information (i.e., exposure data) was provided with this supplement. See Section 6.1.2 for a discussion of dose-response from SELECT.

4.6. Statistics

Dr. Satyajit Ghosh from the Division of Biometrics II reviewed the statistical data supporting the efficacy claims from SELECT and the applicant's proposal to expand the indication of Wegovy (semaglutide) (b) (4) [15] This section discusses the analysis of the primary endpoints and analyses of secondary endpoints pertinent to labeling. For in-depth discussion of the trials and endpoints not immediately relevant to approval or labeling, and details of the statistical methods, refer to the FDA statistical review by Dr. Ghosh.

The efficacy of semaglutide to reduce the risk of MACE in adults with established cardiovascular disease and BMI ≥27 kg/m^2 was evaluated in 1 large, multinational, multicenter, randomized, double-blind, parallel group, placebo-controlled CV outcomes trial. The trial was event driven, and approximately 17,500 adults with established CV disease and obesity or overweight were randomized 1:1 to receive semaglutide once weekly or placebo as an adjunct to standard of care.

The primary endpoint of SELECT was a composite endpoint of time from randomization to first occurrence of 3-point MACE, defined as cardiovascular death, non-fatal MI, and non-fatal stroke. The primary estimand quantified the treatment effect in the intention-to-treat (ITT) population defined as all randomized subjects during the in-trial observation period. All time-to-event endpoints were analyzed using a Cox proportional hazards model with treatment group as fixed factor and an assumption of independent censoring, with the exception of non-CV death (competing risk). Type 1 error was controlled at 0.05 across all primary and key secondary endpoints using sequential testing hierarchy. Missing values were handled using retrieved dropouts.

[15] Ghosh S, statistical review dated February 15, 2024; DARRTS Ref ID 5329857

Secondary endpoints included time to first occurrence of CV death; composite of heart failure (HF) hospitalization, urgent HF visit, or CV death; all-cause death; fatal or non-fatal MI; and fatal or non-fatal stroke.

Dr. Ghosh confirmed the results, including the primary MACE endpoint, prespecified key secondary endpoints, sensitivity analyses, and subgroup analyses. The superiority of semaglutide compared to placebo was established in this trial with a hazard ratio and 95% confidence interval of 0.80 (0.72, 0.90) for the primary endpoint. Results for the individual components of the primary composite endpoint were consistent. Missing data was minimal (3%), and multiple prespecified sensitivity analyses were consistent with the primary analysis. Refer to the FDA statistical review for additional details.

Superiority of semaglutide over placebo was not confirmed for the confirmatory secondary endpoint time to CV death. Based on the prespecified testing order, superiority of semaglutide versus placebo could not be considered statistically significant for the secondary endpoints of time to first composite HF outcome or time to all-cause death, although both achieved nominal statistical significance (one-sided $p < 0.025$).

No major statistical issues were identified in this review. Dr. Ghosh and the statistical team recommend approval of semaglutide to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in the proposed population based on the results of SELECT. The randomized, double-blind, placebo-controlled design allowed Dr. Ghosh to distinguish the treatment effect of semaglutide on CV risk from other influences and provided a quantitative estimate of the treatment effect of the drug. For details of the statistical methods and analyses, refer to the FDA statistical review.

4.7. Devices and Companion Diagnostic Issues

No new information about the device was provided with this supplement.

4.8. Consumer Study Reviews

No consumer studies were conducted with this supplement.

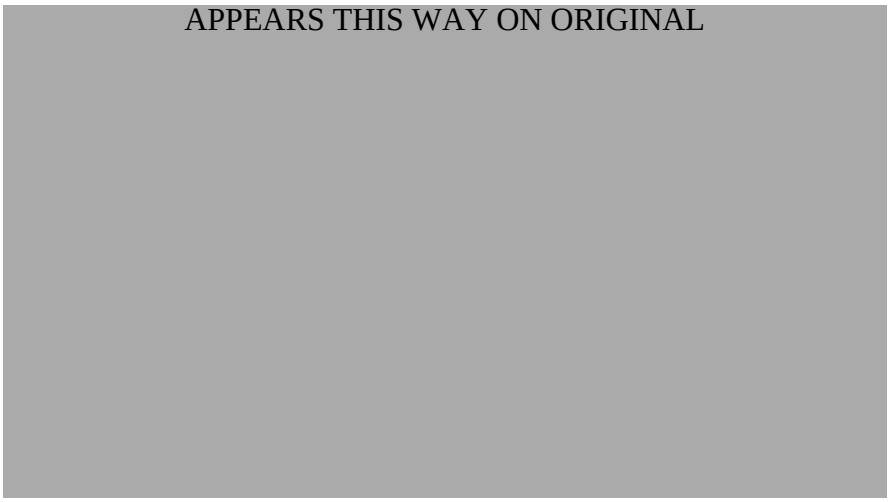
5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Not applicable. Only 1 clinical trial was reviewed in this supplement: EX9536-4388 ("SELECT"; NCT03574597).

5.2. Review Strategy

This efficacy supplement included the results from a single clinical trial: SELECT. I reviewed the relevant clinical efficacy and safety data with input from other disciplines as needed.



6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. SELECT

6.1.1. Study Design

Overview and Objective

The primary objective of the SELECT trial was to demonstrate that semaglutide 2.4 mg (Wegovy) SC once-weekly lowers the incidence of major adverse cardiovascular events (MACE) versus placebo when both are added to standard-of-care in subjects with established CV disease and overweight or obesity.

Trial Design

SELECT was a randomized, double-blind, placebo-controlled, multinational CV outcomes trial comparing semaglutide 2.4 mg (Wegovy) SC weekly to placebo in a 1:1 randomization in subjects with established CV disease and overweight or obesity (BMI ≥ 27 kg/m^2).

The trial was event driven, with trial closure being performed when the targeted number of primary endpoint events was reached. With the assumed event rate (see below) and a recruitment period of 28 months, the trial duration was estimated to be 59 months from start of randomization to end of follow-up (5 weeks) for the last subject. The trial duration for an individual subject was estimated to be from 31 to 59 months. Trial period completion was defined as when the randomized subject had completed the final scheduled visit or when the randomized subject died during the trial.

The trial was designed to have 90% overall power to confirm superiority of the primary endpoint. The assumed true hazard ratio (HR) of 0.83 at a 1-sided significance level of 2.5% was based on a conservative assessment of the observed point estimate for the HR in the SUSTAIN 6 trial,[16] which was 0.74 (95% CI 0.58, 0.95) for a similar definition of MACE.

The annualized rate of subjects with a first MACE was estimated to be 2.0% (i.e., semaglutide 1.8% and placebo 2.2%). With a sample size of 17500 subjects randomized 1:1, the planned 1225 first MACE events were therefore estimated to be accrued at month 59 (~5 years).

[16] Ozempic (semaglutide) prescribing information

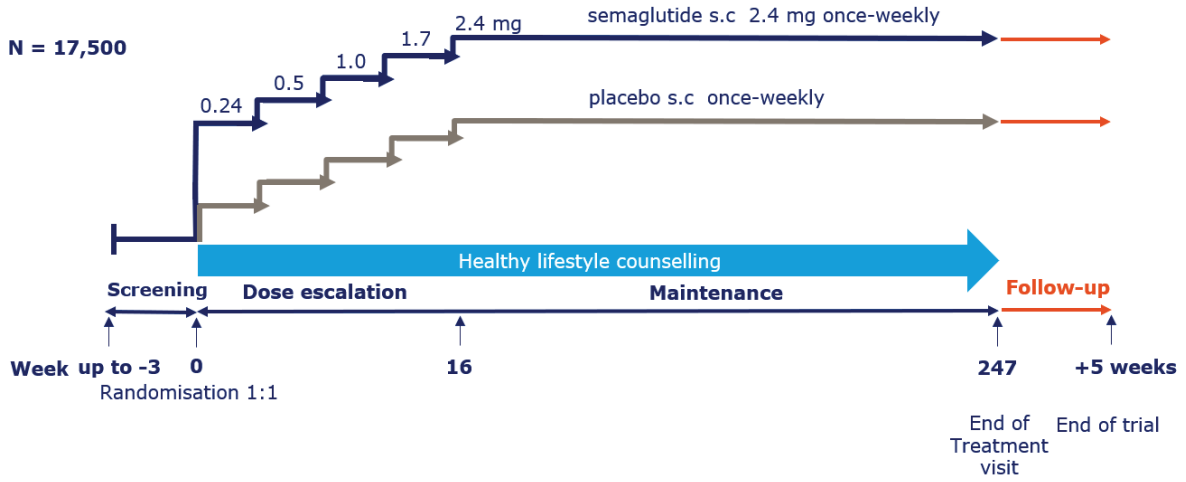
Table 1. Planned Number of Subjects and Timelines for SELECT

Randomisation scheme	Total number of subjects to be randomised	Number of subjects with an event	Duration of recruitment period	Duration of trial	Time from LPFV to LPLV	Mean observation time
1:1	17,500	≥1,225	28 months (2 year and 4 months)	59 months (4 years and 11 months)	31 months (2 years and 7 months)	44 months (3 years and 8 months)

Source: SELECT protocol, Table 10-3

The trial schematic below illustrates the study design, including the 16-week dose-escalation period, consistent with dose-escalation described in Wegovy product labeling. The recommended target dose was 2.4 mg, the maintenance dose studied in the phase 3 program at the time of SELECT study design. All subjects were to aim to reach the recommended target dose of 2.4 mg semaglutide once weekly or the corresponding volume of placebo. If a subject did not tolerate the recommended target dose of 2.4 mg once-weekly, the subject could stay at a lower dose level, preferably 1.7 mg once-weekly, but efforts were to be made to minimize these instances. Note that Wegovy was initially approved at a recommended maintenance dose of 2.4 mg SC once weekly; a subsequent NDA efficacy supplement[11] allowed for a 1.7 mg maintenance dose in product labeling if needed for tolerability.

Figure 1. Trial Design

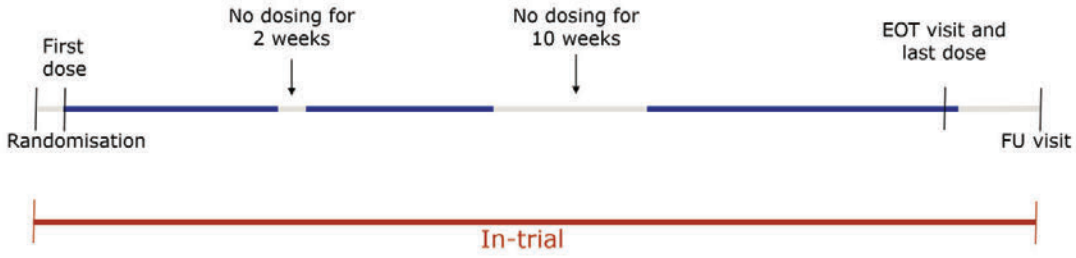


Source: SELECT protocol, Figure 5-1

Analysis Observation Periods

The in-trial observation period covered the time from randomization to the last day of the trial, regardless of treatment adherence. Figure 2 provides an example:

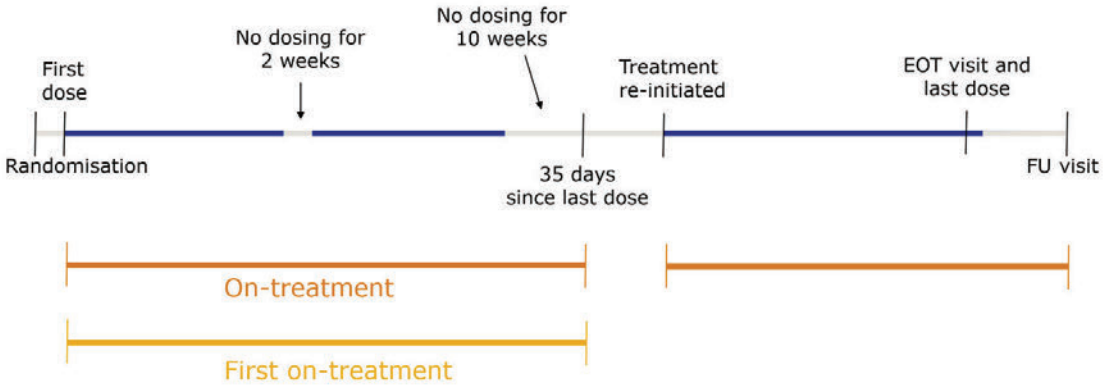
Figure 2. In-Trial Observation Period Example



Source: SELECT CTR, Figure 9-3

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 in-between if treatment had been paused for more than 35 consecutive days. The first on-treatment observation period was defined as the on-treatment observation period until first time being off treatment for more than 35 days. Thus, it was the first of the time intervals (if more than 1) in the on-treatment observation period. See Figure 3 for an example on on-treatment observation period and first on-treatment observation period.

Figure 3. On-Treatment and First On-Treatment Observation Period Examples



Source: SELECT CTR, Figure 9-4

Eligibility Criteria

Key inclusion criteria were as follows: male or female aged ≥ 45 years, BMI ≥ 27 kg/m^2, and

established CV disease (prior myocardial infarction, prior ischemic or hemorrhagic stroke, and/or symptomatic peripheral arterial disease).

Key exclusion criteria were as follows: CV event within 60 days, NYHA class IV heart failure, history of type 1 or type 2 diabetes mellitus, HbA1c ≥ 6.5%, glucose-lowering agent or GLP-1 RA within 90 days, history of chronic pancreatitis, acute pancreatitis within 180 days, personal or first-degree relatives with MEN type 2 or MTC, end-stage renal disease, malignant neoplasms within 5 years, or severe psychiatric disorder.

Study Endpoints

The primary endpoint was the time from randomization to first occurrence of a component of a composite endpoint consisting of CV death, non-fatal myocardial infarction, or non-fatal stroke (i.e., 3-point MACE).

Full endpoint definitions were included in the EAC charter and were based on standardized definitions such as the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials;[17] see the appendix of this review in Section 13.1 for additional references. Definitions of the components of the composite are summarized as follows:

- Myocardial infarction: in general, the diagnosis of MI requires the combination of:
    - Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings);
      And
    - Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

- Stroke: defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Persistence of symptoms is an acceptable indicator of acute infarction. In the absence of brain imaging studies, new neurological symptoms lasting ≥ 24 hours should be considered a stroke event.

- Cardiovascular death: includes death resulting from an acute myocardial infarction (MI),[18]

[17] Hicks KA, et al. 2017 Cardiovascular and stroke endpoint definitions for clinical trials. Circulation. 2018; 137: 961-72.
[18] Death by any CV mechanism (e.g., arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days after a MI, related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia

sudden cardiac death,[19] death due to heart failure (HF),[20] death due to stroke,[21] death due to cardiovascular (CV) procedures,[22] death due to CV hemorrhage,[23] and death due to other CV causes.[24]

The primary composite endpoint is considered clinically meaningful and less subject to "noise" from additional endpoints, such as revascularization or unstable angina, for which reporting can be subjective and treatment can vary by geographic location. The applicant was encouraged to evaluate a 3-point MACE endpoint during early design discussions. For example, in the Type C meeting minutes from the guidance meeting held March 12, 2018, "FDA noted that evaluation of expanded five-point MACE will not add much clinically useful information beyond analysis of primary three-point MACE. … Also, FDA reminded the sponsor that a failure to demonstrate an effect on three-point MACE would be a problem, regardless of other data collected."

Confirmatory secondary endpoints were tested in a hierarchical fashion to control type I error as time from randomization to CV death; first occurrence of a composite heart failure endpoint consisting of heart failure hospitalization, urgent heart failure, or CV death; and all-cause death.

Supportive secondary endpoints were time from randomization to first occurrence of:

- An expanded composite CV endpoint consisting of: CV death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or unstable angina requiring hospitalization
- A composite endpoint consisting of: all-cause death, non-fatal myocardial infarction, or nonfatal stroke
- Non-fatal myocardial infarction
- Non-fatal stroke
- Coronary revascularization
- Unstable angina requiring hospitalization
- Heart failure hospitalization or urgent heart failure visit
- HbA1c ≥ 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 (randomization), onset of persistent eGFR < 15 ml/min/1.73m^2, initiation of chronic

[19] Death that occurs unexpectedly and not within 30 days of an acute MI
[20] Death in association with clinically worsening symptoms and/or signs of HF regardless of HF etiology
[21] Death after a stroke that is either a direct consequence of the stroke or a complication of the stroke
[22] Death caused by the immediate complications of a cardiac procedure
[23] Death related to hemorrhage such as a non-stroke intracranial hemorrhage (e.g., subdural hematoma), non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade
[24] CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease)

renal replacement therapy (dialysis or transplantation), or renal death[25]

Additional supportive secondary endpoints included:

- For subjects with a screening HbA1c < 5.7%, time from randomization to HbA1c ≥ 5.7%
- For subjects with a screening HbA1c ≥ 5.7%, proportion of subjects with HbA1c < 5.7% at each visit where HbA1c is assessed
- Change from randomization to year 2 in:
    - Systolic blood pressure
    - Diastolic blood pressure
    - Pulse
    - hsCRP
    - Lipids (total cholesterol, HDL-C, LDL-C, TG)
    - Percent body weight
    - Waist circumference
    - Patient reported outcomes: EuroQol Five Dimensions Five Level (EQ-5D-5L) questionnaire (EQ-5D index score and EQ-5D-VAS)
    - HbA1c

Exploratory endpoints included:

- Being a current smoker at year 2
- Total number of hospitalized days to end of trial
- Total number of hospitalizations to end of trial
- Change from randomization to week 117 in glycemic status (normoglycemia, pre-diabetes, or T2D)
- Change from randomization to year 2 in patient reported outcomes of total score Weight Related Sign and Symptom Measure (WRSSM)

Not all results are presented in this review.

Statistical Analysis Plan

Reviewers from the Division of Biometrics II reviewed the SAP and amendments; the most recent review in DARRTS is dated June 23, 2022. The SAP was considered generally acceptable. Dr. Satyajit Ghosh is the statistical reviewer for this sNDA; a summary of the statistical conclusions is in Section 4.6. Please refer to Dr. Ghosh's review for more details.[15]

[25] This component consists of events from central laboratory and outcome from event adjudication. UACR: urinary albumin-to-creatinine ratio. A persistent change in estimated glomerular filtration rate (eGFR) is defined as having 2 consecutive samples meeting the criteria. The 2 samples must be at least 4 weeks apart. A persistent change in macroalbuminuria is defined as having 2 out of 3 consecutive post-baseline samples above the limit for macroalbuminuria. The 2 samples above the limit must be at least 4 weeks apart.

Of note, the trial design included 1 pre-planned interim testing for superiority of the primary endpoint when 817 events (two-thirds of the planned total events) of the primary endpoint were accrued. The DMC was to evaluate the unblinded interim result and make a recommendation to terminate the trial early for superiority if appropriate, using the sequential stopping boundary as guidance (specified in the DMC charter). The Data Access Management Plan outlined the personnel with access to these data to maintain trial integrity.

A prespecified 2-way tipping-point analysis based on the approach described in Zhao et al.[26] was performed to evaluate the potential impact of missing data for the 543 subjects (semaglutide: 259; placebo: 284) who had withdrawn consent or were lost-to-follow-up (LTFU).

Two additional prespecified sensitivity analyses were performed by imputing event times for subjects who withdrew or were LTFU. If the imputed event time occurred after the subject's planned end-of-trial time the subject was censored at the planned end-of-trial time:

- One analysis used an estimated annual event rate from subjects who discontinued treatment permanently but remained in the trial. The imputations were done by treatment group.

- The other analysis avoided conditioning on the future by using an estimated annual event rate for subjects who discontinued treatment at any point in the trial. The imputations were done by treatment group.

Protocol Amendments

The following amendments were considered substantial and impacted all or most countries:

- Amendment 4 dated March 7, 2019: addressed inclusion of interim testing for superiority

- Amendment 8 dated January 4, 2021: addressed changes to allow for simultaneous participation in the SELECT trial and COVID-19 trials and expansion of the AE collection to include the reporting of non-serious COVID-19 events

- Amendment 9 dated February 9, 2022: heart failure composite endpoint moved from supportive secondary endpoints to confirmatory secondary endpoints

6.1.2. Study Results

[26] Zhao Y, Herring AH, Zhou H, Ali MW, Koch GG. A multiple imputation method for sensitivity analyses of time-to-event data with possibly informative censoring. J Biopharm Stat. 2014;24(2):229-53.

Compliance with Good Clinical Practices

The applicant attested that this trial was conducted in accordance with the principles of the Declaration of Helsinki, ICH GCP, and FDA 21 CFR 312.50 and 312.56.

Financial Disclosure

The total number of investigators with reportable financial disclosures or certification of due diligence was small out of the total number of investigators in the trial (69/4714, 1.5%). See the Financial Disclosure form in the appendix of this review, Section 13.2, for further information.

Patient Disposition and Baseline Characteristics

A total of 21089 subjects were screened for this trial, of which 3480 (16.5% of all screened) were screening failures. The most frequent cause of a screening failure was HbA1c ≥ 6.5% (49.5% of screening failures); the subject had a disorder, unwillingness or inability, which in the investigator's opinion, that might jeopardize the subject's safety or compliance with the protocol (13.9% of screening failures); or the subject did not have established CV disease (6.4% of screening failures). In addition, 10.2% of screening failures did not return for randomization and 11.0% of screening failures withdrew their consent prior to randomization.

All unique randomized subjects were to be analyzed according to the treatment they were assigned at randomization. This was referred to as the full analysis set (FAS). If a subject was randomized more than once, only the subject ID and treatment corresponding to the first randomization was included in the FAS, and the additional subject ID was excluded from the FAS. The list of excluded subject IDs is as follows:

Table 2. Subject IDs Excluded from FAS

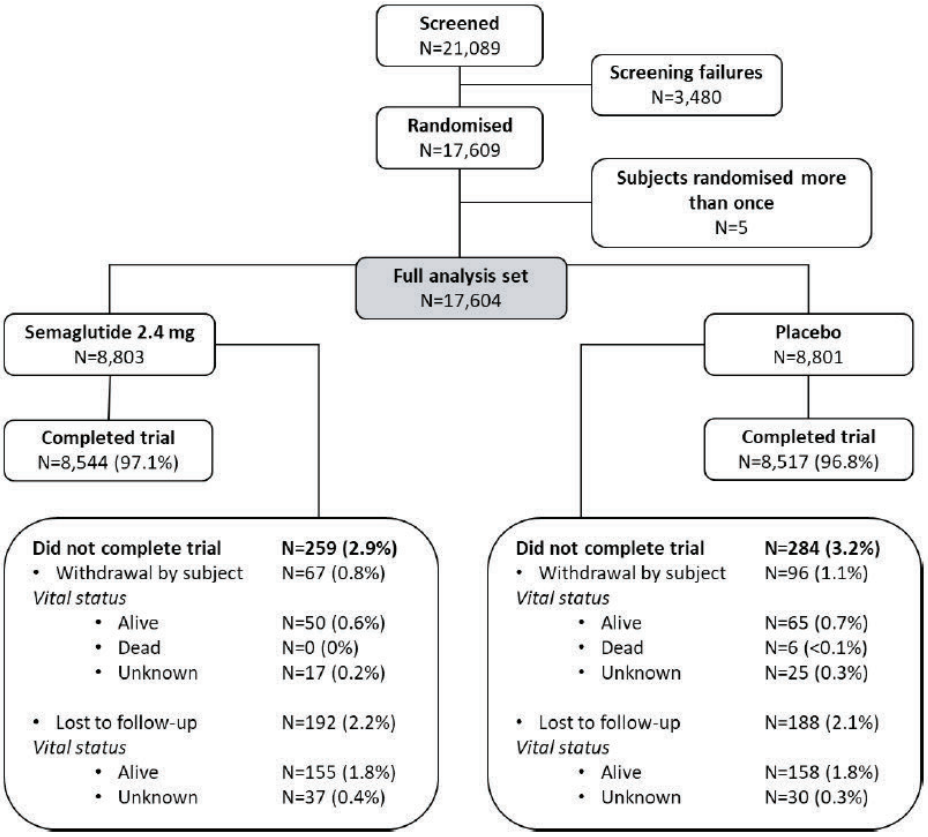
Subject ID	Country	Site	Randomized treatment	Reason for exclusion in FAS
(b) (6)	Brazil	2144	Placebo	Subject was randomized as (b) (6) (placebo)
	South Africa	3125	Semaglutide	Subject was randomized as (b) (6) (placebo)
	United States	3480	Semaglutide	Subject was randomized as (b) (6) (semaglutide)
	United States	3556	Placebo	Subject was randomized as (b) (6) (semaglutide)
	United States	3598	Placebo	Subject was randomized as (b) (6) (placebo)

Source: SELECT CTR, Table 16.2.3.1

The disposition of trial subjects is illustrated in Figure 4. Vital status was known for 99.4% of subjects in both groups. A total of 97.1% of subjects randomized to semaglutide and 96.8% of

subjects randomized to placebo completed the trial. A trial completer was defined as a subject who either attended the end-of-trial follow-up visit or who died while active in the trial.

Figure 4. Subject Disposition



Source: SELECT CTR, Figure 10-1

A total of 17604 subjects were randomized to semaglutide (N=8803) or placebo (N=8801) and included in the FAS. The overall median time in-trial was 41.8 months (3.48 years), and overall median on-treatment time was 38.2 months (3.18 years).

As shown in Figure 2 in the section on analysis observation periods above (i.e., schematic of the 'in-trial' period), there could be a gap in time between randomization and first dose. The applicant was asked to clarify how events (efficacy or safety) that occurred in this gap were addressed in the primary 'in-trial' analysis. The applicant noted that it was possible for the subject to start the weekly study drug dose on a later day than the randomization day, so that the preferred weekday for weekly injection was chosen.

A total of 1284 (7.3%) subjects started first study dose on a later day than the randomization

day, and the majority (N=1187) started first dose less than 7 days after randomization. According to the applicant, no MACE events occurred between randomization and start of first study dose. A total of 4 SAEs occurred between randomization and start of first study dose. All 4 SAEs (cardiac failure, peripheral arterial occlusive disease, peripheral artery stenosis, and vascular stent stenosis) were reported in the semaglutide group.

Reviewer comment: The applicant concluded that these events do not have an impact on trial conclusions, and I agree.

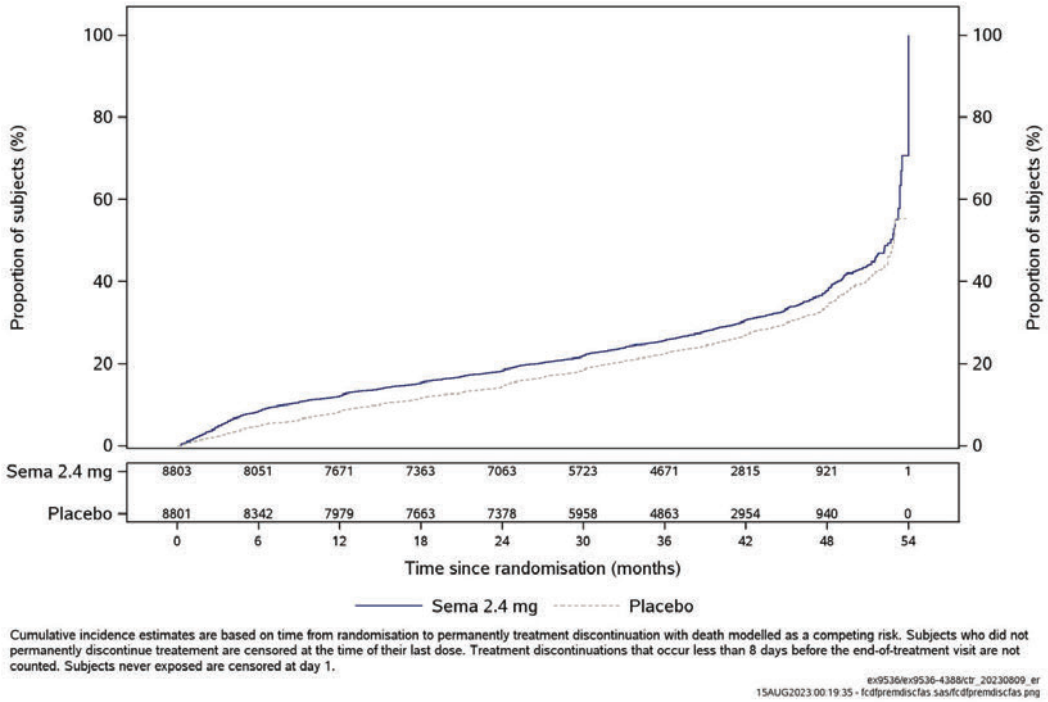
A total of 2694 (30.6%) of semaglutide- and 2375 (27.0%) of placebo-treated subjects discontinued treatment. The primary reasons for trial product discontinuation are listed in Table 3 below, and time to permanent discontinuation is plotted in Figure 5. Discontinuations were gradual over time throughout the trial and were slightly higher for semaglutide vs. placebo subjects. Discontinuations due to adverse events (AEs) are discussed further in Section 8.4.3.

Table 3. Disposition, Trial Product Discontinued

	Semaglutide N=8803	**Placebo N=8801**
Trial product permanently discontinued	2654 (30.6)	2375 (27.0)
Primary reason		
Adverse event	1434 (16.3)	696 (7.9)
Unintentional treatment discontinuation[a]	252 (2.9)	327 (3.7)
Currently no contact with the subject	71 (0.8)	101 (1.1)
Lack of effect	64 (0.7)	244 (2.8)
COVID-19 pandemic	39 (0.4)	43 (0.5)
Simultaneous use of prohibited medication	5 (<0.1)	29 (0.3)
Participation in another clinical trial anytime during the trial	3 (<0.1)	4 (<0.1)
Other	511 (5.8)	647 (7.4)
Missing	306 (3.5)	265 (3.0)
a As described in eCRF form "Trial Product Dosage Change," reasons for "Unintentional treatment discontinuation" may be: *Subject is admitted to hospital or other health care facility; Subject is temporarily out of the area; Subject moved too far away; Subject is unable to maintain trial treatment for socio-economic reasons*		

Source: SELECT CTR, Table 14.1.1

Figure 5. Proportion of Subjects Over Time Who Have Permanently Discontinued



Source: SELECT CTR, Figure 14.1.10

At randomization, mean age was 61.6 years with 38.2% at least 65 years and 7.8% at least 75 years old. A total of 72.3% were male, 10% were of Hispanic or Latino ethnicity, 84% of subjects were White, 8.2% were Asian, and 3.8% were Black or African American. A total of 20.7% of subjects were from the United States.

Reviewer comment: Ethnic and racial minorities that make up larger proportions of the U.S. population are not well-represented in this trial. This is a study limitation.

Demographic characteristics are summarized below and were generally well-balanced between groups.

Table 4. Demographic Characteristics (Selected)

	Semaglutide N=8803	**Placebo N=8801**
Age, mean (SD), years	61.6 (8.9)	61.6 (8.8)
Age group, n (%)		
< 55	2057 (23.4)	2094 (23.8)
55 to < 65	3387 (38.5)	3338 (37.9)

65 to < 75	2656 (30.2)	2706 (30.7)
75 to < 85	680 (7.7)	638 (7.2)
≥ 85	23 (0.3)	25 (0.3)
Sex, n (%)		
Female	2448 (27.8)	2424 (27.5)
Male	6355 (72.2)	6377 (72.5)
Region, n (%)		
Asia	1100 (12.5)	1101 (12.5)
Europe	3326 (37.8)	3366 (38.2)
North America	2200 (25.0)	2201 (25.0)
United States	1821 (20.7)	1831 (20.8)
Other	2177 (24.7)	2133 (24.2)
Race, n (%)		
American Indian or Alaska Native	23 (0.3)	21 (0.2)
Asian	720 (8.2)	727 (8.3)
Black or African American	348 (4.0)	323 (3.7)
Native Hawaiian or Other Pacific Islander	3 (<0.1)	5 (<0.1)
White	7387 (83.9)	7404 (84.1)
Other	227 (2.6)	247 (2.8)
Not Reported	95 (1.1)	74 (0.8)
Ethnicity, n (%)		
Hispanic or Latino	914 (10.4)	908 (10.3)
Not Hispanic or Latino	7794 (88.5)	7817 (88.8)
Not Reported	95 (1.1)	76 (0.9)

Source: SELECT CTR, Tables 10-2 and 14.1.14

Regarding other baseline characteristics, mean BMI was 33 kg/m^2, mean body weight was 96.7 kg, and mean HbA1c was 5.8%. The majority of subjects had hypertension (81.8%) and were treated with statins (87.6%) (see Table 9 further below for more details on concomitant medications at randomization). Baseline cardiovascular and metabolic parameters were generally well-balanced between groups.

Table 5. Baseline Characteristics (Selected)

	Semaglutide N=8803	**Placebo N=8801**
BMI, mean (SD), kg/m^2	33.30 (5.03)	33.37 (5.04)
BMI group, n (%)		
< 30	2555 (29.0)	2469 (28.1)
30 to < 40	5380 (61.1)	5440 (61.8)
≥ 40	868 (9.9)	892 (10.1)

CV inclusion criteria, n (%)		
Myocardial infarction	6729 (76.4)	6709 (76.2)
Stroke	2058 (23.4)	2052 (23.3)
Symptomatic peripheral artery disease	754 (8.6)	771 (8.8)
HbA1c, mean (SD), %	5.78 (0.34)	5.78 (0.33)
HbA1c groups, n (%)		
< 5.7%	2925 (33.2)	2980 (33.9)
≥ 5.7%	5877 (66.8)	5819 (66.1)
Glycemic status, n (%)		
Prediabetes	5701 (64.8)	5661 (64.3)
Normoglycemia	3101 (35.2)	3139 (35.7)
Systolic blood pressure, mean (SD), mmHg	131.0 (15.6)	130.9 (15.3)
Lipids, mean (SD), mg/dL		
Total cholesterol	155.5 (25.8)	156.0 (25.4)
LDL-C	78.5 (43.7)	78.5 (43.6)
HDL-C	44.1 (25.5)	44.2 (25.0)
Triglycerides	138.6 (51.8)	139.5 (50.8)
Chronic kidney disease, n (%)	991 (11.3)	975 (11.1)
eGFR, mean (SD), mL/min/1.73m^2	82.44 (17.48)	82.48 (17.32)
Waist circumference, mean (SD), cm	111.3 (13.1)	111.4 (13.1)
Chronic heart failure, n (%)	2155 (24.5)	2131 (24.2)
NYHA class		
NYHA class I	715 (8.1)	656 (7.5)
NYHA class II	1277 (14.5)	1263 (14.4)
NYHA class III	156 (1.8)	208 (2.4)
Type		
HFpEF	1174 (13.3)	1099 (12.9)
HFrEF	654 (7.4)	693 (7.9)
Unknown	326 (3.7)	337 (3.8)

Source: SELECT CTR, Tables 14.1.14, 14.1.15, 14.1.24, 14.2.154, 14.2.159, 14.2.164, and 14.2.169

In a search of past medical history, 87 participants randomized to semaglutide, and 97 subjects randomized to placebo, had a history of bariatric surgery.[27]

[27] Preferred terms: Gastric bypass, Gastric banding, Sleeve gastrectomy, Gastrectomy, Metabolic surgery, Gastroplasty, Bariatric gastric balloon insertion, and Gastric stapling.

Protocol Violations/Deviations

Protocol deviations (PDs) were categorized as important or non-important. Important PDs were deviations that could significantly impact the completeness, accuracy and/or reliability of the trial data or that could significantly affect the subject's rights, safety, or well-being. The sponsor concludes that these important PDs were overall not considered to have an impact on trial conduct, subject safety, or data interpretation. I do not have significant concerns, as it appears that corrective action was taken to address PDs as they were discovered, and they did not appear to have affected the conduct of the trial in a systematic way.

SELECT reported 3 important trial-level PDs, 4 important country-level PDs, 853 important site-level PDs, and 2188 important subject-level PDs.

The 3 trial-level PDs were as follows; all were addressed adequately:

- Study procedures/assessments (confirmatory secondary endpoints): The PD concerned potentially missing heart failure (HF) and unstable angina pectoris (UAP) endpoints in the final data, due to the process of how the data was reported. To be captured for adjudication, each HF hospitalization, urgent HF visit, and hospitalization for UAP were to be reported as separate AEs, and sites were to report subsequent hospitalizations/urgent visits as part of the initially reported AE, if that AE was ongoing at the time. The potential events were reviewed by Safety Operations Advisers for potential unreported HF, urgent visits/hospitalizations, and hospitalizations for UAP. Events identified as meeting criteria for adjudication that had not been reported to the adjudication committee were all provided to the EAC for review and adjudication.

- Study procedures/assessments (safety focus assessment): It was discovered that eGFR calculations were not always performed by the laboratory when creatinine is measured (was supposed to occur); 916 missing values were found. This was completed retroactively by the laboratory. None of the eGFRs had a value < 15 mL/min/1.73m^2 or 50% reduction from baseline.

- Privacy and data protection (other): A total of 68 site users across different countries had been given read/write access to the electronic data capture system (EDC) for up to 3 other sites in addition to their own site. A total of 7 sites were involved with the unintended associations: 2116 (Belgium), 2464 (Greece), 2707 and 2709 (Japan), 2773 and 2779 (Latvia), and 2800 (Malaysia). Site 2779 did not have any subjects recorded in EDC at this point. None of the users with unintended access to the sites in Japan logged into EDC during the incident A total of 39 users did not log in with the sites to which they were granted unintended access. A total of 28 users logged in while associated with an unintended site. It is not possible to track viewed data; however, the audit trail confirms that no data was

entered or modified by these users. One user from site 2112 logged in and performed data entry for subject (b) (6) at site 2116 (both sites in Belgium). The affected user apparently realized the mistake instantly and immediately deleted the data, to the extent possible. Data that could not be deleted was subsequently corrected by site 2116. The incident was immediately escalated to the EDC supplier' the supplier terminated the incorrect access and took corrective action. The Novo Nordisk Data Protection Office (DPO) concluded that that the subjects are unlikely to have been identified during this incident and due to the confidentiality obligations of health care professionals, it is also unlikely that the incidence had any consequences for the subjects.

The 4 country-level PDs were as follows; all were addressed adequately:

- Informed consent (Argentina): Monitors remotely accessed individual subjects' source data during the COVID-19 pandemic without subject consent. Upon discovery, the local guidance for remote data access was updated as per global guidance to include the requirement for subjects to be informed of, and agree to (written or verbal), remote access of data.

- Study procedures/assessments (Greece): Country-specific additional laboratory assessments and full AE reporting [Protocol, Appendix 9] were not being performed as required because the local protocol and ICF had been incorrectly translated. Upon discovery, the local protocol and ICF were corrected and approved by the relevant national regulatory authority and central ethics committee. Site staff were trained in the correct procedure for safety reporting. Missing laboratory samples were collected from subjects at the next visit.

- AE and other safety procedures (Mexico): Investigators were not notified of SUSARs in a timely fashion according to regulatory requirements and Novo Nordisk policy. Upon discovery, the pending SUSAR reports were sent to investigators and a process was implemented to ensure subsequent safety reports were handled in a timely manner.

- Privacy and data protection (Mexico): The PD concerned a platform that was created as a virtual room to share educational information with subjects. It was detected that Novo Nordisk personnel and the vendor as administrators could access subjects' personal information (email and date of birth) in the platform. In total 98 subjects had been registered on the platform. Upon discovery, access to the platform was restricted.

Site- and subject-level PDs are outlined in Table 6 and Table 7.

Overall, 10.6% of subjects reported important PDs, evenly distributed between treatment groups. Most PDs were related to deviations in adverse event (AE) and other safety procedures (3.9%) and treatment administration (3.2%).

Table 6. Site- and Subject-Level Important Protocol Deviations

Protocol deviation category subcategory	Site level N (%)	Subject level N (%)	Total PDs N (%)
Informed consent	164 (100)	298 (100)	462 (100)
Study activities before IC signed	6 (3.7)	22 (7.4)	28 (6.1)
Wrong version of IC signed	18 (11.0)	29 (9.7)	47 (10.2)
Missing/late reconsent of IC	97 (59.1)	117 (39.3)	214 (46.3)
Otherwise incorrect IC process	12 (7.3)	48 (16.1)	60 (13.0)
Other	31 (18.9)	82 (27.5)	113 (24.5)
Inclusion/exclusion criteria	3 (100)	116 (100)	119 (100)
Eligibility criteria violated	3 (100)	101 (87.1)	104 (87.4)
Discontinuation/withdrawal criteria violated	0	10 (8.6)	10 (8.4)
Other deviations from eligibility process	0	2 (1.7)	2 (1.7)
Other	0	3 (2.6)	3 (2.5)
Treatment administration	291 (100)	607 (100)	898 (100)
Wrong dun or expired trial product	243 (83.5)	411 (67.7)	654 (72.8)
Treatment non-compliance	27 (9.3)	159 (26.2)	186 (20.7)
Other	21 (7.2)	37 (6.1)	58 (6.5)
Study procedures/assessments	266 (100)	119 (100)	385 (100)
Confirmatory secondary endpoint(s)	6 (2.3)	0	6 (1.6)
Documentation/delegation of tasks	98 (36.8)	46 (38.7)	144 (37.4)
Safety focus assessment	5 (1.9)	11 (9.2)	16 (4.2)
Other assessments	25 (9.4)	18 (15.1)	43 (11.2)
Trial product handling	4 (1.5)	3 (2.5)	7 (1.8)
Other deviations to study procedures	14 (5.3)	6 (5.0)	20 (5.2)
Other	114 (42.9)	35 (29.4)	149 (38.7)
AE and other safety procedures	53 (100)	773 (100)	826 (100)
SAE and other AEs requiring addition reporting	36 (67.9)	678 (87.7)	714 (86.4)
Safety procedures related to adverse events	11 (20.8)	53 (6.9)	64 (7.7)
Technical complaint reporting	0	1 (0.1)	1 (0.1)
Other	6 (11.3)	41 (5.3)	47 (5.7)
Concomitant medication/medical intervention	5 (100)	126 (100)	131 (100)
Medication/medical intervention disallowed	5 (100)	124 (98.4)	129 (98.5)
Disallowed dose/change of dose	0	2 (1.6)	2 (1.5)
Subject visit schedule	3 (100)	22 (100)	25 (100)
Other	3 (100)	22 (100)	25 (100)
Privacy and data protection	67 (100)	125 (100)	192 (100)
Fraud/misconduct	1 (1.5)	0	1 (0.5)
Participant privacy/data protection	32 (47.8)	100 (80.0)	132 (68.8)
Other	34 (50.7)	25 (20.0)	59 (30.7)
Participant contact schedule	1 (100)	2 (100)	3 (100)
Contact scheduled out of window	1 (100)	2 (100)	3 (100)
Other	0	0	0

%: percentage of total number of PDs within category, N: number of PDs within category and subcategory.
DUN: dispensing unit number, excl: exclusion, IC: informed consent, incl: inclusion, Not allocated: PDs for screening failures and subjects not allocated to treatment, PD: protocol deviation, rand: randomization, SAE: serious adverse event.

Source: SELECT CTR, Table 10-15

Table 7. Subject-Level Important Protocol Deviations

Protocol deviation category subcategory	Sema 2.4 mg N (%)	Placebo N (%)	Not allocated N (%)	Total N (%)
Informed consent	143 (100)	135 (100)	20 (100)	298 (100)
Study activities before IC signed	8 (5.6)	8 (5.9)	6 (30.0)	22 (7.4)
Wrong version of IC signed	9 (6.3)	18 (13.3)	2 (10.0)	29 (9.7)
Missing/late reconsent of IC	68 (47.6)	48 (35.6)	1 (5.0)	117 (39.3)
Otherwise incorrect IC process	20 (14.0)	27 (20.0)	1 (5.0)	48 (16.1)
Other	38 (26.6)	34 (25.2)	10 (50.0)	82 (27.5)
Inclusion/exclusion criteria	56 (100)	60 (100)	0	116 (100)
Eligibility criteria violated	53 (94.6)	48 (80.0)	0	101 (87.1)
Discontinuation/withdrawal criteria violated	3 (5.4)	7 (11.7)	0	10 (8.6)
Other deviations from eligibility process	0	2 (3.3)	0	2 (1.7)
Other	0	3 (5.0)	0	3 (2.6)
Treatment administration	350 (100)	257 (100)	0	607 (100)
Wrong dun or expired trial product	242 (69.1)	169 (65.8)	0	411 (67.7)
Treatment non-compliance	82 (23.4)	77 (30.0)	0	159 (26.2)
Other	26 (7.4)	11 (4.3)	0	37 (6.1)
Study procedures/assessments	49 (100)	67 (100)	3 (100)	119 (100)
Confirmatory secondary endpoint(s)	0	0	0	0
Documentation/delegation of tasks	17 (34.7)	28 (41.8)	1 (33.3)	46 (38.7)
Safety focus assessment	4 (8.2)	7 (10.4)	0	11 (9.2)
Other assessments	9 (18.4)	9 (13.4)	0	18 (15.1)
Trial product handling	0	3 (4.5)	0	3 (2.5)
Other deviations to study procedures	3 (6.1)	3 (4.5)	0	6 (5.0)
Other	16 (32.7)	17 (25.4)	2 (66.7)	35 (29.4)
AE and other safety procedures	352 (100)	420 (100)	1 (100)	773 (100)
SAE and other AEs requiring additional reporting	311 (88.4)	367 (87.4)	0	678 (87.7)
Safety procedures related to AEs	25 (7.1)	28 (6.7)	0	53 (6.9)
Technical complaint reporting	0	1 (0.2)	0	1 (0.1)
Other	16 (4.5)	24 (5.7)	1 (100)	41 (5.3)
Concomitant medication/medical intervention	32 (100)	94 (100)	0	126 (100)
Medication/medical intervention disallowed	31 (96.9)	93 (98.9)	0	124 (98.4)
Disallowed dose/change of dose	1 (3.1)	1 (1.1)	0	2 (1.6)
Subject visit schedule	7 (100)	15 (100)	0	22 (100)
Other	7 (100)	15 (100)	0	22 (100)
Privacy and data protection	60 (100)	64 (100)	1 (100)	125 (100)
Fraud/misconduct	0	0	0	0
Participant privacy/data protection	47 (78.3)	53 (82.8)	0	100 (80.0)
Other	13 (21.7)	11 (17.2)	1 (100)	25 (20.0)
Participant contact schedule	0	2 (100)	0	2 (100)
Contact scheduled out of window	0	2 (100)	0	2 (100)
Other	0	0	0	0

%: percentage of total number of PDs within category, N: number of PDs within category and subcategory.
DUN: dispensing unit number, excl: exclusion, IC: informed consent, incl: inclusion, Not allocated: PDs for screening failures and subjects not allocated to treatment, PD: protocol deviation, rand: randomization, SAE: serious adverse event.

Source: SELECT CTR, Table 10-16

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Subjects were on-treatment an average of 82.5% of the planned on-treatment period in the semaglutide group and 87.7% in the placebo group. 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 in both treatment groups (range 0.0 to 53.6 months), with a mean no-dosing duration of 7.9 months in the semaglutide group and 5.6 months in the placebo group.

Table 8 below shows that overall, 60.5% of subjects did not have any treatment discontinuation periods, although this proportion was lower for the semaglutide group (56.6%) than the placebo group (64.4%).

The most frequent reason for no dosing in both groups was 'AE': semaglutide, n = 2600 (29.5% of 8803 subjects); placebo, n = 1299 (14.8% of 8801 subjects). In this subgroup of subjects who reported an AE as a reason for discontinuation, the mean no-dosing duration was 16.5 months for semaglutide and 12.2 months for placebo.

Table 8. On-Treatment and No-Dosing Periods

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

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

Source: SELECT CTR, Table 10-14

Concomitant Medication

At randomization, the use of concomitant medications and their types were well-balanced. Approximately 92% were receiving CV medication, primarily beta-blockers, ACE inhibitors, or angiotensin receptor blockers. Approximately 90% were on lipid-lowering medication, primarily statins. Approximately 86% of subjects were receiving platelet aggregation inhibitors, mainly acetylsalicylic acid. Approximately 34% of subjects were receiving diuretics.

Table 9. Concomitant CV-Related Medication Ongoing at Randomization

	Semaglutide N=8803	**Placebo N=8801**
Cardiovascular medications	8122 (92.3)	8074 (91.7)
Beta blockers	6182 (70.2)	6175 (70.2)
ACE inhibitors	3963 (45.0)	3966 (45.1)
Angiotensin receptor blockers	2618 (29.7)	2569 (29.2)
Calcium channel blockers	2407 (27.3)	2331 (26.5)
Lipid-lowering drugs	7928 (90.1)	7929 (90.1)
Statins	7716 (87.7)	7709 (87.6)
Ezetimibe	1188 (13.5)	1144 (13.0)
Fibrates	213 (2.4)	266 (2.0)
PCSK9 inhibitors	177 (2.0)	162 (1.8)
Platelet aggregation inhibitors	7612 (86.5)	7569 (86.0)
Acetylsalicylic acid	6909 (78.5)	6860 (77.9)
P2Y12 inhibitors	2925 (33.2)	2998 (34.1)
Diuretics	2922 (33.2)	2978 (33.8)
Loop diuretics	1075 (12.2)	1134 (12.9)
Thiazides	1020 (11.6)	1007 (11.4)
Aldosterone antagonists	893 (10.1)	927 (10.5)
Anti-angina agents	1707 (19.4)	1770 (20.1)
Antithrombotic medication	1086 (12.3)	1150 (13.1)
Direct oral anticoagulant	738 (8.4)	784 (8.9)
Vitamin K antagonists	336 (3.8)	340 (3.9)
Antiarrhythmic agents	266 (3.0)	329 (3.7)

Source: SELECT CTR, Table 10-7

The only information that was captured regarding concomitant medication change during the SELECT trial was for the treatment or prevention of CV diseases, treatment of overweight or obesity, treatment of diabetes and its complications (for those who developed diabetes during

the trial), treatment of an SAE (or as an alternative etiology for the cause of an SAE), and in relation to COVID-19 prevention or treatment.

Initiation of a medication after randomization could be due to adding a new medication or switching from 1 product to another which was perceived as a change in medication by the investigator.

The most frequently reported concomitant medication initiated after randomization was 'COVID-19 vaccines,' received by 60.4% of subjects overall with similar proportions between treatment groups.

The proportion of subjects initiating any CV-related medication after randomization was slightly lower with semaglutide than with placebo, consistent with fewer CV events in the semaglutide arm. As many of these CV medications have proven CV benefit themselves, this provides some reassurance that the observed treatment effect is likely not confounded in favor of semaglutide by concomitant medication.

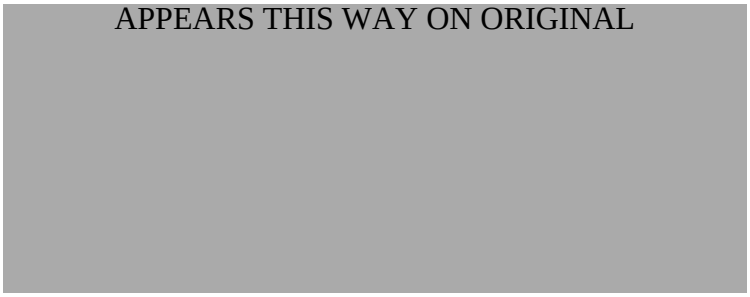


Table 10. Cardiovascular Medication Initiated During the Trial

	Sema 2.4 mg N (%)	Placebo N (%)
Number of subjects	8803	8801
Cardiovascular medications	2735 (31.1)	2963 (33.7)
Beta blockers	1307 (14.8)	1312 (14.9)
ACE inhibitors	834 (9.5)	904 (10.3)
Angiotensin receptor blockers	886 (10.1)	1021 (11.6)
Calcium channel blockers	924 (10.5)	1132 (12.9)
Angiotensin Receptor-Neprilysin Inhibitor (ARNI)	151 (1.7)	195 (2.2)
Lipid lowering drugs	2046 (23.2)	2475 (28.1)
Statins	1493 (17.0)	1778 (20.2)
Bile acid sequestrants	10 (0.1)	6 (<.1)
Fibrates	87 (1.0)	136 (1.5)
Ezetimibe	724 (8.2)	983 (11.2)
PCSK-9 inhibitors	148 (1.7)	195 (2.2)
Eicosapentaenoic acid ethyl ester	17 (0.2)	41 (0.5)
Bempedoic acid	21 (0.2)	39 (0.4)
Omega-3-acid ethyl ester	2 (<.1)	11 (0.1)
Other omega 3-triglycerides	16 (0.2)	18 (0.2)
Diuretics	1139 (12.9)	1585 (18.0)
Thiazides	332 (3.8)	443 (5.0)
Loop diuretics	539 (6.1)	789 (9.0)
Aldosterone antagonists	392 (4.5)	495 (5.6)
Other potassium sparring diuretics	11 (0.1)	12 (0.1)
Thiazide-like diuretics	192 (2.2)	284 (3.2)
Platelet aggregation inhibitors	1172 (13.3)	1296 (14.7)
Acetylsalicylic acid	557 (6.3)	620 (7.0)
P2Y12 inhibitors	764 (8.7)	875 (9.9)
Other	52 (0.6)	62 (0.7)
Anti-Thrombotic medications	1114 (12.7)	1204 (13.7)
Vitamin K antagonists	89 (1.0)	108 (1.2)
DOAC	564 (6.4)	616 (7.0)
Heparin	656 (7.5)	702 (8.0)
Anti-arrhythmic agents	344 (3.9)	366 (4.2)
Anti-angina agents	735 (8.3)	783 (8.9)

Source: SELECT CTR, Table 10-8

Concomitant weight management medications were infrequently initiated in the trial, and by fewer participants in the semaglutide arm than the placebo arm (Table 11). Despite GLP-1 RAs not being permitted in the trial, a total of 157 subjects received GLP-1RAs; a subset of these specifically for an indication of 'antiobesity' (semaglutide and liraglutide, Table 11). Overall, there was a higher incidence of initiation of drugs prescribed for weight management to subjects in the placebo arm compared to the semaglutide arm.

Table 11. Weight Management Medication Initiated in the Trial

	Sema 2.4 mg N	Sema 2.4 mg (%)	Placebo N	Placebo (%)
Number of subjects	8803		8801	
Other Antiobesity Drugs, A08AX	34	(0.4)	118	(1.3)
Semaglutide	28	(0.3)	92	(1.0)
Liraglutide	6	(<.1)	27	(0.3)
Angelica Acutiloba Root;atractylodes Spp. Rhizome;calcium Sulfate;ephedra Spp. Herb;forsythia Spp. Fruit;gardenia Jasminoides Fruit;glycyrrhiza Spp. Root;ligusticum Officinale Rhizome;mentha Canadensi	0		6	(<.1)
Cellulose Microcrystalline;citric Acid	2	(<.1)	0	
Centrally Acting Antiobesity Products, A08AA	8	(<.1)	33	(0.4)
Bupropion;naltrexone	4	(<.1)	19	(0.2)
Phentermine;topiramate	4	(<.1)	3	(<.1)
Phentermine	0		7	(<.1)
Lorcaserin	1	(<.1)	4	(<.1)
Bupropion Hydrochloride;naltrexone Hydrochloride	0		2	(<.1)
Peripherally Acting Antiobesity Products, A08AB	1	(<.1)	10	(0.1)
Orlistat	1	(<.1)	10	(0.1)
Herbal Antiobesity Preparations, A08AW	0		1	(<.1)
Garcinia Gummi-Gutta	0		1	(<.1)
Fucus Vesiculosus Powder	0		1	(<.1)

Source: SELECT CTR, Table 14.1.34

Glucose-lowering medications (except GLP-1 RA) could be initiated during the trial if the subject developed diabetes. Initiation of glucose-lowering medication after baseline was lower in the semaglutide group than the placebo group. The most frequently used glucose-lowering medications after baseline were biguanides/metformin (semaglutide 1.2% and placebo 5.7%). As noted previously, some subjects did receive GLP-1 RAs despite being prohibited according to the protocol.

Table 12. Glucose-Lowering Medication Initiated in the Trial

	Sema 2.4 mg N (%)	Placebo N (%)
Number of subjects	8803	8801
Biguanides/Metformin	110 (1.2)	504 (5.7)
Sulfonylureas	4 (<.1)	31 (0.4)
SGLT2 inhibitors	213 (2.4)	332 (3.8)
Thiazolidinediones	1 (<.1)	3 (<.1)
Alpha glucosidase inhibitors	0	1 (<.1)
DPP-4 inhibitors	6 (<.1)	23 (0.3)
GLP-1 receptor agonists [1]	30 (0.3)	100 (1.1)
Insulins	39 (0.4)	69 (0.8)
Other	2 (<.1)	8 (<.1)

Source: SELECT CTR, Table 14.1.25

Finally, new treatment with selected gastrointestinal and psychiatric medications was explored,[28] although this assessment is limited in that only such medications that were used in association with an SAE were to be collected. Neither the indication for the drug nor the reason it was reported was provided. There was a slightly higher number of semaglutide- vs. placebo-treated subjects who initiated any type of gastrointestinal medication. For psychiatric medications, there was slightly lower numerical incidence of hypnotics and sedatives, psychostimulants, and antidementia drugs, but slightly higher numerical incidence of antipsychotics, anxiolytics, and antidepressants in the semaglutide- vs. placebo-treated subjects.

[28] ATC level 2: antidiarrheals, intestinal anti-inflammatory/antiinfective agents, antiemetics and antinauseants, drugs for acid related disorders, drugs for constipation, drugs for functional gastrointestinal disorders; psychoanaleptics and psycholeptics

Table 13. Selected Gastrointestinal and Psychiatric Medications Initiated After Randomization

	Semaglutide N=8803	Placebo N=8801
Drugs for acid related disorders	434 (4.9)	406 (4.6)
Antiemetics and antinauseants	172 (2.0)	170 (1.9)
Drugs for constipation	93 (1.1)	84 (1.0)
Drugs for functional gastrointestinal disorders	54 (0.6)	35 (0.4)
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	52 (0.6)	35 (0.4)
Hypnotics and sedatives	58 (0.7)	66 (0.7)
Antipsychotics	39 (0.4)	24 (0.3)
Anxiolytics	37 (0.4)	32 (0.4)
Psychostimulants, agents used for ADHD and nootropics	32 (0.4)	43 (0.5)
Antidepressants	28 (0.3)	26 (0.3)
Anti-dementia drugs	5 (0.1)	16 (0.2)

Source: Reviewer created from ADCM.xpt dataset

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the time to first external adjudication committee (EAC)-confirmed major adverse cardiovascular (CV) event (MACE), consisting of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke. A total of 1270 first MACE with onset during the in-trial period were confirmed by the EAC.

The primary analysis result of time to *first EAC-confirmed MACE* for the SELECT trial is as follows (semaglutide vs. placebo):[29]

Estimated hazard ratio (HR): 0.80 (95% CI 0.72, 0.90), p < 0.0001

Table 14 enumerates the proportions of the primary MACE endpoint and its components, as well as event rates by 100 patient-years of observation (PYO).

Table 14. Primary Endpoint: First EAC-Confirmed MACE, In-Trial

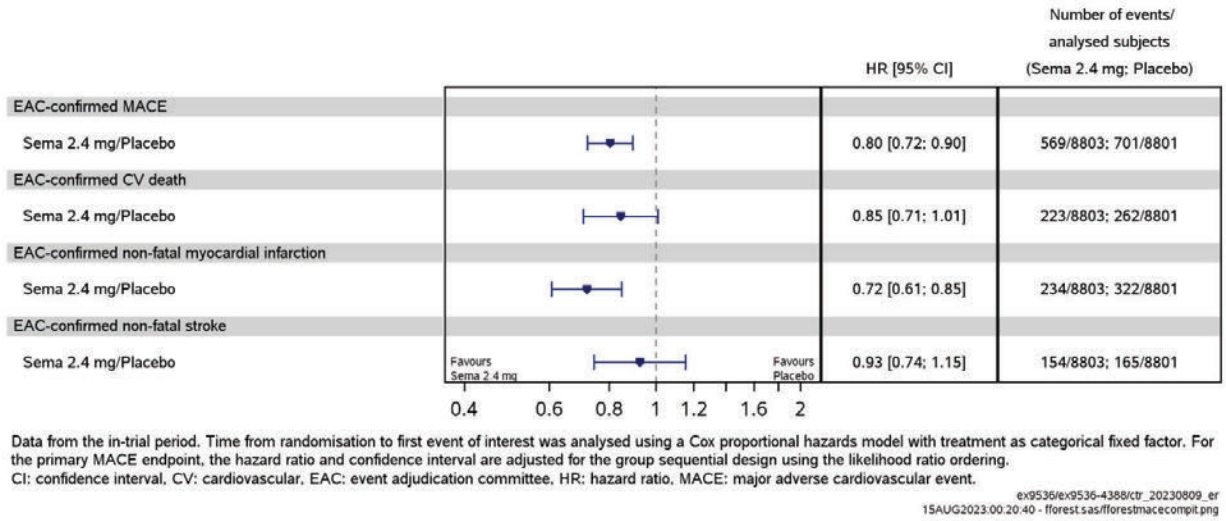
	Semaglutide N=8803		**Placebo N=8801**	
	n (%)	Events/100 PYO	n (%)	Events/100 PYO
MACE	569 (6.5)	2.0	701 (8.0)	2.5
CV death	191 (2.2)	0.7	221 (2.5)	0.8
Acute myocardial infarction, non-fatal	230 (2.6)	0.8	321 (3.6)	1.1
Stroke, non-fatal	148 (1.7)	0.5	159 (1.8)	0.6

Source: SELECT CTR, Table 11-3

A summary of the primary first MACE endpoint and its components is presented in the following forest plot (Figure 6); the individual components are discussed in more detail further below.

[29] Time from randomization to first EAC-confirmed MACE was analyzed using a Cox proportional hazards model with treatment as categorical fixed factor. Subjects without events of interest were censored at the end of their in-trial 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. Adjustment for group sequential design was done using likelihood ratio ordering.

Figure 6. Time from Randomization to First EAC-Confirmed MACE and Components



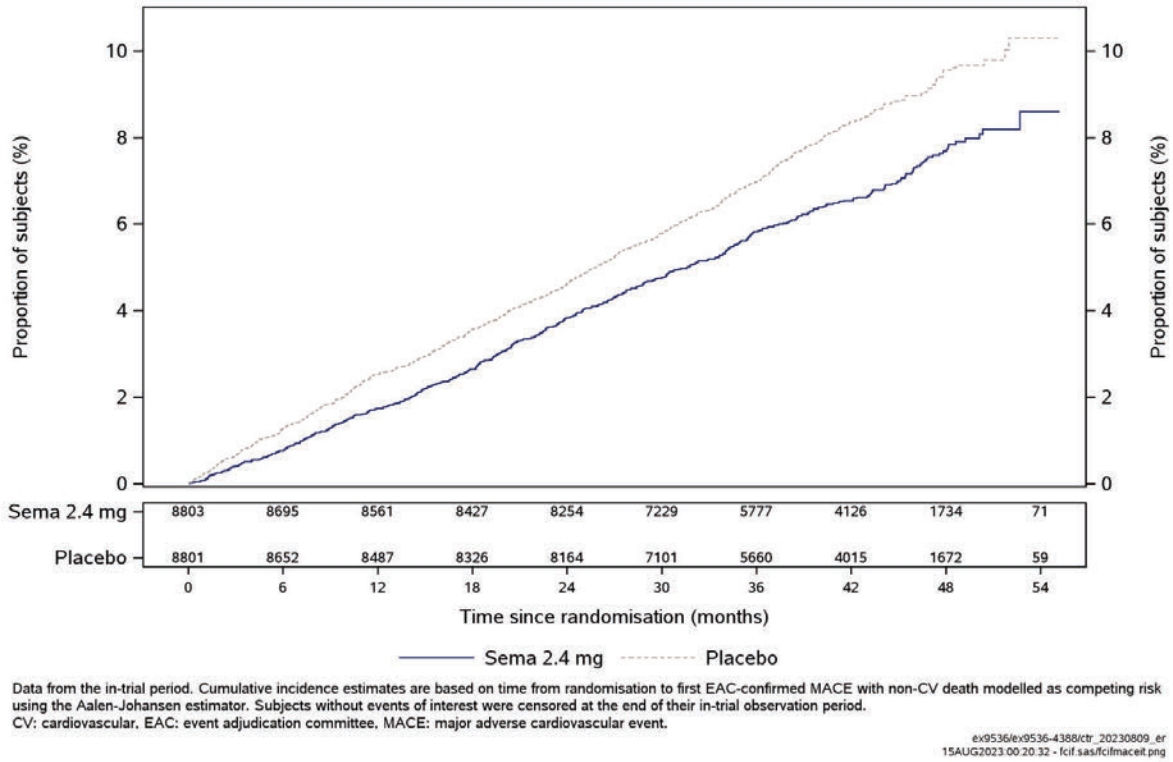
Source: SELECT CTR, Figure 14.2.84

At week 156, the cumulative incidence estimate for first EAC-confirmed MACE was 485/8803 (5.8%) semaglutide-treated subjects and 582/8801 (7.0%) placebo-treated subjects, resulting in an absolute risk difference of -0.011 (95% CI -0.019, -0.004), p=0.0029, and a number needed to treat (NNT) of 88.[30]

Figure 7 illustrates the incidence of MACE over time; notably, the curve separation between treatment arms occurs shortly after trial initiation and continues over time.

[30] SELECT CTR, Table 14.2.12. The estimate of the absolute risk difference is calculated as the difference between the cumulative incidence estimates for each treatment group at week 156. The estimate of the number needed to treat is calculated as 1/(cumulative incidence estimate for placebo minus cumulative incidence estimate for semaglutide). The 156-week timepoint was pre-specified in the SAP for this supplementary analysis.

Figure 7. Time from Randomization to First EAC-Confirmed MACE, In-Trial, Cumulative Incidence Plot



Source: SELECT CTR, Figure 14.2.4

All components of the composite were numerically in favor of semaglutide. The most common events comprising the primary endpoint of first EAC-confirmed MACE – as well as all EAC-confirmed MACE – were non-fatal non-ST elevation myocardial infarction (NSTEMI), non-fatal ischemic stroke, and sudden cardiac death.

Table 15. EAC-Confirmed First MACE, Components

	Semaglutide N=8803	**Placebo N=8801**
First EAC-confirmed MACE	569 (6.5)	701 (8.0)
Acute myocardial infarction, non-fatal	230 (2.6)	321 (3.6)
STEMI	41 (0.5)	52 (0.6)
NSTEMI	138 (1.6)	192 (2.2)
Cannot be determined	51 (0.6)	77 (0.9)
Stroke, non-fatal	148 (1.7)	159 (1.8)
Ischemic	136 (1.5)	141 (1.6)

Hemorrhagic	9 (0.1)	14 (0.2)
Undetermined	3 (<0.1)	4 (<0.1)
Cardiovascular and undetermined cause of death	191 (2.2)	221 (2.5)
Cardiovascular death	128 (1.5)	141 (1.6)
Acute myocardial infarction	12 (0.1)	12 (0.1)
Heart failure	11 (0.1)	12 (0.1)
Sudden cardiac death	90 (1.0)	95 (1.1)
Stroke	9 (0.1)	15 (0.2)
Cardiovascular procedure	2 (<0.1)	2 (<0.1)
Cardiovascular hemorrhage	1 (<0.1)	0
Other	3 (<0.1)	5 (<0.1)
Undetermined cause of death	63 (0.7)	80 (0.9)

Source: SELECT CTR, Table 14.2.2

All MACE (not just first)

Consistent with the primary endpoint of *first* EAC-confirmed MACE, an analysis of *all* MACE demonstrated that MACE occurred at a lower rate with semaglutide (2.2 events per 100 PYO) than with placebo (2.8 events per 100 PYO). All components trended favorably.

Table 16. EAC-Confirmed MACE, All Events

	Semaglutide N=8803	**Placebo N=8801**
All EAC-confirmed MACE	569 (6.5)	701 (8.0)
Acute myocardial infarction, non-fatal	234 (2.7)	322 (3.7)
STEMI	44 (0.5)	54 (0.6)
NSTEMI	142 (1.6)	199 (2.3)
Cannot be determined	55 (0.6)	83 (0.9)
Stroke, non-fatal	154 (1.7)	165 (1.9)
Ischemic	141 (1.6)	148 (1.7)
Hemorrhagic	10 (0.1)	14 (0.2)
Undetermined	3 (<0.1)	4 (<0.1)
Cardiovascular and undetermined cause of death	223 (2.5)	262 (3.0)
Cardiovascular death	146 (1.7)	172 (2.0)
Acute myocardial infarction	12 (0.1)	15 (0.2)
Heart failure	14 (0.2)	16 (0.2)
Sudden cardiac death	98 (1.1)	109 (1.2)
Stroke	15 (0.2)	21 (0.2)
Cardiovascular procedure	2 (<0.1)	4 (0.1)
Cardiovascular hemorrhage	2 (<0.1)	0
Other	3 (<0.1)	7 (0.1)

Undetermined cause of death	77 (0.9)	90 (1.0)

Source: SELECT CTR, Table 14.2.2

Myocardial Infarction

A total of 623 non-fatal myocardial infarctions (MIs) in 556 subjects (of which not all were first events) were confirmed, in 2.7% of semaglutide-treated subjects and 3.7% of placebo-treated subjects. The time from randomization to first EAC-confirmed non-fatal MI event resulted in an estimated HR of 0.72 [95% CI 0.61, 0.85]; semaglutide:placebo. The most frequently reported non-fatal MIs (first and all events) in both treatment groups was NSTEMI (approximately 61% of MIs), and the majority of MIs were type 1 events (approximately 71% of MIs), as categorized by the EAC.

Table 17. EAC-Confirmed Non-fatal Acute Myocardial Infarction, All Events

	Semaglutide N=8803 Obs yrs=29283		**Placebo N=8801 Obs yrs=29112**	
	n (%)	**E (R)**	**n (%)**	**E (R)**
All non-fatal MI	234 (2.7)	253 (0.9)	322 (3.7)	370 (1.3)
STEMI	44 (0.5)	45 (0.2)	54 (0.6)	55 (0.2)
NSTEMI	142 (1.6)	153 (0.5)	199 (2.3)	228 (0.8)
Cannot be determined	55 (0.6)	55 (0.2)	83 (0.9)	87 (0.3)
MI type				
Type I – Spontaneous	166 (1.9)	179 (0.6)	239 (2.7)	263 (0.9)
Type 2 – Ischemic imbalance	32 (0.4)	32 (0.1)	48 (0.5)	49 (0.2)
Type 3 – Death, no biomarker	1 (<0.1)	1 (<0.1)	0	0
Type 4a – PCI related	3 (<0.1)	3 (<0.1)	4 (<0.1)	4 (<0.1)
Type 4b – Stent thrombosis	16 (0.2)	16 (<0.1)	17 (0.2)	17 (<0.1)
Type 5 – CABG related	0	0	1 (<0.1)	1 (<0.1)
Cannot be determined	4 (<0.1)	4 (<0.1)	1 (<0.1)	1 (<0.1)

E: number of events, N: number of subjects, R: events per 100 years of observation, NSTEMI: Non-ST elevation myocardial infarction, PCI: percutaneous coronary intervention, STEMI: ST elevation myocardial infarction, MI: myocardial infarction

Source: SELECT CTR, Table 11-8

A total of 3 MIs were reported to have occurred outside of the in-trial period (semaglutide: 1, placebo: 2). Events of MI were not systematically collected outside the in-trial period.

Stroke

A total of 347 non-fatal strokes in 319 subjects (of which not all were first events) were confirmed, in 1.7% of semaglutide-treated subjects and 1.9% of placebo-treated subjects. The time from randomization to first EAC-confirmed non-fatal stroke resulted in an estimated HR of 0.93 (95% CI 0.74, 1.15); semaglutide:placebo. Most events were categorized as ischemic

stroke (92% of semaglutide events and 90% of placebo events).

Table 18. EAC-Confirmed Non-Fatal Stroke, All Events

	Semaglutide N=8803 Obs yrs=29283		Placebo N=8801 Obs yrs=29112	
	n (%)	E (R)	n (%)	E (R)
All non-fatal stroke	154 (1.7)	170 (0.6)	165 (1.9)	177 (0.6)
Ischemic stroke	141 (1.6)	156 (0.5)	148 (1.7)	159 (0.5)
Large-artery atherosclerosis	9 (0.1)	10 (<0.1)	7 (<0.1)	7 (<0.1)
Cardioembolism	30 (0.3)	30 (0.1)	24 (0.3)	24 (<0.1)
Small-vessel occlusion	4 (<0.1)	5 (<0.1)	7 (<0.1)	7 (<0.1)
Other determined cause	8 (<0.1)	8 (<0.1)	9 (0.1)	9 (<0.1)
Undetermined cause	95 (1.1)	103 (0.4)	105 (1.2)	112 (0.4)
Hemorrhagic stroke	10 (0.1)	11 (<0.1)	14 (0.2)	14 (<0.1)
Undetermined	3 (<0.1)	3 (<0.1)	4 (<0.1)	4 (<0.1)
Notes: Large-artery atherosclerosis include embolus/thrombosis; cardioembolism include high-risk/medium-risk; Small-vessel occlusion include lacune				
E: number of events, N: number of subjects, R: events per 100 years of observation, NSTEMI: Non-ST elevation myocardial infarction, PCI: percutaneous coronary intervention, STEMI: ST elevation myocardial infarction, MI: myocardial infarction				

Source: SELECT CTR, Table 11-11

The largest proportion of ischemic stroke was considered due to 'undetermined cause' by the EAC. The primary reason for cause to be undetermined was that the evaluation was incomplete. For example, a stroke was assessed by an EAC member as most likely ischemic due to the clinical presentation or imaging, but additional testing to identify the etiology (such as vessel imaging or echocardiogram) was unavailable. Discussion from the entire EAC committee (rather than a single adjudicator) was provided in more than half of the events (65 semaglutide, 64 placebo), supporting the diagnostic uncertainty. The most frequent MedDRA terms reported by the investigator for 'undetermined' ischemic stroke is also provided in Table 19, with the most commonly reported PT of 'ischemic stroke.'

Table 19. Reason for 'Undetermined' Ischemic Stroke Etiology and Associated PTs

	Semaglutide N=8803	Placebo N=8801
Ischemic fatal and non-fatal stroke (all events), undetermined cause	100 (1.1)	110 (1.2)
Incomplete evaluation	80 (0.9)	95 (1.1)
Negative evaluation	11 (0.1)	9 (0.1)
Two or more causes identified	11 (0.1)	7 (0.1)
Reported preferred terms (most common):		
Ischemic stroke	46	55
Cerebrovascular accident	13	15

Cerebral infarction	11	16
Lacunar infarction	6	2
Cerebellar infarction	3	2
Transient ischemic attack	2	6

Source: Reviewer created from ADADJ.xpt dataset

Two EAC-confirmed events of stroke (both hemorrhagic) were reported to have occurred outside of the in-trial period (semaglutide: 0, placebo: 2). Events of stroke were not systematically collected outside the in-trial period.

CV Death

A total of 223 subjects (2.5%) randomized to semaglutide vs. 262 subjects (3.0%) randomized to placebo died during the in-trial observation period due to EAC-confirmed CV death (including 'undetermined cause of death', see discussion below), corresponding to rates of 0.8 events per 100 PYO with semaglutide vs. 0.9 events per 100 PYO with placebo. The time from randomization to EAC-confirmed CV death resulted in an estimated HR of 0.85 (95% CI 0.71, 1.01); semaglutide:placebo.

Of the 485 EAC-confirmed CV deaths, 318 (~66%) were cardiovascular deaths as evaluated by the EAC; the most frequent cause of CV death was sudden cardiac death (semaglutide: 1.1% of subjects; placebo: 1.2% of subjects).

Table 20. EAC-Confirmed CV Death

	Semaglutide N=8803 Obs yrs=29283		**Placebo N=8801 Obs yrs=29112**	
	n (%)	**E (R)**	**n (%)**	**E (R)**
CV death	223 (2.5)	223 (0.8)	262 (3.0)	262 (0.9)
Determined CV cause	146 (1.7)	146 (0.5)	172 (2.0)	172 (0.6)
Sudden cardiac death	98 (1.1)	98 (0.3)	109 (1.2)	109 (0.4)
Stroke	15 (0.2)	15 (<0.1)	21 (0.2)	21 (<0.1)
Heart failure	14 (0.2)	14 (<0.1)	16 (0.2)	16 (<0.1)
Acute myocardial infarction	12 (0.1)	12 (<0.1)	15 (0.2)	15 (<0.1)
Cardiovascular procedure	2 (<0.1)	2 (<0.1)	4 (<0.1)	4 (<0.1)
Cardiovascular hemorrhage	2 (<0.1)	2 (<0.1)	0	0
Other	3 (<0.1)	3 (<0.1)	7 (<0.1)	7 (<0.1)
Undetermined cause	77 (0.9)	77 (0.3)	90 (1.0)	90 (0.3)

E: number of events, N: number of subjects, R: events per 100 years of observation, NSTEMI: Non-ST elevation myocardial infarction, PCI: percutaneous coronary intervention, STEMI: ST elevation myocardial infarction, MI: myocardial infarction

Source: SELECT CTR, Table 11-15

Undetermined Cause of Death

In the SELECT trial – and as prespecified in the statistical analysis plan (SAP) – 'undetermined cause of death' is counted in the MACE component for CV death.[17,31] For the 167 subjects who died with undetermined causes – and were subsequently categorized as CV death for MACE analysis – the details provided in the adjudication dataset are summarized in Table 21 below. (Note that the number of subjects with undetermined cause of death differs in Table 15 and Table 21 because the former only includes those deaths that were part of the primary endpoint of first MACE, whereas the latter includes any death.)

An exploratory analysis that evaluated **CV death excluding 'undetermined cause of death'** was consistent with the primary CV death finding, resulting in an **estimated HR of 0.84 (95% CI 0.68, 1.05)**.

In most cases (132/173, 76.3%), the reason that the cause was considered undetermined was that no source documents were obtainable. This was supported by manual review of adjudicator comments in the ADADJ.xpt dataset. As shown in Table 21, most AEs associated with adjudicated "undetermined cause of death" were in the 'Cardiac disorders' SOC and the 'General disorders and administration site conditions' SOC (primarily PT 'Death').

[31] It should be noted that the most recent paper on endpoint definitions [ref 17] notes that "…deaths of undetermined cause should be very few and should be assigned only when a death cannot be attributed to a CV or non-CV cause due to an extreme deficiency of information (e.g., the only available information is "patient died"). Use of this category is discouraged and should be rare in well-run clinical trials in which adequate source documentation is assiduously sought by participating investigators."

Table 21. Details on Fatal Outcomes, Cause Undetermined

	Semaglutide N=8803	Placebo N=8801
Undetermined cause of death	n=77	n=90
Location of death occurrence		
Home	25 (32.5)	24 (26.7)
Hospital	23 (29.9)	32 (35.6)
Other	5 (6.5)	6 (6.7)
Unknown	24 (31.2)	28 (31.1)
Reason for undetermined cause		
No source documents obtainable[a]	56 (72.7)	76 (84.4)
Source documents available, but cause undetermined	21 (27.3)	14 (15.6)
Unwitnessed and unexpected death, patient not observed alive within 24 hours of death	1 (1.3)	1 (1.1)
Competing causes of death, primary cause undetermined	4 (5.2)	5 (5.6)
Insufficient information on circumstances prior to death[b]	15 (19.5)	7 (7.8)
Other	1 (1.3)	1 (1.1)
Adverse events with fatal outcomes classified as of unknown cause	73 (94.8)	90 (100)
Cardiac disorders	28 (36.4)	22 (24.4)
General disorders and administration site conditions	27 (35.1)	39 (43.3)
Death	24 (31.2)	34 (37.8)
Sudden death	1 (1.3)	3 (3.3)
Nervous system disorders	9 (11.7)	14 (15.6)
Central nervous system vascular disorders	8 (10.4)	12 (13.3)
Respiratory, thoracic and mediastinal disorders	4 (5.2)	10 (11.1)
Infections and infestations	4 (5.2)	6 (6.7)
Vascular disorders	3 (3.9)	2 (2.2)
Renal and urinary disorders	3 (3.9)	1 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.6)	1 (1.1)
Gastrointestinal disorders	1 (1.3)	1 (1.1)
Metabolism and nutrition disorders	1 (1.3)	1 (1.1)
Immune system disorders	1 (1.3)	0
Injury, poisoning and procedural complications	1 (1.3)	0
Psychiatric disorders	0	2 (2.2)

a except for an investigator clinical narrative
b incl. death certificate only
c note that there may be more AEs than deaths because

Source: SELECT CTR, Tables 11-16 and 14.3.1.173

Analysis of the primary first MACE endpoint that excluded 'undetermined cause of death' from the 'CV death' portion of the composite was conducted as an exploratory analysis. The result is consistent with the primary analysis: number of events in the semaglutide group=506; number

of events in the placebo group=621; HR 0.80 (95% CI 0.72, 0.90).[32]

Sensitivity Analyses

Pre-specified sensitivity analyses, as per the SAP, were as follows:

1. A 2-way tipping-point analysis to evaluate the potential impact of missing data for the 543 subjects (semaglutide: 259; placebo: 284) who had withdrawn consent or were lost to follow-up (LTFU).

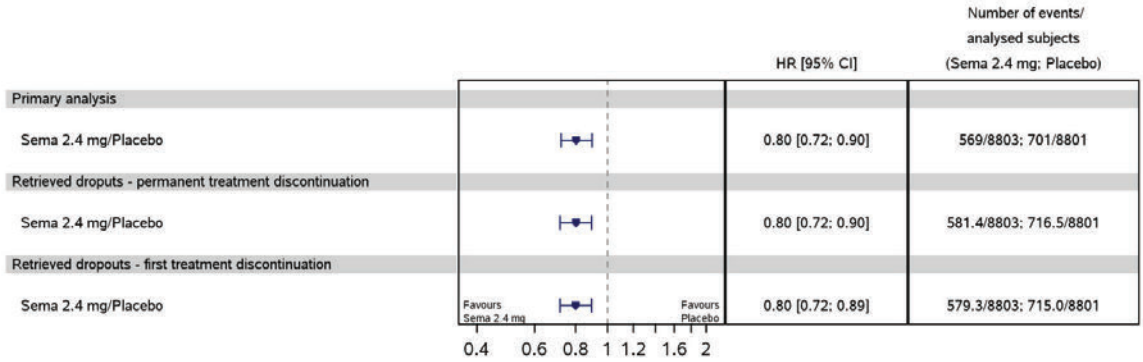
No penalties within the interval of [1/3; 3] led to a change of conclusion of the primary analysis.

2. Two additional prespecified sensitivity analyses were performed by imputing event times for subjects who withdrew or were LTFU. If the imputed event time occurred after the subjects planned end-of-trial time the subject was censored at the planned end-of-trial time:
    a. One analysis used an estimated annual event rate from subjects who discontinued treatment permanently but remained in the trial. The imputations were done by treatment group.
    b. The other analysis avoids conditioning on the future by using an estimated annual event rate for subjects who discontinued treatment at any point in the trial. The imputations were done by treatment group.

The results of both sensitivity analyses were consistent with the result from the primary analysis:

[32] Response to FDA information request, dated 04 Jan 2024, Table 11

Figure 8. Time from Randomization to First EAC-Confirmed MACE and Sensitivity Analyses



Data from the in-trial period. Time from randomisation to first EAC-confirmed MACE was analysed using a Cox proportional hazards model with treatment as categorical fixed factor. Subjects without events of interest were censored at the end of their 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 retrieved dropout analyses, event times for subjects who were lost to follow up or withdrew consent were multiple imputed using event rates from retrieved dropouts in the same treatment arm. Retrieved dropouts were either defined as subjects who permanently discontinued treatment but remained in trial, or subjects who were off treatment for more than 5 weeks at least once, but remained in trial. Event rates were based on observations after the on-treatment period or first on-treatment period respectively. The imputed data sets were analysed using the same Cox regression model as for the primary analysis and results were combined using Rubin's rules.
CI: confidence interval, EAC: event adjudication committee, HR: hazard ratio, MACE: major adverse cardiovascular event.

ex9536/ex9536-4388/ctr_20230809_er
15AUG2023:00:20:43 - fforest:sas/fforestmacesensit.png

Source: SELECT CTR, Figure 14.2.16

Subgroups

The primary MACE endpoint was evaluated for the following demographic subgroups:

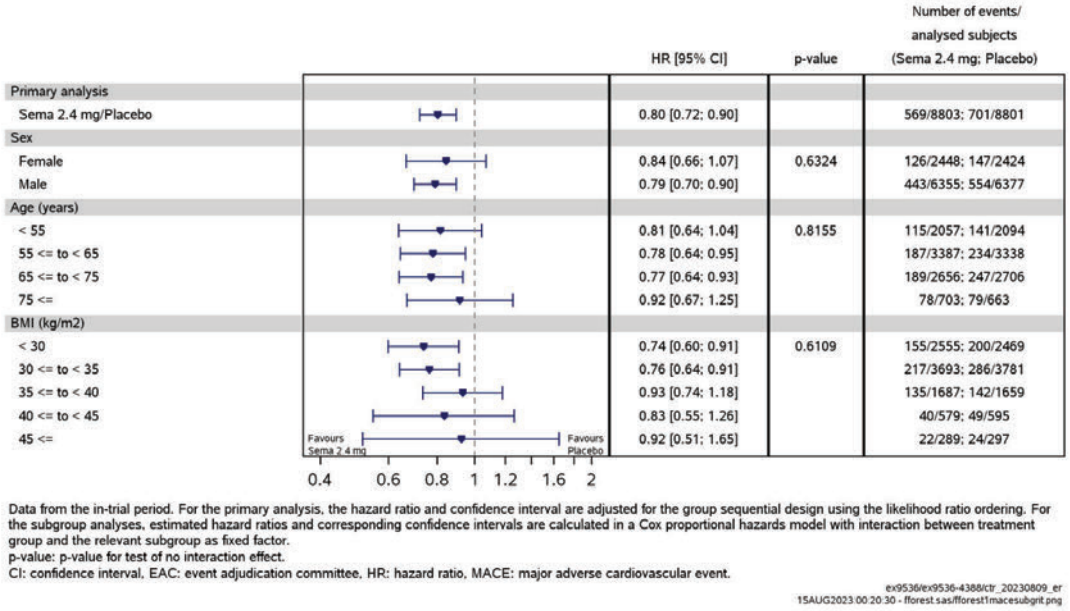
- Sex
- Age
- BMI
- Region (separately for U.S. vs. non-U.S.)
- Race
- Ethnicity

The following baseline disease categories were also evaluated:

- Cardiovascular disease enrollment criterion/criteria
- Congestive heart failure
- Estimated glomerular filtration rate (eGFR)
- HbA1c

Interaction p-values were calculated for all subgroup tests. No p-values were < 0.1 for any of the tested subgroups.

Figure 9. Forest Plot of MACE Primary Endpoint by Sex, Age, and BMI at Baseline

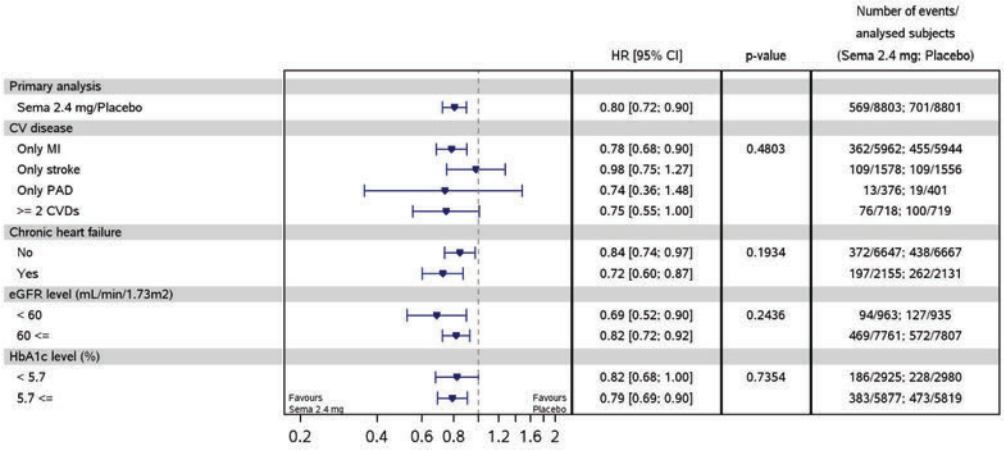


Data from the in-trial period. For the primary analysis, the hazard ratio and confidence interval are adjusted for the group sequential design using the likelihood ratio ordering. For the subgroup analyses, estimated hazard ratios and corresponding confidence intervals are calculated in a Cox proportional 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.

ex9536/ex9536-4388/ctr_20230809_er
15AUG2023 00:20:30 - fforest.sas/fforest1macesubgrit.png

Source: SELECT CTR, Figure 14.2.13

Figure 10. Forest Plot of MACE Primary Endpoint by Baseline Disease Status

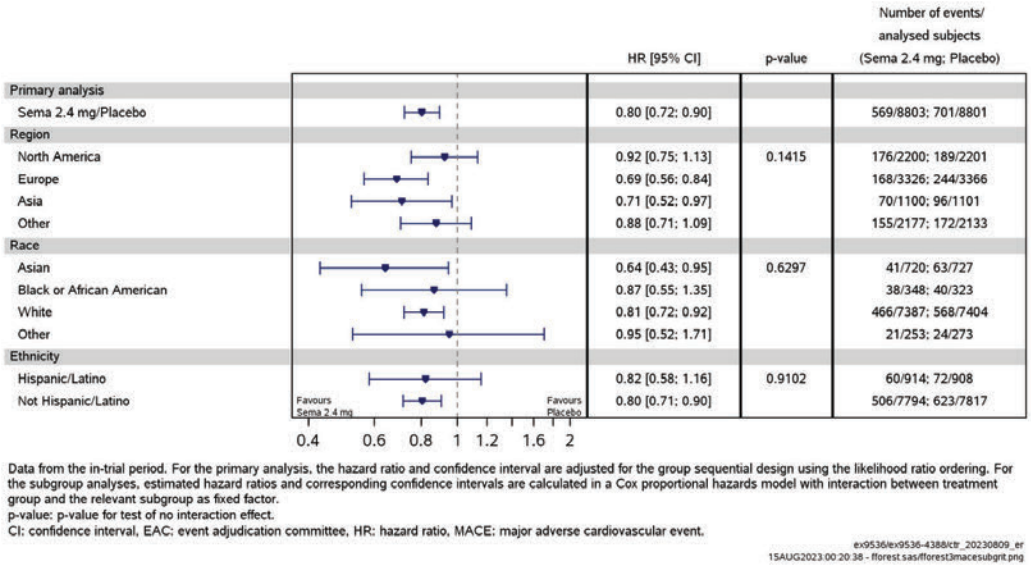


Data from the in-trial period. For the primary analysis, the hazard ratio and confidence interval are adjusted for the group sequential design using the likelihood ratio ordering. For the subgroup analyses, estimated hazard ratios and corresponding confidence intervals are calculated in a Cox proportional 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.

ex9536/ex9536-4388/ctr_20230809_er
15AUG2023 00:20:35 - fforest.sas/fforest2macesubgrit.png

Source: SELECT CTR, Figure 14.2.14

Figure 11. Forest Plot of MACE Primary Endpoint by Race, Ethnicity, and Region



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.

ex9536/ex9536-4388/ctr_20230809_er
15AUG2023 00:20:38 - fforest sas/fforest3macesubgrit.png

Source: SELECT CTR, Figure 14.2.15

United States (US) Subpopulation

The applicant additionally conducted US vs. non-US subgroup analyses. US subjects comprised 20.7% of the trial population (3652/17605).

In the US trial population, there was a lower proportion of trial completers compared to the non-US trial population (91.5% vs. 98.5% for semaglutide, 90.8% vs. 98.4% for placebo). The proportion of US subjects (43.1% [semaglutide], 42.8% [placebo]) who permanently discontinued trial product was higher compared to the non-US trial population (27.3% [semaglutide], 22.8% [placebo]).

At baseline, mean age, HbA1c, body weight, BMI, waist circumference, and hsCRP were slightly higher in the US vs. non-US population. Mean eGFR was slightly lower.

The US trial population included a higher proportion of Black or African American subjects, and a lower proportion of ethnic Hispanic or Latino subjects and Asian subjects compared to the non-US trial population. There was also a higher proportion of females in the US trial population.

Higher proportions of the US trial subjects had stroke and PAD at baseline and a lower proportion of US subjects had MI at baseline compared to the non-US trial population.

The result of the subgroup analysis is presented in Table 22, and the results are consistent with

the full analysis population. The treatment by subgroup interaction was not significant.

Table 22. Time to First EAC-Confirmed MACE, Subgroup for US/Non-US Population

	US		Non-US	
	Semaglutide	**Placebo**	**Semaglutide**	**Placebo**
N	1821	1831	6982	6970
MACE	147 (8.1)	422 (6.0)	166 (9.1)	535 (7.7)
HR (95% CI)	0.88 (0.70, 1.10)		0.78 (0.68, 0.88)	
Treatment/subgroup interaction	0.3402			

Source: Applicability of non-US data for US population in the SELECT trial document, Table 2-4

Interim Analysis

There was 1 interim analysis (IA) planned and conducted in this trial. This was planned when 817 events (two-thirds of the planned total events) of the primary endpoint accrued. The DMC evaluated the interim result in order to make a recommendation to terminate the trial early for superiority if appropriate. The DMC evaluated the unblinded interim results using the group sequential stopping boundary as guidance. Stopping the trial early for superiority was only allowed if the stopping boundary was crossed and the DMC made the decision to recommend early trial termination based on this and other considerations as specified in the DMC charter:

- *The unblinded analysis will reside with the DMC, who based on the interim analysis results can recommend to terminate the trial early for superiority. Recommending to stop the trial early for superiority is only allowed if the p-value is below the pre-specified stopping boundary.*

- *Besides the formal requirement above, the DMC should take into account the totality of data including results of confirmatory secondary endpoints and variability of the treatment effect over time when making recommendation with regards to early trial termination.*

The primary endpoint of time to first adjudicated MACE met the pre-specified Lan-DeMets stopping boundary of a 1-sided p-value < 0.00650 (based on 831 observed events) and furthermore met the applicant-defined decision boundary of a HR ≤ 0.80. The results were as follows:

Table 23. Interim Analysis Results

	Event counts			Treatment effect		Efficacy boundary		
Event type	Total (information fraction[e])	SEM	PBO	Hazard Ratio[f]	95% Confidence Interval[f]	One-sided p-values[g]	P-value boundary[h]	Boundary crossed?
Primary: MACE[a]	831 (0.678)	369	462	0.791	(0.690,0.907)	0.0004	0.00650	Yes
Confirmatory: CV death[b]	279 (0.678)	134	145	0.920	(0.727,1.163)	0.25	0.01857	No
Confirmatory: CV death + HF[c]	381 (0.678)	177	204	0.863	(0.705,1.054)	0.075	0.01857	No
Confirmatory: Death[d]	514 (0.678)	233	281	0.826	(0.693,0.981)	0.016	0.01857	Yes

Abbreviations: CV=cardiovascular; HF=heart failure; PBO=Placebo; SEM=Semaglutide 2.4mg; MACE=major adverse cardiovascular events; SE=standard error. Only events during the in-trial observation period are counted.
a. The primary endpoint includes events adjudicated as CV death (see footnote b), non-fatal myocardial infarction, or non-fatal stroke.
b. This confirmatory endpoint includes deaths adjudicated as CV or undetermined.
c. This confirmatory endpoint includes events adjudicated as CV death (see footnote b) or HF, including HF hospitalization and urgent HF visits.
d. This confirmatory endpoint includes all deaths with an adjudicated cause and date; other deaths are censored at the date reported by the investigators.
e. The trial is fully enrolled with 17,605 subjects, and the information fraction for all endpoints is the number of primary events at the time of the interim analysis divided by the target number of 1,225.
f. The hazard ratio for comparing SEM versus PBO is estimated from a Cox proportional hazards model in the full analysis set population with treatment group as a fixed factor, censoring of competing events, and the exact method for handling ties. The confidence intervals are based on the profile likelihood method.
g. The one-sided p-value is from the score test of the Cox proportional hazards model with treatment group as a fixed factor.
h. Constructed using East according to Lan-DeMets group sequential design for the primary endpoint, and using the spending function per Glimm et al. (2010) for the confirmatory endpoints.

Source: DMC Minutes, Pre-planned DMC IA report, Table 1

Discussion to continue the trial (rather than stop early for efficacy) included the following considerations as per the closed DMC minutes, "emphasizing its premier importance in the landscape of current clinical trials and practice":

- The significant IA result in the primary MACE endpoint is driven by non-fatal MI events with no significant effect on CV death.

- There was an apparent favorable imbalance in COVID-19 deaths. If COVID-19 is driving a difference in all-cause mortality, this could become clearer with additional data collected over the course of 1 more year if the trial were to continue.

- Another year of follow-up would narrow the confidence interval for all-cause mortality and lead to a more convincing result.

- The effect of study drug on non-fatal stroke has looked more favorable over time.

- An additional year of data on the efficacy endpoints may be useful for future meta-analyses and provide information on the components of composite outcomes, such as heart failure categories, and subgroups.

"The DMC considered the pros and cons for recommending to continue (versus to stop) the trial

now with IA stopping criteria met, especially if no benefit on all-cause mortality were observed at the end of the trial. On balance, the DMC suggested there may be more cons for stopping a trial with critical questions of both scientific and public health significance that may be answerable if the trial had continued to its originally planned conclusion."

The DMC voted 4 to continue, 2 to stop early for efficacy, and 1 abstained. All members agreed to support the majority opinion and therefore the DMC recommendation was conveyed as unanimous.

Data Quality and Integrity

Data Monitoring Committee (DMC)

Blinded and un-blinded data analyses during trial conduct were evaluated by the DMC, as described in the DMC charter. Trial integrity was ensured by using an external independent statistical service provider (independent of trial conduct and external to the applicant) to prepare data and analyses for the DMC. I reviewed the DMC meeting minutes and do not have concerns regarding data quality and integrity based on my review.

Event Adjudication

The independent external adjudication committee (EAC) consisted of a Chair and Vice-Chair (cardiologists), cardiologists, neurologists, gastroenterologists, and nephrologists. The EAC conducted ongoing blinded adjudication of selected event types, according to the members' expertise. The members were required to disclose any potential conflict of interest, be independent of the applicant, and had no authorization to impact the protocol or trial conduct. The EAC charter was referenced for event definitions, source documents to be collected per event type, adjudication process, and roles and responsibilities. Event types that were adjudicated by the EAC included those listed in Table 24.

Table 24. Events for Adjudication

Event type (serious and non-serious) including description	Adjudication Outcome
Death: All cause death	• Cardiovascular death • Renal death • Non-cardiovascular, non-renal death
Acute coronary syndrome: Conditions include all types of acute myocardial infarction and hospitalization for unstable angina pectoris	• Acute myocardial infarction • Hospitalization for unstable angina pectoris
Stroke (Stroke and transient ischemic attack): Episode of focal or global neurological dysfunction that could be caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or ischemia, with or without infarction	• Stroke
Coronary artery revascularisation: A catheter-based (percutaneous coronary intervention (PCI)) or a surgical procedure (Coronary artery bypass surgery (CABG)) designed to improve myocardial blood flow	• Coronary revascularisation procedure
Heart failure hospitalisation or urgent heart failure visit: Presentation of the subject for an urgent, unscheduled hospital admission or clinic/office/emergency department visit with a primary diagnosis of heart failure (new episode or worsening of existing heart failure)	• Heart failure hospitalisation • Urgent heart failure visit
Pancreatitis: Any event of pancreatitis should be reported	• Acute pancreatitis
Nephropathy (events leading to renal replacement therapy): Initiation of dialysis treatment (hemodialysis or peritoneal dialysis) or kidney transplantation Note: The underlying condition should be reported as the AE diagnosis	• Chronic renal replacement therapy

Source: EAC Charter

Event definitions were included in the EAC charter and were based on standardized definitions; see the appendix of this review in Section 13.1 for details.

A review of the EAC charter, adjudication-related datasets, a sampling of adjudication packages, and a response to an information request were conducted to evaluate adjudication process and quality control.

As shown in Table 25, all event types excluding death were to undergo primary adjudication. A death adjudication meeting occurred between, at a minimum, 2 cardiologists including an EAC Chair or Vice-Chair, 1 nephrologist, and 1 neurologist.

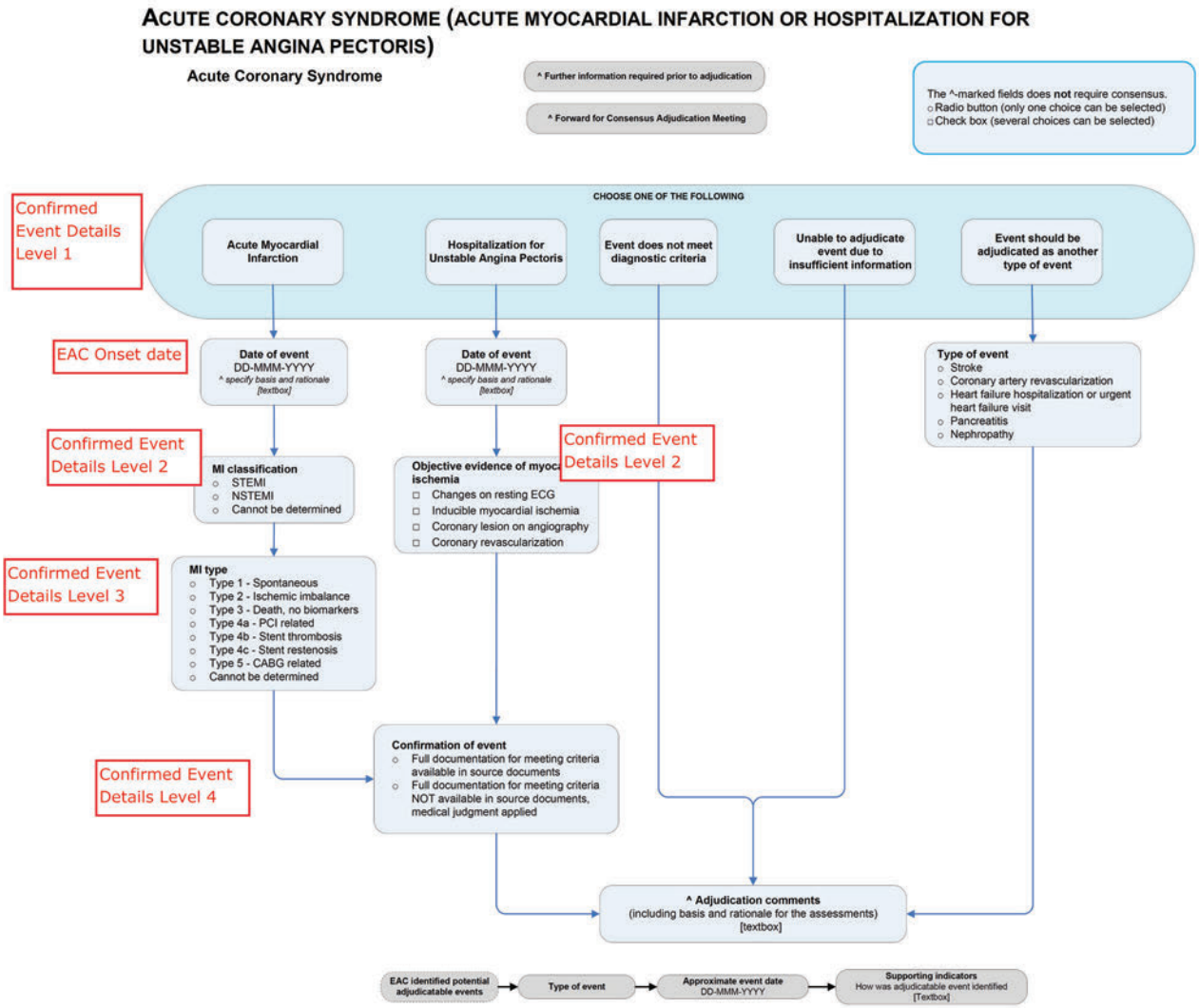
Table 25. Overview of Adjudication Processes

Evaluation Level / Event Types	Primary adjudication	Consensus adjudication meeting	Death adjudication meeting	QC adjudication meeting
Acute coronary syndrome, (cardiology)	+	+	-	+
Coronary artery revascularisation (cardiology)	+	+	-	+
Heart failure (cardiology)	+	+	-	+
Stroke (neurology)	+	+	-	+
Pancreatitis (gastroenterology)	+	+	-	+
Nephropathy (nephrology)	+	+	-	+
Death	-	-	+	+
Required adjudicator participation	2 adjudicators of the relevant specialty	Minimum 2 adjudicators of the relevant specialty 1 EAC Chair or Vice-Chair	2 Cardiologists (including Chair or Vice-Chair) 1 Neurologist 1 Nephrologist	Minimum 2 adjudicators of the relevant specialty 1 EAC Chair or Vice-Chair

Source: Event adjudication charter version 3.0, Table 3

Two adjudicators of the relevant specialty were assigned to events for primary adjudication by the CRO ((b) (4)). The EAC members evaluated each event dossier independently by using the event adjudication system (EAS). Each EAC member completed a primary adjudication form in accordance with the EAC adjudication form flow. An example of the annotated EAC adjudication form flow (for acute coronary syndrome) is shown in Figure 12. This figure highlights that beyond confirming/determining the type of event (Level 1), other event details were adjudicated (in the example below, Levels 2-4). The EAS programmatically compared the 2 completed primary adjudication forms for each event. If all responses for the fields specified for consensus matched, adjudication was considered complete. If the 2 completed primary adjudication forms did not match, the event was classified as a disagreement in the EAS and was advanced to a consensus adjudication meeting. During primary adjudication, each EAC member always had the option to advance the event directly for a consensus adjudication meeting. In addition, a random sample of adjudicated events were selected for quality control (QC) and re-adjudicated in the EAS, to ensure adherence to event definitions. At least 10% of adjudicated events were to complete the QC process.

Figure 12. EAC Adjudication Form Flow in EAS, ACS Example



Source: Response to October 18, 2023 Information Request, Appendix 1

The target timeline to complete primary adjudication was 14 calendar days. If requests for additional documentation (RADs) were issued, timelines were to be put on hold until the event dossier was updated with response from the investigational site and presented to the 2 adjudicators. (When approaching the end of trial or milestones, shorter timeline requirements may have been applied to meet database lock or interim analysis requirements.)

In my assessment of the adjudication process, I manually compared the datasets ADAE.xpt (all adverse events) with ADADJ.xpt (all adjudicated events) for selected MACE. Every preferred term of "acute myocardial infarction" and "ischemic stroke" in the ADAE dataset matched an adjudication record in the ADADJ dataset.

Overall, there were 1640 potential events of acute coronary syndrome (709 semaglutide, 931 placebo), of which 649 (40%) were confirmed as acute MI (263 semaglutide [44%], 386 placebo [37%]), 256 events (16%) were confirmed as hospitalization for unstable angina pectoris (119 semaglutide, 137 placebo), in 583 events (36%) diagnostic criteria were unmet (253 semaglutide, 330 placebo), 28 events (2%) were unable to be adjudicated due to insufficient information (12 semaglutide, 16 placebo), and 124 events (8%) were duplicate events (62 semaglutide, 62 placebo).

Reviewer comment: There were more events reported and sent for adjudication in the placebo arm than in the semaglutide arm. The adjudication process appears to have produced a more conservative result (i.e., toward the null) with 44% of semaglutide potential events and 37% of placebo potential events confirmed as acute MI (component of the primary endpoint).

A total of 118 events (18%) ultimately confirmed as acute MI by the consensus meeting had adjudicator discordance for Level 1 during the primary adjudication process, 60 in semaglutide and 58 in placebo. A total of 82 events (32%) ultimately confirmed as hospitalization for unstable angina had adjudicator discordance, 39 in semaglutide and 54 in placebo. A total of 142 events that were determined to *not* meet diagnostic criteria (i.e., events *not* EAC-confirmed) had adjudicator discordance (24%), 62 in semaglutide and 80 in placebo.[33]

Reviewer comment: A formal concordance analysis was not conducted. However, given the blinded nature of adjudication and the myriad of factors (clinical judgment) involved in adjudication of events from this large, multi-national clinical trial, the discordance does not raise major concerns. Notably, consensus meetings were held for many adjudicated events, not just those that were discordant at Level 1, which allowed for clinical discussion and decision-making.

A similar summary review was undertaken for stroke events. There were 928 potential events of stroke adjudicated: 429 in semaglutide subjects and 499 in placebo subjects. Of the total events, 373 (40%) of events were confirmed as stroke by adjudication (178 semaglutide [41%], 195 placebo [39%]), in 491 events (53%) the diagnostic criteria were unmet (222 semaglutide, 269 placebo), 36 events (4%) were unable to be adjudicated due to insufficient information (16 semaglutide, 20 placebo), and 28 events (3%) were duplicates (13 semaglutide, 15 placebo).

Reviewer comment: Although the treatment difference was not as pronounced, similar to the acute MI events, there were more events reported and sent for adjudication in the placebo arm, and the adjudication process appears to have produced a slightly more conservative result (i.e., towards the null) with 41% of semaglutide potential events and 39% of placebo potential events

[33] Reviewer calculated from ADJDIS.xpt dataset

confirmed as stroke (component of the primary endpoint).

In 153 potential stroke events there was discordance among the adjudicators in determining whether there was a stroke diagnosis [46 events with discordance were ultimately confirmed as stroke (23 semaglutide, 23 placebo), 88 did not meet diagnostic criteria (40 semaglutide, 48 placebo), and 19 events were unable to be adjudicated due to insufficient information (7 semaglutide, 12 placebo)].[33]

Reviewer comment: See comments above regarding event adjudication discordance evaluation.

Efficacy Results – Secondary and other relevant endpoints

Confirmatory secondary endpoints were tested under multiplicity control via a stagewise hierarchical testing scheme using the order as follows:

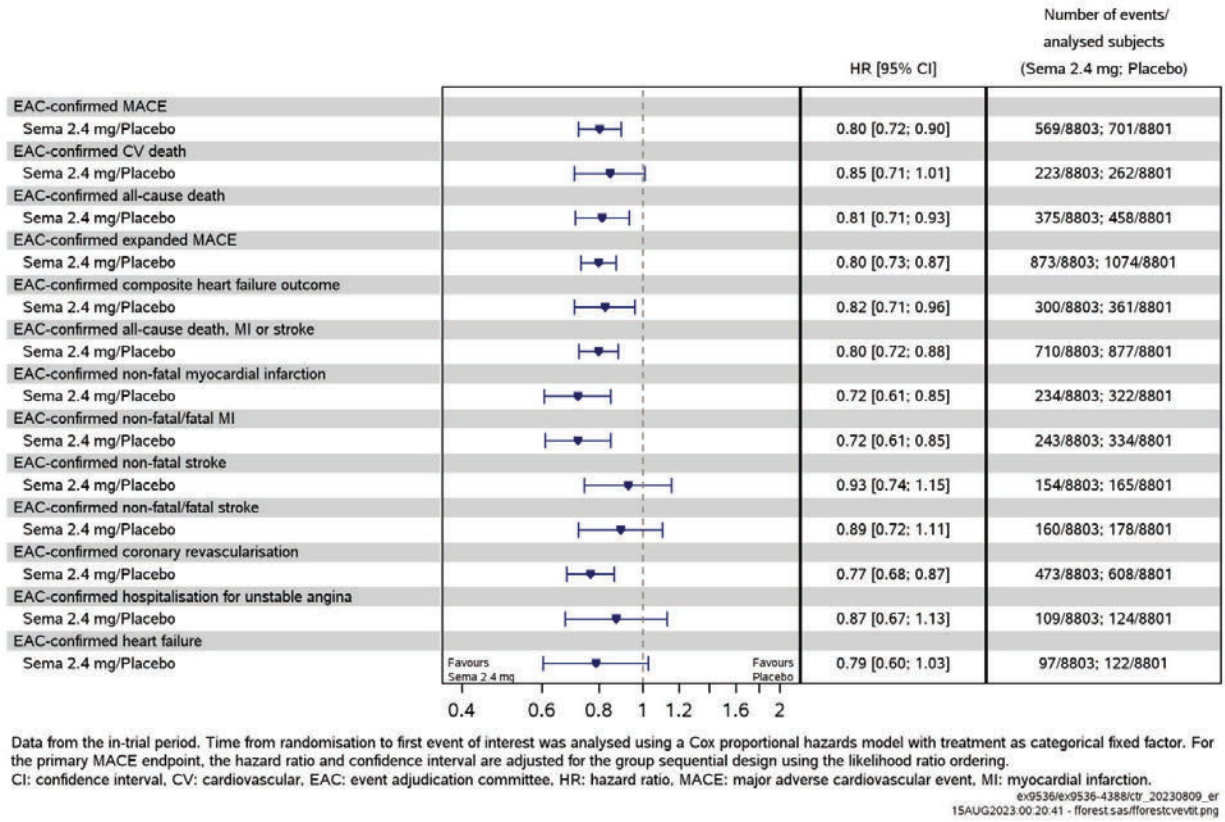
1. Time from randomization to CV death
2. Time from randomization to first occurrence of a composite heart failure (HF) endpoint consisting of HF hospitalization, urgent HF visit, or CV death
3. Time from randomization to all-cause death

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

Estimated HR: 0.85 (95% CI 0.71, 1.01), p = 0.0327

Superiority of semaglutide vs. placebo was therefore not tested for the confirmatory secondary endpoints of time to first EAC-confirmed composite HF outcome comprising the components 'HF requiring hospitalization,' 'urgent HF visit' or 'CV death,' or time to EAC-confirmed all-cause death. A forest plot of HRs and 95% CIs for these and other secondary endpoints are provided in Figure 13, below. These secondary endpoints were generally consistent with the primary endpoint, despite not achieving formal statistical significance.

Figure 13. Time from Randomization to First EAC-Confirmed CV Event



Data from the in-trial period. Time from randomisation to first event of interest was analysed using a Cox proportional hazards model with treatment as categorical fixed factor. For the primary MACE endpoint, the hazard ratio and confidence interval are adjusted for the group sequential design using the likelihood ratio ordering.
CI: confidence interval, CV: cardiovascular, EAC: event adjudication committee, HR: hazard ratio, MACE: major adverse cardiovascular event, MI: myocardial infarction.
ex9536/ex9536-4388/ctr_20230809_er
15AUG2023:00:20:41 - fforest.sas/fforestcvevtit.png

Source: SELECT CTR, Figure 14.2.85

Details on confirmatory and certain related secondary CV endpoints are discussed below.

Heart Failure

According to the EAC charter, a heart failure (HF) event included hospitalization for heart failure or urgent outpatient visits.

A heart failure hospitalization was defined as an event where the patient was admitted to the hospital with a primary diagnosis of HF, the length-of-stay extended for at least 24 hours, the patient exhibited new or worsening HF symptoms, and the patient had objective evidence of new or worsening HF. Further details regarding the HF definitions were provided in the EAC charter and can be found in the references cited in the appendix of this review (Section 13.1). These events were to be adjudicated by the EAC.

The numbers and proportions of subjects with first composite HF events were 300 and 3.4% with semaglutide vs. 361 and 4.1% with placebo (Table 26). As presented in Figure 13 above,

this resulted in an **estimated HR of 0.81 (95% CI 0.71, 0.96)**. The majority of events were of CV death, including undetermined cause of death (203 vs. 240), although a favorable numeric imbalance was also seen for the HF-specific endpoints of HF hospitalization (95 vs. 113) and urgent HF visit (2 vs. 8).

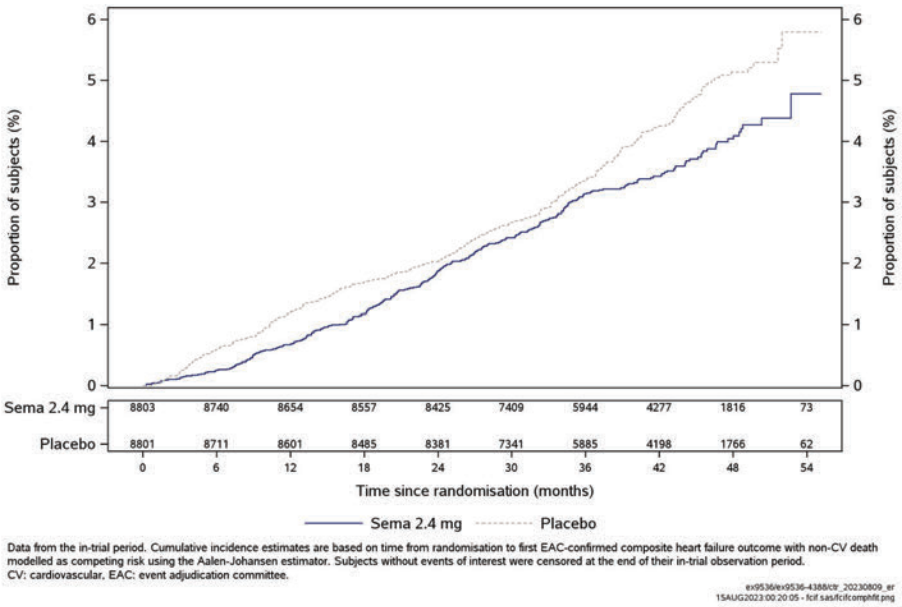
Table 26. First EAC-Confirmed Composite Heart Failure Events

	Semaglutide N=8803 Obs yrs=29165		**Placebo N=8801 Obs yrs=28944**	
	n (%)	**rate**	**n (%)**	**rate**
First EAC-confirmed composite HF outcome	300 (3.4)	1.0	361 (4.1)	1.2
Heart Failure	97 (1.1)	0.3	121 (1.4)	0.4
HF hospitalization	95 (1.1)	0.3	113 (1.3)	0.4
Urgent HF visit	2 (<0.1)	<0.1	8 (0.1)	<0.1
CV and undetermined cause of death	203 (2.3)	0.7	240 (2.7)	0.8
CV death	133 (1.5)	0.5	154 (1.7)	0.5
Acute myocardial infarction	11 (0.1)	<0.1	14 (0.2)	<0.1
Heart failure	4 (<0.1)	<0.1	5 (0.1)	<0.1
Sudden cardiac death	97 (1.1)	0.3	104 (1.2)	0.4
Stroke	15 (0.2)	<0.1	20 (0.2)	<0.1
Cardiovascular procedure	2 (<0.1)	<0.1	4 (<0.1)	<0.1
Cardiovascular hemorrhage	2 (<0.1)	<0.1	0	0
Other	2 (<0.1)	<0.1	7 (0.1)	<0.1
Undetermined cause of death	70 (0.8)	0.2	86 (1.0)	0.3
rate: events per 100 years of observation				

Source: SELECT CTR, Table 14.2.30

The cumulative incidence plot shown in Figure 14, below, shows the time course of events during the trial, with separation of curves early (within the first 6 months). Treatment difference appears to attenuate in the middle of the trial, with an apparent increase of events in the placebo arm and separation of curves again after 36 months.

Figure 14. Cumulative Incidence Plot of Time to First EAC-Confirmed Composite Heart Failure Outcome



Source: SELECT CTR, Figure 14.2.32

In the evaluation of *all* events, the results were similar. A total of 97 semaglutide-treated subjects (1.1%) and 122 placebo-treated subjects (1.4%) had any HF event, which included HF hospitalization (97 vs. 116) and urgent HF visit (7 vs. 11), Table 27.

HF events were classified as heart failure with preserved ejection fraction (HFpEF), heart failure with mid-range ejection fraction (HFmrEF), heart failure with reduced ejection fraction (HFrEF), or unknown. HFpEF events drove the nominal difference between groups, Table 27.

With HFpEF, patients present with HF signs and symptoms as the result of high left ventricular (LV) filling pressure despite normal or near normal LV ejection fraction (LVEF; ≥ 50 percent).[34] Obesity is commonly associated with HFpEF, and weight loss may improve symptoms and/or outcomes.[35] (b) (5)

[34] www.uptodate.com, Treatment and prognosis of heart failure with preserved ejection fraction. Accessed January 27, 2024.
[35] Borlaug BA, et al. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets, Cardiovasc Res 2022; 118 (18):3434–50.

(b) (5)

(b) (5)

Table 27. EAC-Confirmed Heart Failure Events (All Events)

	Sema 2.4 mg					Placebo				
	N	(%1)	E	(%2)	R	N	(%1)	E	(%2)	R
Number of subjects	8803					8801				
Observation time	29283					29112				
All EAC-confirmed HF events	97	(1.1)	150	(100)	0.5	122	(1.4)	177	(100)	0.6
HF hospitalisation	97	(1.1)	142	(94.7)	0.5	116	(1.3)	166	(93.8)	0.6
Urgent HF visit	7	(<.1)	8	(5.3)	<.1	11	(0.1)	11	(6.2)	<.1
EAC classification of the event										
HFpEF	22	(0.2)	34	(22.7)	0.1	37	(0.4)	46	(26.0)	0.2
HFmrEF	20	(0.2)	26	(17.3)	<.1	23	(0.3)	27	(15.3)	<.1
HFrEF	55	(0.6)	76	(50.7)	0.3	52	(0.6)	79	(44.6)	0.3
Unknown	13	(0.1)	14	(9.3)	<.1	24	(0.3)	25	(14.1)	<.1

Notes: HFpEF was defined as LVEF≥50% (normal) with relevant structural heart disease (LVH and/or LAE) or diastolic dysfunction; HFmrEF was defined as LVEF 40-49% (mild LV dysfunction) with relevant structural heart disease (LVH and/or LAE) or diastolic dysfunction; HFrEF was defined as LVEF <30-39 (moderate LV dysfunction) or LVEF<30% (severe LV dysfunction). Data from the in-trial period.

%1: percentage of subjects in full analysis set with at least one event, %2: percentage of total number of events, E: number of events, N: number of subjects, R: events per 100 years of observation, EAC: event adjudication committee, HFmrEF: heart failure with mid-range ejection fraction, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced injection fraction.

Source: SELECT CTR, Table 11-21

(b) (4)

All-Cause Death

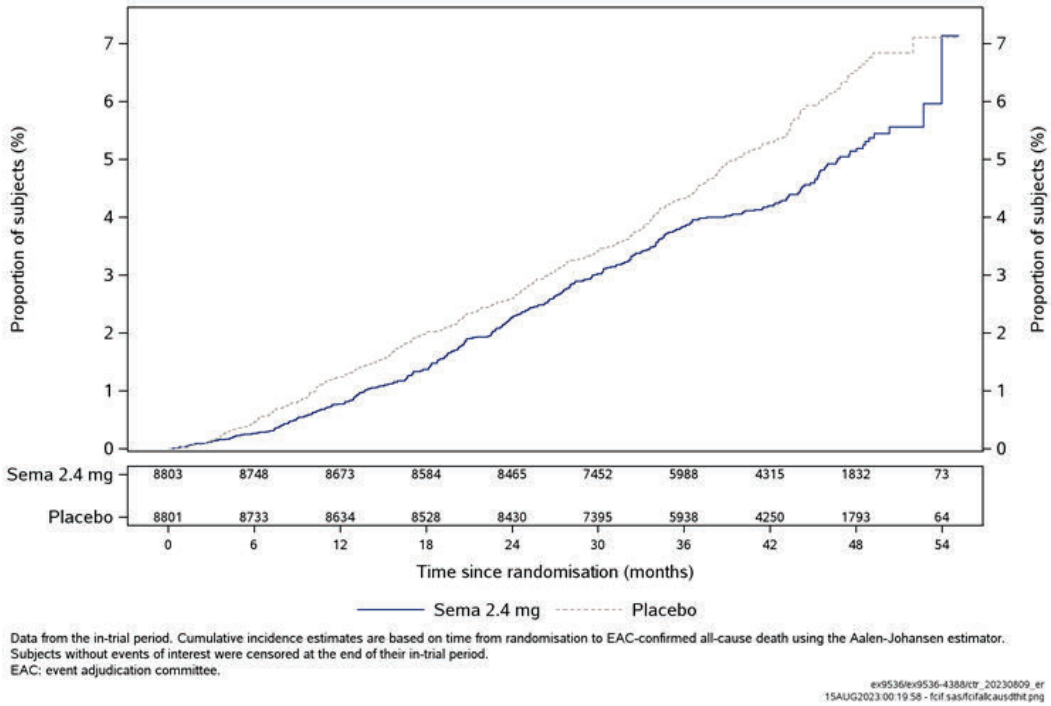
Section 8.4.1 elaborates on non-CV deaths for safety. This section comments on all-cause death as an efficacy endpoint; although not formally tested, its clinical importance is acknowledged: 1) all-cause death does not rely on adjudication for classification (i.e., avoids misclassification in situations where causes of death are complex and multifactorial), and 2) all-

(b) (4)

cause death is not impacted by ascertainment bias (in SELECT, vital status was available in 99.6% of subjects).

Overall, there were 375 deaths (4.3%) in the semaglutide arm and 458 deaths (5.2%) in the placebo arm; HR 0.81 (95% CI 0.71, 0.93). The time to all-cause death is shown in the figure below. Separation of the curves occurs by 6 months, with another decrease in death rate in the semaglutide group after about 36 months in-trial.

Figure 15. Time to All-Cause Death



Source: SELECT CTR, Figure 11-12

Time from randomization to first occurrence of EAC-confirmed all-cause death, non-fatal MI, or non-fatal stroke was a supportive secondary endpoint addressing the primary objective. A total of 332 subjects on semaglutide (3.8%) and 398 subjects on placebo (4.5%) died of any cause as the first event in the composite endpoint. First non-fatal MI and first non-fatal stroke are shown in Table 28, below. The estimated HR for the composite was 0.80 (95% CI 0.72, 0.88).

Table 28. First EAC-Confirmed All-Cause Death, Non-Fatal MI, or Non-Fatal Stroke

	Sema 2.4 mg					Placebo				
	N	(%1)	E	(%2)	R	N	(%1)	E	(%2)	R
Number of subjects	8803					8801				
Observation time, (years)	28655					28297				
First EAC-confirmed event	710	(8.1)	710	(100)	2.5	877	(10.0)	877	(100)	3.1
All-cause death	332	(3.8)	332	(46.8)	1.2	398	(4.5)	398	(45.4)	1.4
Non-fatal MI	230	(2.6)	230	(32.4)	0.8	320	(3.6)	320	(36.5)	1.1
Non-fatal stroke	148	(1.7)	148	(20.8)	0.5	159	(1.8)	159	(18.1)	0.6

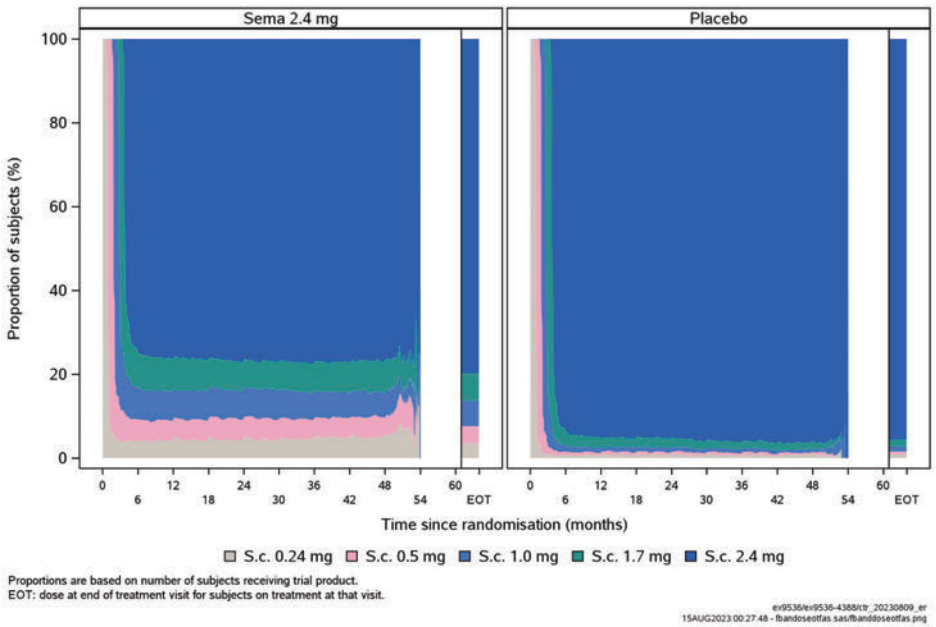
Note: Data from the in-trial period.
%1: percentage of subjects in full analysis set with at least one event, %2: percentage of total number of events, E: number of events, N: number of subjects, R: events per 100 years of observation, EAC: event adjudication committee, MI: myocardial infarction.

Source: SELECT CTR, Table 11-5

Dose/Dose Response

Study drug was administered once weekly, with dose escalation every 4th week until the maintenance dose (semaglutide 2.4 mg or equivalent placebo) was reached, consistent with the Wegovy label. After the initial 16 weeks of dose escalation, approximately 75% of subjects who were on-treatment at that time in the semaglutide group were receiving the planned 2.4 mg dose (Figure 16). Among those who were on treatment, the proportions of subjects on each dose remained consistent throughout the trial.

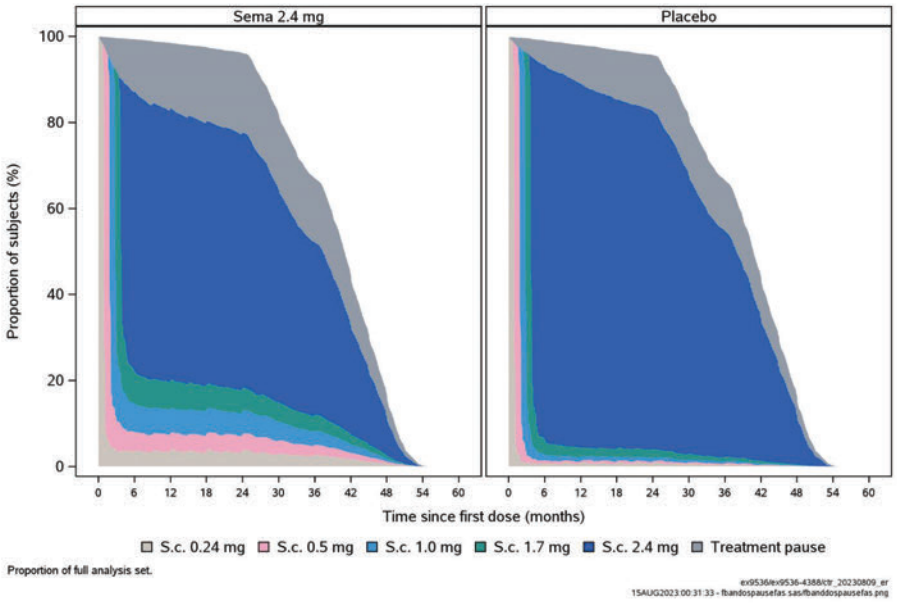
Figure 16. Proportion of Subjects On-Treatment Receiving Each Dose Level



Source: SELECT CTR, Figure 14.1.12

Figure 17 illustrates the proportions of subjects on each dose level, including those on treatment pause.

Figure 17. Proportion of Subjects Receiving Each Dose Level or On Treatment Pause



Source: SELECT CTR, Figure 14.1.11

Post hoc (post-randomization) analyses that evaluated the primary endpoint by dose group were conducted to explore whether allowing for a more permissive down-titration approach to dosing would still allow for acceptable efficacy. The applicant conducted a number of relevant analyses; the exploratory analysis shown in Table 29 evaluated first MACE by most common dose.

All estimated HRs remained below 1 for all dose groups analyzed. Although there seemed to be a reverse dose effect, the applicant points out that the reasons for staying on, or down-titrating to, a lower dose may not be the same in the 2 treatment groups, and patients who are more frail, sick, or susceptible to side effects could be those who required lower doses. Nevertheless, the applicant's interpretation is that the CV benefits of semaglutide may persist on doses lower than 2.4 mg.

Reviewer comment: It should be noted that I had an internal discussion with Dr. Edwin Chow (FDA Clinical Pharmacology) about the exploration of the primary endpoint by dose group. In Dr. Chow's opinion, because the analyses of time to first MACE by dose group were based on post-randomized group comparisons, and the results are not clearly dose-related – likely due to confounding by reason for dose-reduction – these findings are uninterpretable.

Nevertheless, given the strength of the results overall, I believe that limiting the labeled dose to 2.4 mg or 1.7 mg could result in patients being taken off a drug that is beneficial for reduction of CV events. These findings are also consistent with semaglutide (Ozempic) at doses of 0.5 mg or 1 mg being shown to reduce CV events in patients with T2D. Labeling should allow for dose flexibility for tolerability.

Table 29. Time to First MACE by Most Common Dose Group

	N	Observation time (years)	Events E (%)	R	Hazard ratio	95% CI
Most common dose: 0 mg						
Sema 2.4 mg	1697	5490	111 (6.5)	2.0		
Placebo	1133	3610	79 (7.0)	2.2		
Sema 2.4 mg / Placebo					0.92	[0.69; 1.23]
Most common dose: 0.24 mg						
Sema 2.4 mg	311	887.7	46 (14.8)	5.2		
Placebo	103	126.0	54 (52.4)	42.9		
Sema 2.4 mg / Placebo					0.18	[0.12; 0.27]
Most common dose: 0.5 mg						
Sema 2.4 mg	336	1010	41 (12.2)	4.1		
Placebo	46	73.0	21 (45.7)	28.8		
Sema 2.4 mg / Placebo					0.17	[0.10; 0.29]
Most common dose: 1 mg						
Sema 2.4 mg	482	1504	39 (8.1)	2.6		
Placebo	76	165.2	23 (30.3)	13.9		
Sema 2.4 mg / Placebo					0.20	[0.12; 0.33]
Most common dose: 1.7 mg						
Sema 2.4 mg	422	1359	33 (7.8)	2.4		
Placebo	160	453.9	25 (15.6)	5.5		
Sema 2.4 mg / Placebo					0.45	[0.27; 0.75]
Most common dose: 2.4 mg						
Sema 2.4 mg	5555	18404	299 (5.4)	1.6		
Placebo	7283	23869	499 (6.9)	2.1		
Sema 2.4 mg / Placebo					0.78	[0.67; 0.90]

Data from the in-trial period. Time from randomisation to first EAC-confirmed MACE was analysed separately within each dose group using a Cox proportional hazards model with treatment as factor. Subjects without events of interest were censored at the end of their in-trial period.
N: number of subjects contributing to the analysis. E: number of first events, (%): percentage of subjects with at least one event. R: events per 100 years of observation.
CI: confidence interval, EAC: event adjudication committee, MACE: major adverse cardiovascular event.
Source: Statistical information request, dated January 29, 2024, Table 5

Durability of Response

As displayed in the cumulative incidence plot for primary MACE (Figure 7), first MACE occurred throughout the entire in-trial observation period, with a lower incidence for semaglutide than placebo that continued over time.

Persistence of Effect

The persistence of the weight loss effect was described in the original Wegovy review (during the randomized withdrawal period of study 4376, weight was regained after study drug discontinuation). Persistence of the cardiovascular effect after drug discontinuation was not evaluated in the SELECT trial.

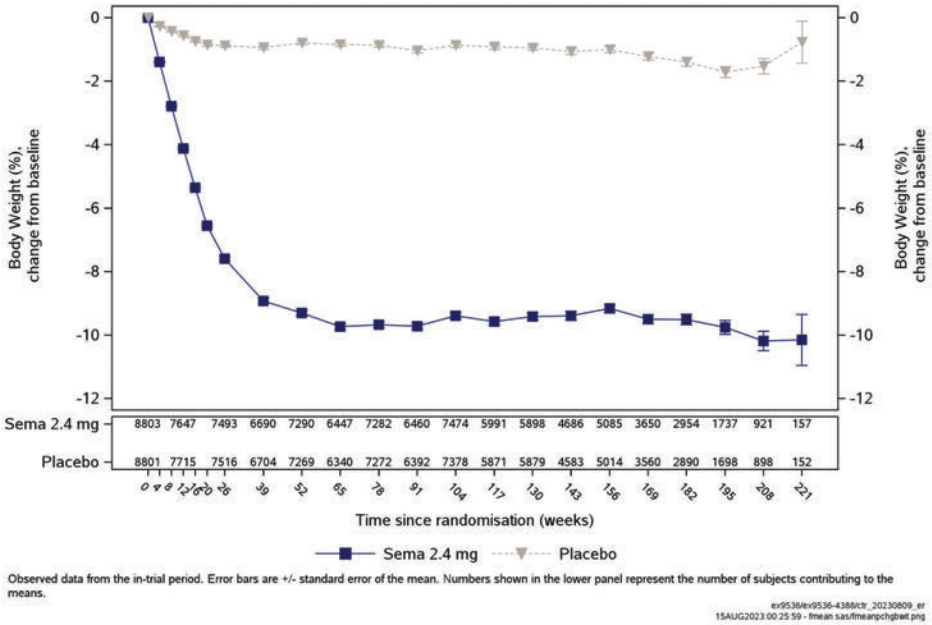
Additional Analyses Conducted on the Individual Trial

Supportive secondary endpoints, such as changes in body weight, glycemia, blood pressure, lipids, and others were measured at week 104 of this trial, a longer study duration than the original phase 3 premarketing trials that were designed to support treatment benefit for chronic weight management (generally 68 weeks, which included a 16-week dose-escalation period and a 52-week maintenance period).

Body Weight

At baseline, mean body weight was 96.5 kg for the semaglutide group and 96.8 kg for the placebo group. The percent change from baseline in body weight at week 104 was -9.39% in the semaglutide group and -0.88% in the placebo group, with a treatment difference of -8.51 percentage points (95% CI -8.75, -8.27). As seen in Figure 18, mean weight loss plateaued at approximately 65 weeks and remained essentially stable over time.

Figure 18. Body Weight (%) Change from Baseline by Week

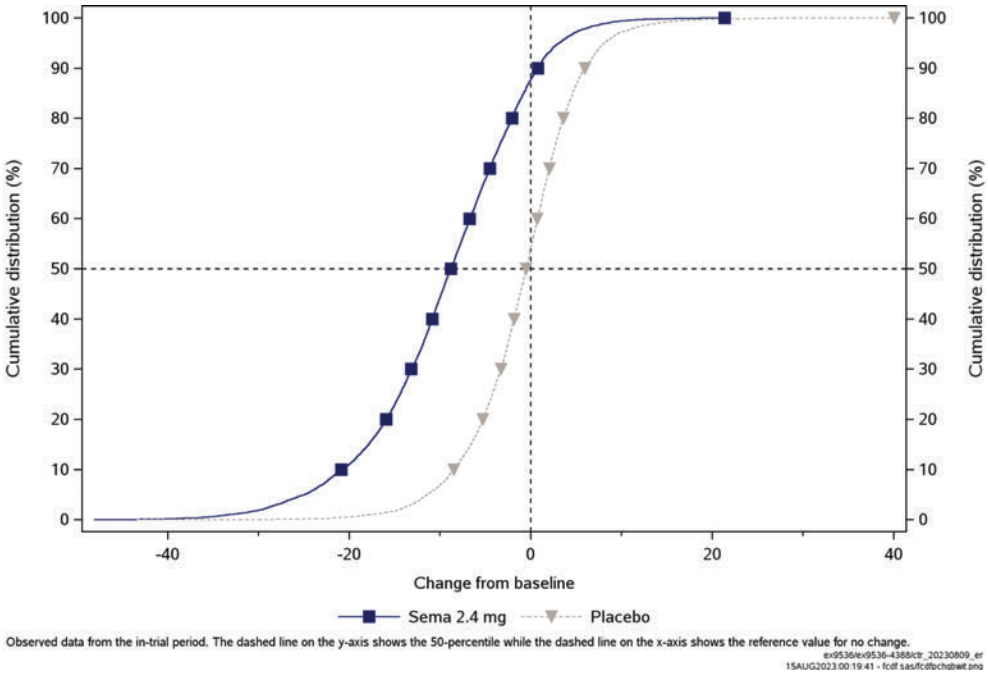


Source: SELECT CTR, Figure 14.2.111

Similarly, a cumulative distribution figure shows a leftward shift for semaglutide vs. placebo (Figure 19). At week 104, approximately 58% of semaglutide-treated subjects and 18% of placebo-treated subjects lost at least 5% of body weight; the proportions of those who lost 10% body weight were 38% and 6%, and the proportion of those who lost 15% were 20% and 1%,

respectively, for semaglutide and placebo.[39]

Figure 19. Body Weight (%) Change from Baseline at Week 104, Cumulative Distribution Function Plot



Source: SELECT CTR, Figure 14.2.116

Waist Circumference

At baseline, mean waist circumference was 111.3 cm for the semaglutide group and 111.4 cm for the placebo group. The change in mean waist circumference from baseline at week 104 was -7.56 cm in the semaglutide group and -1.03 cm in the placebo group, with and estimated treatment difference of -6.53 cm (-6.79, -6.27).[40]

Glycemic Status

At baseline, mean HbA1c was 5.78% in both the semaglutide and placebo groups. Although subjects with diabetes were not eligible for the trial, 7 subjects (3 in the semaglutide group and 4 in the placebo group) had HbA1c ≥ 6.5% at screening and were randomized in error.

The estimated change in mean HbA1c (%-point) from baseline at week 104 for the 2 treatment

[39] SELECT CTR, Table 14.2.119
[40] SELECT CTR, Table 14.2.124

groups and the estimated treatment difference are presented in Table 30, showing a favorable change in the semaglutide group.

Table 30. Mean Change in HbA1c at Week 104

Treatment	N	Baseline Mean	Week 104 Mean	Change from Baseline ANCOVA
Semaglutide	8803	5.78%	5.47%	-0.31
Placebo	8801	5.78%	5.79%	+0.01
Semaglutide vs. Placebo		Between treatment difference (95% CI)		
		-0.32 (-0.33, -0.31)		

Glycemic status was categorized by the investigator as normoglycemia, prediabetes, or type 2 diabetes based on the evaluation of all available relevant information according to ADA criteria.[41] At baseline, approximately 65% of subjects had pre-diabetes and 35% were normoglycemic, and this was balanced between groups. An end-of-trial shift table (Table 31) suggests that more subjects on placebo had deterioration of glycemic status than semaglutide-treated subjects, and conversely, more subjects on semaglutide had improvements in glycemic status vs. placebo.

Table 31. Glycemic Status at End of Trial, Shift Table

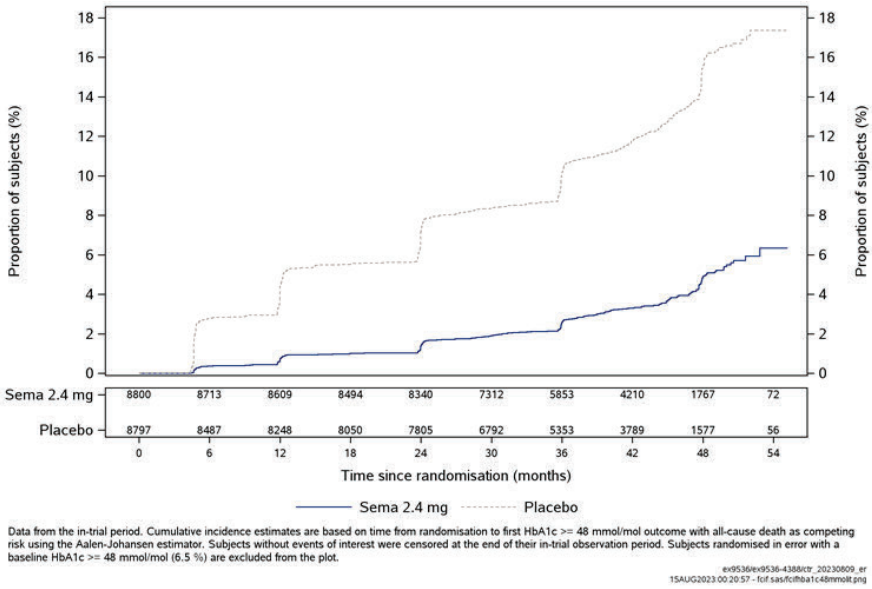
Glycemic status at end-of-trial	Semaglutide	Placebo
N	7819 (88.8)	7676 (87.2)
Normoglycemia at baseline		
Normoglycemia	2324 (26.4)	1849 (21.0)
Pre-diabetes	358 (4.1)	840 (9.5)
Diabetes	46 (0.5)	71 (0.8)
Pre-diabetes at baseline		
Normoglycemia	2856 (32.4)	1080 (12.3)
Pre-diabetes	2015 (22.9)	3083 (35.0)
Diabetes	220 (2.5)	753 (8.6)

Source: SELECT CTR, Table 14.2.205

The proportions in each treatment group with at least 1 occurrence of HbA1c ≥ 6.5% in the trial are 3.5% for semaglutide and 12.0% for placebo. Time from randomization to first occurrence of HbA1c ≥ 6.5% is shown in the figure below.

[41] American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S13-S27.

Figure 20. Time from Randomization to First Occurrence of HbA1c of 6.5% or Greater



Source: SELECT CTR, Figure 11-26

Reviewer comment: The clinical significance of the shifts and time to event is unclear. For example, it is unknown if the fewer "diabetes" diagnoses in the semaglutide group are true prevention of the disease state versus masking due to effects on blood glucose. Effects on clinical outcomes related to hyperglycemia, such as microvascular complications, would be helpful in interpreting these data.

Blood Pressure

At baseline, mean systolic blood pressure (SBP) was 131 mmHg and mean diastolic blood pressure (DBP) was 79 mmHg in both treatment groups. Nominally statistically significant decreases in SBP and DBP were observed at week 104 in the semaglutide group compared to placebo. It should be noted that this trial was not designed to evaluate semaglutide on blood pressure; however, an approximately 3 mmHg decrease in SBP in the semaglutide arm would be likely clinically meaningful.[42]

[42] FDA Draft Guidance for Industry: *Assessment of Pressor Effects of Drugs*; February 2022.

Table 32. SBP Change from Baseline at Week 104

	FAS	N	Estimate	SE	95% CI	p-value
Week 104						
Systolic Blood Pressure (mmHg)						
Mean at Week 104 (visit 14)						
Sema 2.4 mg	8803	8602	127.18	0.16		
Placebo	8801	8567	130.49	0.16		
Change from baseline at Week 104 (visit 14)						
Sema 2.4 mg	8803	8602	-3.82	0.16		
Placebo	8801	8567	-0.51	0.16		
Treatment difference at Week 104 (visit 14)						
Sema 2.4 mg - Placebo			-3.31		[-3.75 ; -2.88]	<.0001

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. Mean estimates were adjusted according to observed baseline distribution.
N: number of subjects contributing to the analysis, p-value: two-sided p-value for test of no difference.
CI: confidence interval, FAS: Full analysis set, SE: Standard error.

Source: SELECT CTR, Table 14.2.131

Table 33. DBP Change from Baseline at Week 104

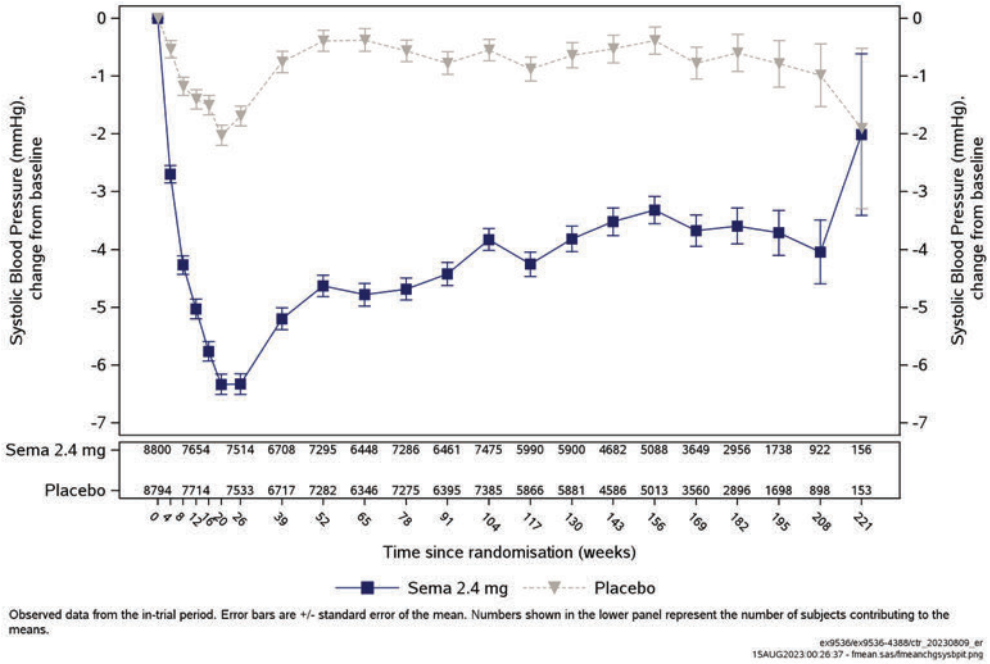
	FAS	N	Estimate	SE	95% CI	p-value
Week 104						
Diastolic Blood Pressure (mmHg)						
Mean at Week 104 (visit 14)						
Sema 2.4 mg	8803	8602	78.30	0.10		
Placebo	8801	8567	78.85	0.10		
Change from baseline at Week 104 (visit 14)						
Sema 2.4 mg	8803	8602	-1.02	0.10		
Placebo	8801	8567	-0.47	0.10		
Treatment difference at Week 104 (visit 14)						
Sema 2.4 mg - Placebo			-0.55		[-0.83 ; -0.27]	0.0001

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. Mean estimates were adjusted according to observed baseline distribution.
N: number of subjects contributing to the analysis, p-value: two-sided p-value for test of no difference.
CI: confidence interval, FAS: Full analysis set, SE: Standard error.

Source: SELECT CTR, Table 14.2.138

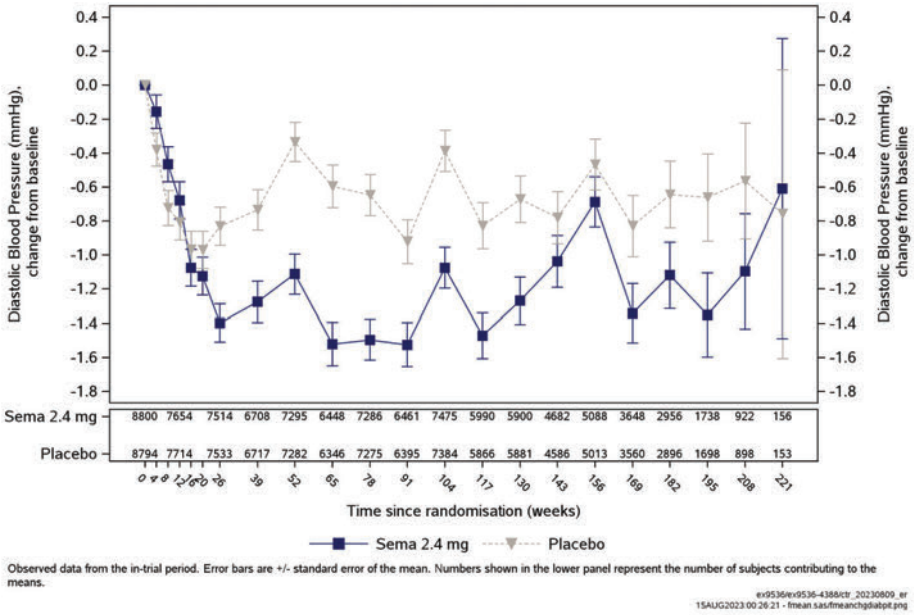
Peak SBP decrease was seen in both groups around 20 weeks, with attenuation of effect over time (Figure 21). Changes in DBP over time were more variable in both groups (Figure 22).

Figure 21. SBP Change from Baseline Over Time



Source: SELECT CTR, Figure 14.2.130

Figure 22. DBP Change from Baseline Over Time



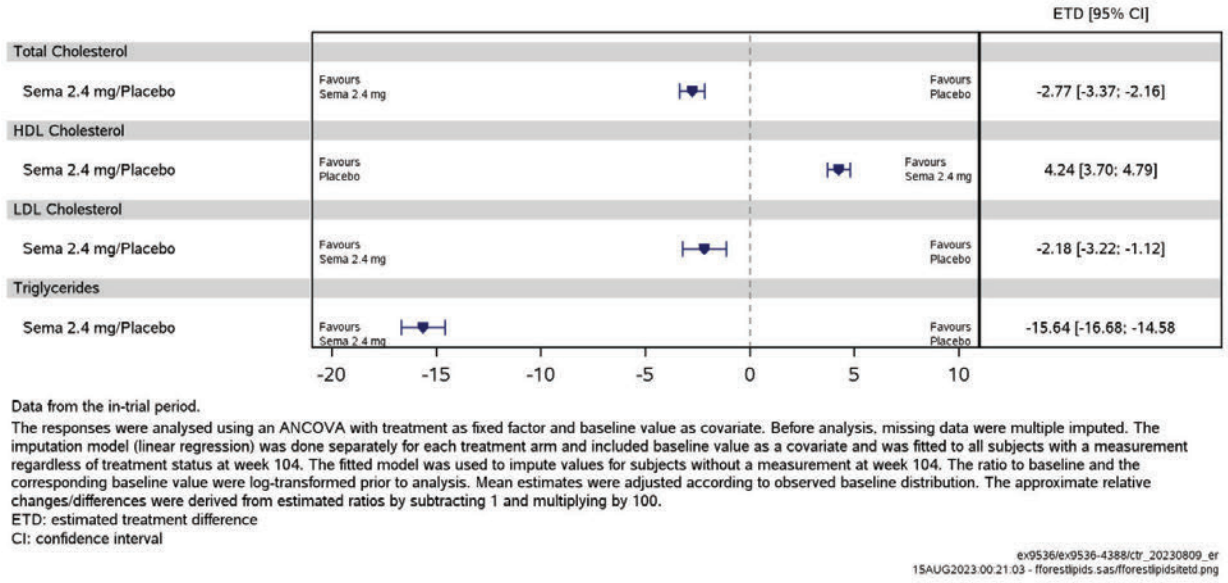
Source: SELECT CTR, Figure 14.2.137

Lipids

At baseline, lipid parameters were similar between treatment groups; see Table 5. Despite 87.6% of subjects on statins at baseline, LDL-C was not optimally treated in this population with established ASCVD (baseline: 78.5 mg/dL), although it is likely reflective of what is achievable in a real-world clinical scenario.

At week 104, change in total cholesterol was -4.63% for semaglutide and -1.92% for placebo;[43] change in LDL-C was -5.25% for semaglutide and -3.14% for placebo;[44] change in HDL-C was +4.68% for semaglutide and +0.59 for placebo;[45] and change in TG was -18.34% for semaglutide and -3.20% for placebo.[46] Estimated treatment differences were therefore relatively small; see Figure 23.

Figure 23. Estimated Treatment Difference in Percent Change from Baseline in Lipids



Source: SELECT CTR, Figure 14.2.175

Kidney Function

The potential effect of semaglutide on kidney function in SELECT was assessed by time to first occurrence of a 5-component composite nephropathy endpoint, as a supportive secondary

[43] SELECT CTR, Table 14.2.158
[44] SELECT CTR, Table 14.2.163
[45] SELECT CTR, Table 14.2.168
[46] SELECT CTR, Table 14.2.173

endpoint:

- Onset of persistent macroalbuminuria (UACR >300 mg/g)
- Persistent 50% reduction in eGFR
- Onset of persistent eGFR <15 ml/min/1.73 m^2
- Initiation of chronic renal replacement therapy (dialysis or transplantation) – evaluated by the EAC
- Renal death – evaluated by the EAC

A total of 353 first composite nephropathy events with onset during the in-trial observation period occurred, with 1.8% of semaglutide participants reporting an event (rate of 0.5 events per 100 PYO), vs. 2.2% of placebo participants (rate of 0.7 events per 100 PYO). This apparent treatment difference was primarily attributable to a smaller number of persistent macroalbuminuria events with semaglutide vs. placebo (Table 34).

Table 34. First Composite Nephropathy Event

	Semaglutide N=8803 n (%)	**Placebo N=8801 n (%)**
First composite nephropathy event	155 (1.8)	198 (2.2)
Persistent macroalbuminuria	144 (1.6)	179 (2.0)
Persistent reduction in eGFR	9 (0.1)	15 (0.2)
Onset of persistent eGFR < 15 mL/min/1.73m^2	1 (<0.1)	1 (<0.1)
Initiation of chronic renal replacement therapy	1 (<0.1)	3 (<0.1)
Dialysis	1 (<0.1)	3 (<0.1)
Renal death	0	0
Persistent macroalbuminuria is defined as UACR >300 mg/g Persistent reduction in eGFR is defined as 50% reduction in eGFR compared with baseline (randomization) Chronic renal replacement therapy is defined as dialysis or transplantation Persistent is defined as having 2 consecutive measurements at least 4 weeks apart fulfilling the criteria The eGFR was calculated using the CKD-EPI formula. Events not related to eGFR were EAC-confirmed		

Source: SELECT CTR, Table 11-23

Other Supportive Secondary and Exploratory Efficacy Outcomes

Patient reported outcomes

- The EuroQol five dimensions five level (EQ-5D-5L) questionnaire is a PRO tool. The tool is used to estimate the impact on subjects' health-related quality of life and provides 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. At baseline, mean EQ-5D-VAS score was 77.15 both in the semaglutide group and in the placebo group. Change in mean EQ-5D-VAS score from baseline at week 104 was a

supportive secondary endpoint. The mean change from baseline in semaglutide was +2.52 and in placebo +0.92, with an estimated treatment difference of 1.60 (1.16, 2.04).

- The weight-related signs and symptoms measure (WRSSM) is a PRO questionnaire designed to assess symptoms commonly associated with overweight and obesity. WRSSM total scores range from 0 to 4, with higher scores reflecting worse symptomatology. At baseline, mean WRSSM total score was 1.12 for the semaglutide 2.4 mg group and 1.13 for the placebo group. Change in WRSSM was analyzed descriptively. At week 104, mean change in semaglutide was -0.26 and in placebo -0.12.

Hospitalizations

Two exploratory endpoints derived from all-cause hospitalizations were analyzed as: 1) a recurrent event process, and 2) duration, i.e., length of stay in hospital. All-cause death was considered a competing risk (terminal event). Observations were censored as time-to-event endpoints.

- In the semaglutide group, number of hospitalizations was 5347 and in the placebo group 5941 for the in-trial period, with an estimated mean ratio of 0.90 (0.85, 0.95).

- Number of hospitalization days per subject were estimated for weeks 52, 104, 156, and 208 for each of the 2 treatment groups based on the observed data; at week 104, estimated mean ratio was 0.85 (0.76, 0.96).

hs-CRP

At baseline, geometric mean hsCRP was 1.96 mg/L for the semaglutide group and 1.91 mg/L for the placebo group. At week 104, the geometric mean hsCRP was 1.16 mg/L and 1.86 mg/L for the placebo group, for a treatment ratio of 0.62 (0.60, 0.64).

Smoking status

At baseline, the proportion of smokers was 16.9% for the semaglutide group and 16.6% for the placebo group. At week 104, the proportions of subjects who were smokers were 15.7% in both treatment groups, with an odds ratio of 0.94 (0.82, 1.08). The finding was similar at week 52. Semaglutide did not appear to affect smoking status in this study.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Not applicable to this review; there is only 1 trial.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

SELECT is the first trial to demonstrate a beneficial effect on MACE with a drug intended to treat a manifestation of obesity. Its CV benefit appears consistent across important demographic and clinical subgroups, but there are some uncertainties. The trial's racial diversity was not reflective of the US population and only 28% of the study population was female. However, strengths of the study are its size and duration. Despite many subjects starting and stopping drug or taking lower doses for reasons of tolerability, the result was robust and clinically meaningful. This suggests that the benefit will be achieved in a "real-world" postmarket setting.

7.2.2. Other Relevant Benefits

It is noted that there were numerically fewer subjects with deaths related to COVID-19 in the semaglutide group (n=43) vs. the placebo group (n=65). While this is not part of the primary endpoint and was not assessed formally in the hierarchy, it is worth considering how the pandemic may have impacted the primary endpoint and overall benefits and risks of semaglutide in this population. It is plausible that as COVID-19 morbidity and mortality particularly affect patients with obesity, the treatment effect of semaglutide might have benefited these patients. It may also be that ascertainment challenges during the pandemic could have contributed to misclassification or problems with capture of events. The strength of the all-cause mortality endpoint is reassuring in this regard given the low amount of missing data and lack of reliance on supporting documentation for adjudication.

Three supplementary analyses were conducted by the applicant to assess the impact of the COVID-19 pandemic on the primary endpoint. The analyses address 2 scenarios: one where MACE have been impacted by an increased MACE rate and potentially a different treatment effect for events occurring concurrently with COVID-19 infection; the other with a reduced MACE rate due to concurrent COVID-19 infection leading to fewer CV deaths as the subject died (prematurely) of COVID-19 infection and not their underlying atherosclerotic disease.

- Time from randomization to first MACE without concurrent COVID-19 SAE: The definition of MACE was modified so any MACE occurring concurrently with a COVID-19 SAE in a subject

was not considered a MACE. The observation period and censoring were not changed. Any subsequent MACE could qualify to be the first MACE for the subject.

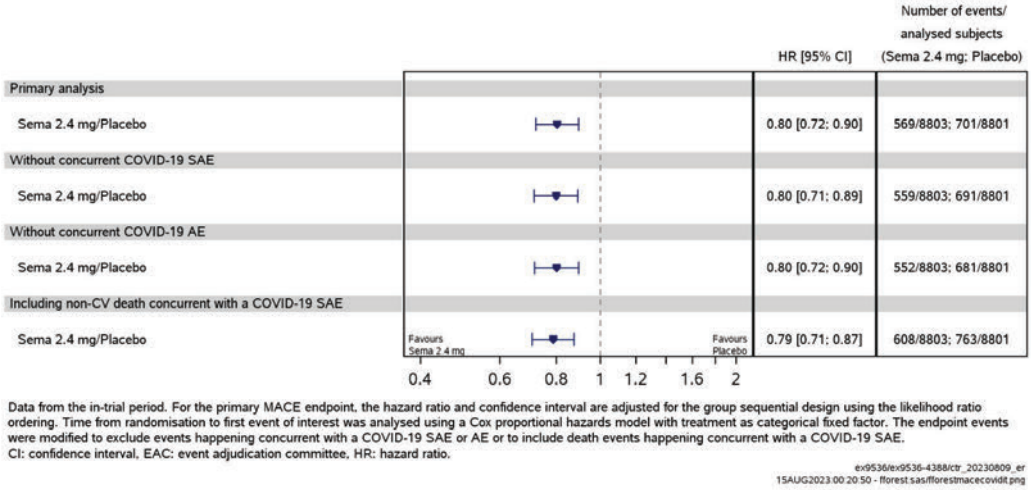
- Time from randomization to first MACE without concurrent COVID-19 AE: The definition of MACE was modified so any MACE occurring concurrently with a COVID-19 AE in a subject was not considered a MACE. The observation period and censoring were not changed. Any subsequent MACE could qualify to be the first MACE for the subject.

- Time from randomization to first MACE or non-CV death occurring concurrently with a COVID-19 SAE. The definition of MACE was modified to include non-CV deaths potentially related to COVID-19. The observation period and censoring were not changed.

A MACE was considered concurring with a COVID-19 AE if the event occurred in the time period from the start day of the COVID-19 AE and until 30 days after the last of the following 2 dates: the stop date of the COVID-19 AE or the end of hospitalization date for a hospitalization reported together with the COVID-19 AE.

The results of the supplementary analyses were consistent with the result from the primary analysis (Figure 24).

Figure 24. COVID-19 Impact on Primary Endpoint, Sensitivity Analyses



Data from the in-trial period. For the primary MACE endpoint, the hazard ratio and confidence interval are adjusted for the group sequential design using the likelihood ratio ordering. Time from randomisation to first event of interest was analysed using a Cox proportional hazards model with treatment as categorical fixed factor. The endpoint events were modified to exclude events happening concurrent with a COVID-19 SAE or AE or to include death events happening concurrent with a COVID-19 SAE.
CI: confidence interval, EAC: event adjudication committee, HR: hazard ratio.

ex9536/ex9536-4388/ctr_20230809_er
15AUG2023 00:20:50 - florest.sas/fforestmacecovidit.png

Source: SELECT CTR, Figure 14.2.217

7.3. Integrated Assessment of Effectiveness

The results of the SELECT trial meet the statutory requirement for substantial evidence of efficacy for cardiovascular risk reduction in a population of patients with obesity without type 2

diabetes. This determination is based on a single adequate and well-controlled clinical trial as defined in FDA guidance,[47] given the size of the trial and its clinically meaningful and statistically persuasive effect on cardiovascular outcomes (MACE). The primary analysis is supported by favorable findings for each of the components, consistency in subgroups, similar results when evaluating for missing data in sensitivity analyses, and (although not formally statistically significant) a reduction in all-cause mortality with good vital status collection. In addition, highly similar effects of semaglutide in a population of patients with type 2 diabetes[48] strongly support this finding in SELECT and, although not necessary for approval, can be considered supportive evidence.

Because this is the first drug that has ever been demonstrated to reduce CV risk in a population of patients with overweight and obesity without diabetes, the mechanism of the effect is a matter of interest. For example, it is noted that the separation of the cumulative incidence curves occurred very early in the trial, suggesting that the effects may not be mediated by weight loss alone. Furthermore, as semaglutide and other members of the GLP-1 RA class have also demonstrated CV risk reduction in T2D, causes of CV benefit may be multifactorial. The applicant conducted a post hoc evaluation[49] of potential mediators of MACE reduction with semaglutide, including SBP, LDL-C, hsCRP, body weight, and HbA1c. Table 35 suggests that the estimated percentage mediation ranges from 11% (LDL-C) to 42% (hsCRP), and overall ~38%, although the results are not statistically significant and, therefore, should be interpreted with caution. The applicant suggests that approximately 60% of the semaglutide effect may not be explained by mediators measured in the trial; however, this analysis is considered exploratory based on its post hoc nature, lack of statistical significance, and inability to assess unmeasured confounders. The methods and assumptions underlying the results were not formally reviewed by the statistical review team.

[47] Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (December 2019)
[48] Ozempic (semaglutide) USPI
[49] Vansteelandt S, Linder M, Vandenberghe S, Steen J, Madsen J. Mediation analysis of time-to-event endpoints accounting for repeatedly measured mediators subject to time-varying confounding. Stat Med. 2019;38(24):4828 40.

Table 35. Time from Randomization to First EAC-Confirmed MACE Adjusted for Potential Mediators

	Probability of no event at 36 months										
		Sema 2.4 mg		Total effect			Direct effect			Percentage mediation	
Variable	Sema 2.4 mg	adjusted	Placebo	Estimate	95% CI		Estimate	95% CI		Estimate	95% CI
Body Weight (kg)	0.941	0.939	0.929	0.012	[0.004;	0.019]	0.009	[-0.001;	0.019]	19.5	[-31.9; 109.8]
HbA1c (%)	0.941	0.938	0.929	0.012	[0.004;	0.019]	0.008	[-0.001;	0.018]	29.0	[-18.1; 121.7]
hsCRP (mg/l)	0.941	0.936	0.929	0.013	[0.005;	0.020]	0.007	[-0.001;	0.016]	42.1	[18.0; 110.6]
SBP (mmHg)	0.941	0.940	0.929	0.012	[0.004;	0.019]	0.010	[0.002;	0.018]	14.3	[-5.5; 51.7]
LDL cholesterol (mmol/L)	0.942	0.940	0.930	0.012	[0.005;	0.020]	0.011	[0.003;	0.018]	10.9	[1.1; 36.2]
All	0.942	0.937	0.929	0.012	[0.005;	0.020]	0.008	[-0.004;	0.018]	37.9	[-19.2; 160.8]

FAS in-trial. Probabilities of no event are estimated using Vansteelandt mediation analysis for repeatedly measured mediators. The treatment effects are evaluated as difference in probabilities of no event. Percentiles based on 1000 bootstrap replicates are used to calculate confidence intervals.
BW: body weight; CI: confidence interval, EAC: event adjudication committee, FAS: full analysis set; HbA1c: glycosylated haemoglobin, hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; MACE: major cardiovascular event; SBP: systolic blood pressure.

Source: Module 5.3.5.3, Potential mechanisms for cardiovascular risk reduction of semaglutide 2.4 mg, Table 1-1

APPEARS THIS WAY ON ORIGINAL

8. Review of Safety

8.1. Safety Review Approach

Because of the experience with the safety of semaglutide and other GLP-1 RAs in large global clinical programs for T2D and CWM, as well as years of post-marketing experience, the applicant undertook a somewhat streamlined collection of safety in SELECT. 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 collection via a specific event form [see Table 36, below], and events for adjudication). Non-serious AEs not fulfilling 1 or more of the listed criteria were not systematically collected. Endpoints relating to EAC-confirmed events for evaluation of cardiovascular events, mortality, heart failure, and kidney outcomes are described in Section 6.1.2.

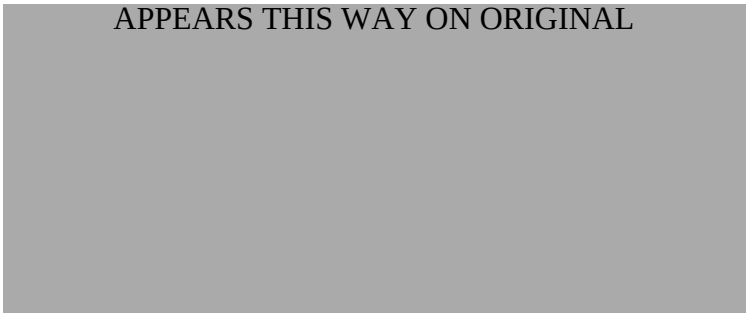


Table 36. AEs Requiring Additional Data Collection (via specific event forms) and Events for Adjudication

Event type (serious and non-serious) including description	Adjudication Outcome	Additional form required
Death: All-cause death	• CV death • Renal death • Non-CV, non-renal death	Adjudication form
Acute coronary syndrome: Conditions include all types of acute MI and hospitalisation for UAP	• Acute MI • Hospitalisation for UAP	Adjudication form
Stroke (Stroke and transient ischemic attack): Episode of focal or global neurological dysfunction that could be caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or ischemia, with or without infarction	• Stroke	Adjudication form
Coronary artery revascularisation: A catheter-based (PCI) or a surgical procedure (CABG) designed to improve myocardial blood flow	• Coronary revascularisation procedure	Adjudication form
HF hospitalisation or urgent HF visit: Presentation of the subject for an urgent, unscheduled hospital admission or clinic/office/emergency department visit with a primary diagnosis of heart failure (new episode or worsening of existing heart failure)	• HF hospitalisation • Urgent HF visit	Adjudication form
Pancreatitis: Any event of pancreatitis should be reported	• Acute pancreatitis	Adjudication form Specific event form
Nephropathy (events leading to renal replacement therapy): Initiation of dialysis treatment (haemodialysis or peritoneal dialysis) or kidney transplantation Note: The underlying condition should be reported as the AE diagnosis	• Chronic renal replacement therapy	Adjudication form
Acute renal failure: Abrupt decrease in renal function, e.g. one of the following: 1) ≥0.3 mg/dL (≥26.5 µmol/L) increase in serum creatinine within 48 hours 2) ≥1.5 times increase in serum creatinine within 7 days 3) urine volume <0.5 mL/kg/h for 6 hours	Not applicable	Specific event form
Gallbladder disease: Event of biliary colic, cholecystitis and other forms of gallbladder disease	Not applicable	Specific event form
Malignant neoplasm: Malignant neoplasm by histopathology or other substantial clinical evidence	Not applicable	Specific event form

Event type (serious and non-serious) including description	Adjudication Outcome	Additional form required
Medication error (accidental errors): A medication error concerning trial products is defined as: • Administration of wrong drug. Note: Use of wrong DUN is not considered a medication error unless it results in a confirmed administration of wrong drug. • Wrong route of administration, such as intramuscular instead of subcutaneous. • Accidental overdose administration of more than 2.4 mg/week or a higher dose than intended during dose escalation, however, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur. Treatment pauses should not be reported as a medication error	Not applicable	Specific event form
Misuse or abuse of trial product: Misuse is when the trial product is intentionally and inappropriately used. Abuse of trial product is persistent or sporadic, intentional excessive use, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm)	Not applicable	Specific event form

Abbreviations: AE = adverse event; CABG = coronary artery bypass surgery; CV = cardiovascular; DUN = dispensing unit number; HF = heart failure; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Source: SELECT CTR, Table 9-5

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety evaluation was based on the FAS using the in-trial observation period. Subjects were on treatment for an average of 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.

Table 37. Participant Exposure by Duration

	≥ 1 dose	≥12 months	≥24 months	≥36 months	≥48 months
Semaglutide	N=8794	N=7509	N=6808	N=4382	N=897
Placebo	N=8782	N=7932	N=7261	N=4716	N=961

Source: SELECT CTR, Table 10-14

8.2.2. Relevant characteristics of the safety population:

As the safety population is the same as the efficacy population (FAS), the reader is referred to Section 6.1.2 for discussion of the subject characteristics. Specific medical history is discussed in relevant sections of the safety review.

8.2.3. Adequacy of the safety database:

The safety database is adequate; this is a large, multi-year CVOT.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The SELECT trial was a well-conducted, high-quality trial, with an event adjudication committee (EAC) that was utilized to evaluate a number of events and had several layers of quality control.

Adjudication quality control is described in the discussion of efficacy in Section 6.1.1.

A single site was noted as an outlier for AE reporting. Site 3031 (location: Russian Federation) enrolled 50 subjects but had no reported AEs or adjudicated events. When the applicant was queried about this site, they noted the Novo Nordisk affiliate in Russia has worked with site 3031 for many years and the site has successfully taken part in several trials and passed audits. In the SELECT trial, it is correct that there were no SAEs reported, however, in other Novo Nordisk trials, there were SAEs reported by the site. Thus, the site staff reported adverse events if any occurred. Over the course of 5 years, 32 monitoring visits were made to the site. During the monitoring visits, the monitor is reviewing source documents for SAEs. Per monitoring

report, adverse events not requiring reporting per protocol were noted in the source documents at site and reporting of adverse events were discussed with investigator at some monitoring visits. In the country level trial monitoring for Russia, it was observed that no SAEs were reported at site 3031.

Five other sites were noted to not have reported any adverse events; however, those sites only randomized 1 or 2 subjects each.

8.3.2. Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 was used to code AEs in SELECT. During the review, I did not have significant concerns about how SAE preferred terms were mapped from investigators' verbatim terms as they were evaluated.

8.3.3. Routine Clinical Tests

Routine clinical tests included vital signs, safety labs (chemistry and hematology), pregnancy tests, and body weight. Testing occurred more frequently early in the trial (see Table 38 for timing of testing). The scope of routine clinical tests was appropriate for a CVOT of this size and duration evaluating a drug with a well-characterized safety profile.

Table 38. SELECT Flowchart

	Screening	Randomisation	Dose escalation period				Maintenance period																		End of treatment	End of trial
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V-EOT[a]	P-FU[a]
Timing of Visit (Weeks)	Up to -3[b]	0	4	8	12	16	20	26	39	52	65	78	91	104	117	130	143	156	169	182	195	208	221	234	End of treatment	V-EOT + 5 weeks
Visit Window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Informed consent Appendix 3	X																									
Demography[c]	X																									
Barriers and motivation interview (9)	X																									
Childbearing potential	X																									
In/exclusion criteria (6.1)(6.2)	X																									
Hand out ID card	X																									
Randomisation criteria(6.4)		X																								
Medical history/ Concomitant illness (9.4)		X																								
Tobacco Use[d]		X								X				X				X				X			X	
Concomitant medication (7.8)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-questionnaire (9.1.3)		X					X			X				X				X				X			X	
Weight related sign and symptom measure (9.1.3)		X					X			X				X				X				X			X	

	Screening	Randomisation	Dose escalation period				Maintenance period																		End of treatment	End of trial
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V-EOT[a]	P-FU[a]
Timing of Visit (Weeks)	Up to -3[b]	0	4	8	12	16	20	26	39	52	65	78	91	104	117	130	143	156	169	182	195	208	221	234	End of treatment	V-EOT + 5 weeks
Visit Window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Subject engagement assessment[e] (9.1.3)							X			X				X				X				X				
Height (9.1.1)	X																									
Body Weight (9.1.1)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Waist Circumference (9.1.1)		X					X			X				X				X				X			X	
Vital Signs (9.4.3)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[f] (Appendix 2)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (9.4.2)	X																								X	
Central laboratory assessments																										
HbA_{1c} (Appendix 2)	X						X			X				X				X				X			X	
Haematology[g] (Appendix 2)		X					X			X				X				X				X			X	
Biochemistry[g,h] (Appendix 2)		X					X			X				X				X				X			X	
Lipids[g] (Appendix 2)		X					X			X				X				X				X			X	

	Screening	Randomisation	Dose escalation period				Maintenance period																		End of treatment	End of trial
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V-EOT[a]	P-FU[a]
Timing of Visit (Weeks)	Up to -3[b]	0	4	8	12	16	20	26	39	52	65	78	91	104	117	130	143	156	169	182	195	208	221	234	End of treatment	V-EOT + 5 weeks
Visit Window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
High sensitive C-reactive protein[g] (Appendix 2)		X					X			X				X				X				X			X	
Urinalysis[g] (Appendix 2)		X					X			X				X				X				X			X	
Biosamples for future analysis (biobank, genetics)[i] (Appendix 2)		X																								
Biosamples for future analysis (biobank, biomarkers)[j] (Appendix 2)		X					X							X												
Non-SAE hospitalisation (9.1.4.1)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events[j] (9.2)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaints (9.2.8, Appendix 6)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Evaluation of glycaemic status (9)		X						X			X				X				X				X			X
Trial product dose (7.1)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IWRS session	X	X		X		X		X		X		X		X		X		X		X		X		X	X	
Dispensing visit		X		X		X		X		X		X		X		X		X		X		X		X		
Drug accountability (7.5)				X		X		X		X		X		X		X		X		X		X		X	X	
Healthy lifestyle counselling session (7.7)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

	Screening	Randomisation	Dose escalation period				Maintenance period																	End of treatment	End of trial
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V-EOT[a]	P-FU[a]
Timing of Visit (Weeks)	Up to -3[b]	0	4	8	12	16	20	26	39	52	65	78	91	104	117	130	143	156	169	182	195	208	221	234	End of treatment	V-EOT + 5 weeks
Visit Window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Hand out directions for use[k] (7.1.1)		X		X		X		X		X		X		X		X		X		X		X		X		
Hand out dose reminder card		X	X	X	X	X																				
Training in trial product, pen-handling[l] (7.1.1)		X	X	X	X	X				X				X				X				X				
Ensure updated contact persons list (9)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Breast neoplasms follow-up[m] (9.4)																									X	X
Colon neoplasms follow-up (9.4)																									X	X
End of trial																										X

[a] End of treatment and End of trial visits will be scheduled according to trial completion
[b] It can take up to 3 weeks from screening of first subject to delivery of trial product
[c] Demography consists of date of birth, sex, ethnicity and race (according to local regulation)
[d] Tobacco use/smoking is defined as smoking at least one cigarette or equivalent daily

[e] Only for a sub-set of subjects
[f] Only applicable for women of childbearing potential; urine HCG. For country specific requirements, please see Appendix 9: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden, United Kingdom.
[g] Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden, United Kingdom: For country specific requirements, please see Appendix 9
[h] Calcitonin ≥ 100 ng/L must lead to discontinuation of study drug

[i] Only applicable for subjects that have provided informed consent for genetics and biomarkers
[j] Only serious adverse events and selected other adverse events are required to be reported

[k] Mandatory at the randomisation visit and then "as needed" at subsequent visits
[l] Training must be repeated at the yearly visits, i.e. visit 10, visit 14, visit 18 and visit 22 and as needed
[m] For all female subjects

Source: Protocol EX9536-4388 v7.0, Section 2

8.4. Safety Results

8.4.1. Deaths

A total of 833 randomized subjects died in the SELECT trial, of which 375 (4.3%) were randomized to semaglutide and 458 (5.2%) to placebo. An additional 7 patients (all randomized to placebo) died outside the in-trial observation period.

All deaths in randomized subjects were sent for adjudication to determine CV death;[50] renal death;[51] or non-CV, non-renal death.[52] The death adjudication meetings included the EAC Chair or Vice-Chair, 1 additional cardiologist, 1 neurologist, and 1 nephrologist.

A total of 318 deaths (38.2% of total deaths) were adjudicated as CV deaths; 348 (41.8%) were non-CV, non-renal death; and 167 (20.0%) were undetermined. No deaths were adjudicated as renal death. Deaths for which the EAC could not determine the cause were presumed to be CV deaths in the statistical analyses of CV outcomes. See further discussion in Section 6.1.2.

The investigators' reports of SAEs with fatal outcome are also reported; the numbers and types can vary from the EAC evaluation due to differences in the determination of onset date of the fatal SAE and the cause. A total of 371 subjects (4.2%) in the semaglutide group and 460 subjects (5.2%) in the placebo group had an SAE with a fatal outcome with onset during the in-trial period. Investigator-defined fatal SAEs by SOC are listed in Table 39 below. The "General disorders and administration site conditions" SOC included PTs such as "Death," "Sudden cardiac death," "Sudden death," and "Cardiac death." Approximately two-thirds of the events in the "Infections and infestations" SOC in both groups were due to COVID-19.

---

[50] See definition in Section 6.1.1

[51] Renal death was defined in the EAC charter as a non-CV death that is due to the direct consequences of severely impaired renal function. A renal death is the consequence of insufficient or no renal replacement therapy where this would have been indicated, e.g., subjects declining renal replacement therapy, renal replacement therapy not being available, renal replacement therapy being considered futile by both physician and subject, death occurring before renal replacement therapy could be implemented when it was indicated, or death due to complications of renal replacement therapy.

[52] Non-CV (non-renal) death was defined in the EAC charter as any death with a specific cause that is neither thought to be CV or renal in nature (as separately defined in the EAC charter). The following causes of death were to be used when classifying a non-CV, non-renal death: pulmonary, gastrointestinal, hepatobiliary, pancreatic, infection (includes sepsis), inflammatory [e.g., systemic inflammatory response syndrome (SIRS)]/immune (including autoimmune; may include anaphylaxis from environmental), hemorrhage (that is neither CV bleeding nor a stroke), non-CV procedure or surgery, trauma (includes homicide), suicide, nonprescription drug reaction or overdose, prescription drug reaction or overdose (may include anaphylaxis), neurological (non-CV; excludes CV death from ischemic stroke, hemorrhagic stroke, or undetermined cause of stroke or CV hemorrhage of central nervous system), malignancy, other non-CV causes.

Table 39. SAEs with Fatal Outcome, Investigator-Determined

	Semaglutide N=8803	Placebo N=8801
Fatal SAEs	371 (4.21)	460 (5.23)
Female	72 (2.94)	91 (3.75)
Male	299 (4.70)	369 (5.79)
Cardiac disorders	116 (1.32)	132 (1.50)
General disorders and administration site conditions	77 (0.87)	98 (1.11)
Infections and infestations	72 (0.82)	101 (1.15)
COVID-19 pneumonia	27 (0.31)	35 (0.40)
COVID-19	18 (0.20)	31 (0.35)
Neoplasms benign, malignant and unspecified	62 (0.70)	62 (0.70)
Nervous system disorders	37 (0.42)	47 (0.53)
Respiratory, thoracic and mediastinal disorders	36 (0.41)	46 (0.52)
Injury, poisoning and procedural complications	11 (0.12)	17 (0.19)
Vascular disorders	10 (0.11)	10 (0.11)
Renal and urinary disorders	7 (0.08)	6 (0.07)
Gastrointestinal disorders	6 (0.07)	13 (0.15)
Psychiatric disorders	6 (0.07)	5 (0.06)
Blood and lymphatic system disorders	3 (0.03)	1 (0.01)
Metabolism and nutrition disorders	2 (0.02)	3 (0.03)
Hepatobiliary disorders	1 (0.01)	8 (0.09)
Immune system disorders	1 (0.01)	0
Skin and subcutaneous system disorders	1 (0.01)	0
Investigations	0	1 (0.01)
Surgical and medical procedures	0	1 (0.01)

Source: SELECT CTR, Table 14.3.1.15

This section of the review will focus on non-CV deaths.

A total of 152 subjects (1.7%) randomized to semaglutide and 196 subjects (2.2%) randomized to placebo were confirmed by the EAC as non-CV death. An overview of the classification of non-CV deaths is shown in Table 40 for the in-trial period. The most frequently reported non-CV deaths were due to infection and malignancy.

The causes of death with (small) numerical imbalances not in favor of semaglutide were suicide and neurological (non-CV) causes.

- Suicide and events of suicidal ideation and behaviors are discussed further in Section 8.5.2.

- The 4 neurological events leading to death in semaglutide-treated subjects as adjudicated by the EAC were: progressive amyotrophic lateral sclerosis (ALS) [PT=amyotrophic lateral sclerosis]; complications of progressive Parkinson's disease [PT=sepsis]; progressive

neurological decline with myasthenia or autoimmune encephalitis [PT=encephalitis autoimmune]; and corticobasal degeneration [PT=corticobasal degeneration]. The placebo subject was adjudicated as cause of death due to Lewy body dementia [PT=dementia with Lewy bodies].

Non-CV deaths with imbalances in favor of semaglutide included infections. Serious adverse events with fatal outcome in the 'Infections and infestations' system organ class (SOC) included (semaglutide vs. placebo): COVID-19 pneumonia (n=27, 0.31% vs. n=35, 0.40%) and COVID-19 (n=18, 0.20% vs. 31, 0.35%). COVID-19 is discussed further in Section 8.5.13.

Table 40. Causes of Non-CV Death

	Semaglutide N=8803	Placebo N=8801
Non-CV death	152 (1.7)	196 (2.2)
Infection (including sepsis)	62 (0.7)	87 (1.0)
Malignancy	55 (0.6)	60 (0.7)
Trauma	11 (0.1)	19 (0.2)
Pulmonary	8 (<0.1)	12 (0.1)
Suicide	5 (<0.1)	3 (<0.1)
Gastrointestinal	3 (<0.1)	5 (<0.1)
Neurological (non-CV)	4 (<0.1)	1 (<0.1)
Hemorrhage	1 (<0.1)	4 (<0.1)
Hepatobiliary	1 (<0.1)	3 (<0.1)
Non-CV procedure or surgery	0	1 (<0.1)
Prescription drug reaction or overdose	0	1 (<0.1)
Other[a]	2 (<0.1)	0
Renal	0	0
a 1 event each of electrocution and encephalitis concurrent with acute kidney failure and respiratory failure		

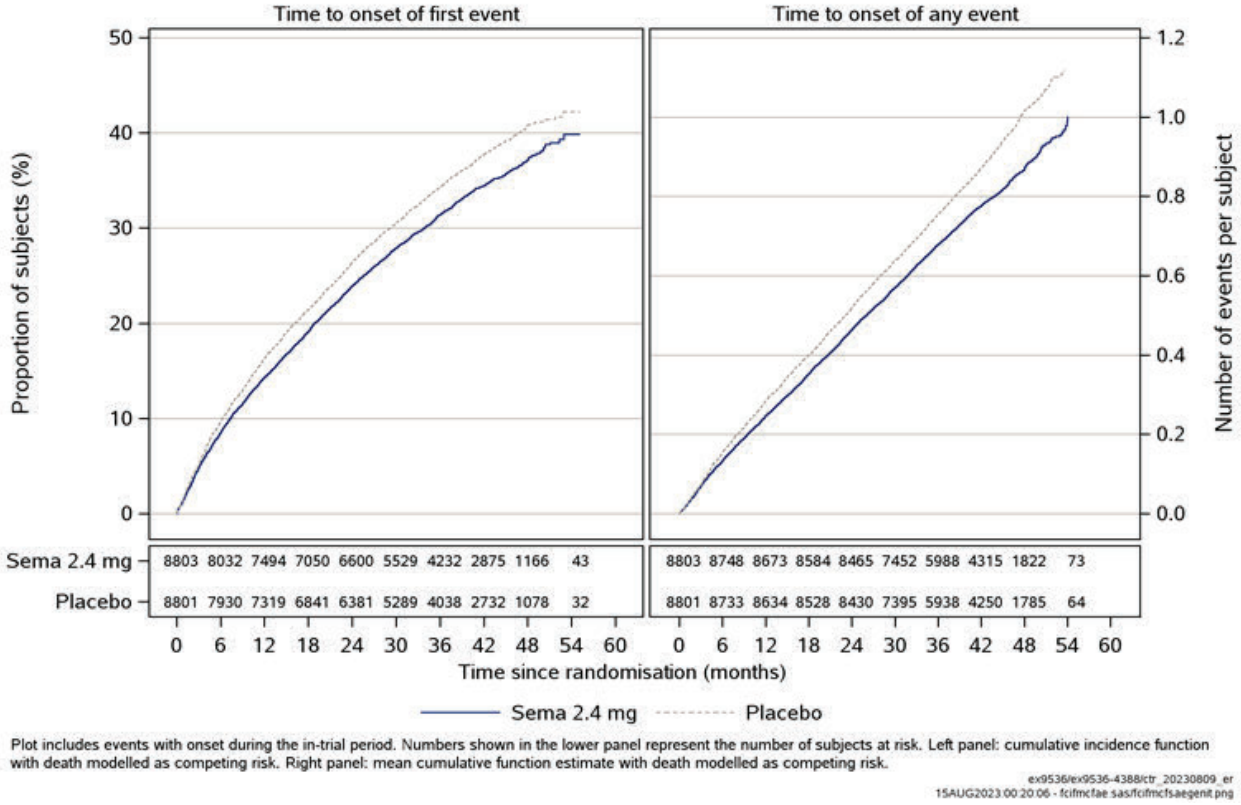
Source: SELECT CTR, Table 11-18

8.4.2. Serious Adverse Events

This section discusses fatal and non-fatal SAEs as reported by the investigator. Because most AEs were generally only systematically collected if they were serious (see Section 8.1 for a full discussion of targeted AE collection), these events make up the bulk of the safety review and are also discussed in Section 8.5, analysis of submission-specific safety concerns.

A total of 6622 SAEs were reported in 2941 (33.4%) semaglutide-treated subjects and a total of 7507 SAEs were reported in 3204 (36.4%) placebo-treated subjects. As shown in Figure 25, the onset of SAEs was evenly distributed throughout the in-trial period, with a steeper slope for time to first SAEs and any SAE in the placebo group versus the semaglutide group.

Figure 25. Time to Onset of In-Trial SAEs



Plot includes events with onset during the in-trial period. Numbers shown in the lower panel represent the number of subjects at risk. Left panel: cumulative incidence function with death modelled as competing risk. Right panel: mean cumulative function estimate with death modelled as competing risk.

ex9536/ex9536-4388/ctr_20230809_er
15AUG2023 00:20:06 - fcifmcfae.sas/fcifmcfsaegenit.png

Source: SELECT CTR, Figure 12-3

SAEs summarized by SOC and PT are in the table below, with several PTs noted for interest (e.g., COVID-19-related) or because of numerical imbalances not in favor of semaglutide (discussed further below). Some AEs are discussed in the discussion of safety focus areas, such as malignant neoplasms, gastrointestinal disorders, and gallbladder-related disorders, in Section 8.5.

The SOCs with SAEs that showed an unfavorable numerical imbalance for semaglutide were gastrointestinal disorders (semaglutide 3.9% vs. placebo 3.7%), hepatobiliary disorders (1.4% vs. 1.2%), blood and lymphatic system disorders (0.9% vs. 0.7%), psychiatric disorders (0.7% vs. 0.6%), ear and labyrinth disorders (0.3% vs. 0.2%) and congenital, family and genetic disorders (0.1% for both groups). Other SAE groupings of interest were explored in Section 8.5, with submission-specific safety issues.

Table 41. Serious Adverse Events

Body System or Organ Class	Semaglutide N=8803		Placebo N=8801	
	n	%	n	%
All SAEs	**2941**	**33.4**	**3204**	**36.4**
Cardiac disorders	1008	11.5	1184	13.5
Supraventricular tachycardia	18	0.2	7	0.1
Infections and infestations	624	7.1	738	8.4
COVID-19	124	1.4	137	1.6
COVID-19 pneumonia	119	1.4	148	1.7
Nervous system disorders	444	5.0	496	5.6
Syncope	65	0.7	55	0.6
Surgical and medical procedures	433	4.9	548	6.2
Neoplasms benign, malignant and unspecified	405	4.6	402	4.6
Prostate cancer	60	0.7	54	0.6
Gastrointestinal disorders	342	3.9	323	3.7
Inguinal hernia	39	0.4	24	0.3
Diarrhea	23	0.3	16	0.2
Gastrointestinal hemorrhage	22	0.2	15	0.2
Injury, poisoning and procedural complications	305	3.5	313	3.6
Fall	51	0.6	35	0.4
General disorders and administration site conditions	273	3.1	316	3.6
Musculoskeletal and connective tissue disorders	236	2.7	254	2.9
Osteoarthritis	84	1.0	79	0.9
Vascular disorders	231	2.6	259	2.9
Renal and urinary disorders	192	2.2	198	2.2
Acute kidney injury	79	0.9	105	1.2
Nephrolithiasis	25	0.3	24	0.3
Ureterolithiasis	20	0.2	10	0.1
Respiratory, thoracic and mediastinal disorders	180	2.0	276	3.1
Hepatobiliary disorders	126	1.4	105	1.2
Cholelithiasis	44	0.5	31	0.4
Bile duct stone	16	0.2	10	0.1
Blood and lymphatic system disorders	83	0.9	62	0.7
Anemia	36	0.4	30	0.3
Metabolism and nutrition disorders	67	0.8	76	0.9
Hypoglycemia	3	<0.1	1	<0.1
Reproductive system and breast disorders	65	0.7	43	0.5
Benign prostatic hyperplasia	34	0.4	21	0.2
Psychiatric disorders	59	0.7	49	0.6
Depression	13	0.1	10	0.1
Anxiety	6	<0.1	3	<0.1
Major depression	2	<0.1	5	<0.1
Eye disorders	41	0.5	41	0.5
Investigations	34	0.4	41	0.5
Ear and labyrinth disorders	27	0.3	16	0.2
Vertigo	18	0.2	7	0.1

Endocrine disorders	19	0.2	20	0.2
Skin and subcutaneous tissue disorders	19	0.2	20	0.2
Congenital, familial and genetic disorders	12	0.1	9	0.1
Product issues	11	0.1	16	0.2
Immune system disorders	11	0.1	14	0.2

Source: Reviewer created from ADAE.xpt, confirmed with SELECT CTR, Table 14.3.1.3

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In SELECT, AEs leading to trial product discontinuation were defined as those AEs where action taken was either drug withdrawn or drug interrupted.

A higher proportion of subjects randomized to semaglutide (30.3%) versus randomized to placebo (16.0%) had AEs leading to trial product discontinuation (withdrawn or interrupted). The imbalance was mostly driven by more gastrointestinal (GI) AEs in the semaglutide group. There were almost twice as many psychiatric disorders that led to discontinuation in the semaglutide group, including events relating to depression, sleep disorders, and anxiety, although the overall incidence was low (1.0% vs. 0.6%). Although the numbers were relatively small, there were also more events of dizziness, headache, and syncope leading to discontinuation. Decreased appetite and abnormal loss of weight also led to treatment discontinuation. Approximately 80% of the AEs in the semaglutide 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.

Table 42. AEs Leading to Discontinuation (Permanent or Temporary)

	Semaglutide N=8803	**Placebo N=8801**
AEs leading to discontinuation	2669 (30.3)	1408 (16.0)
Gastrointestinal disorders	1613 (18.3)	323 (3.7)
Nausea	710 (8.1)	66 (0.8)
Diarrhea	451 (5.1)	66 (0.8)
Vomiting	319 (3.6)	18 (0.2)
Constipation	194 (2.2)	33 (0.4)
Dyspepsia	139 (1.6)	15 (0.2)
Abdominal pain	103 (1.2)	28 (0.3)
Nervous system disorders	274 (3.1)	185 (2.1)
Dizziness	71 (0.8)	24 (0.3)
Headache	38 (0.4)	14 (0.2)
Syncope	20 (0.2)	11 (0.1)
Dysgeusia	13 (0.2)	2 (<0.1)
Lethargy	13 (0.2)	0

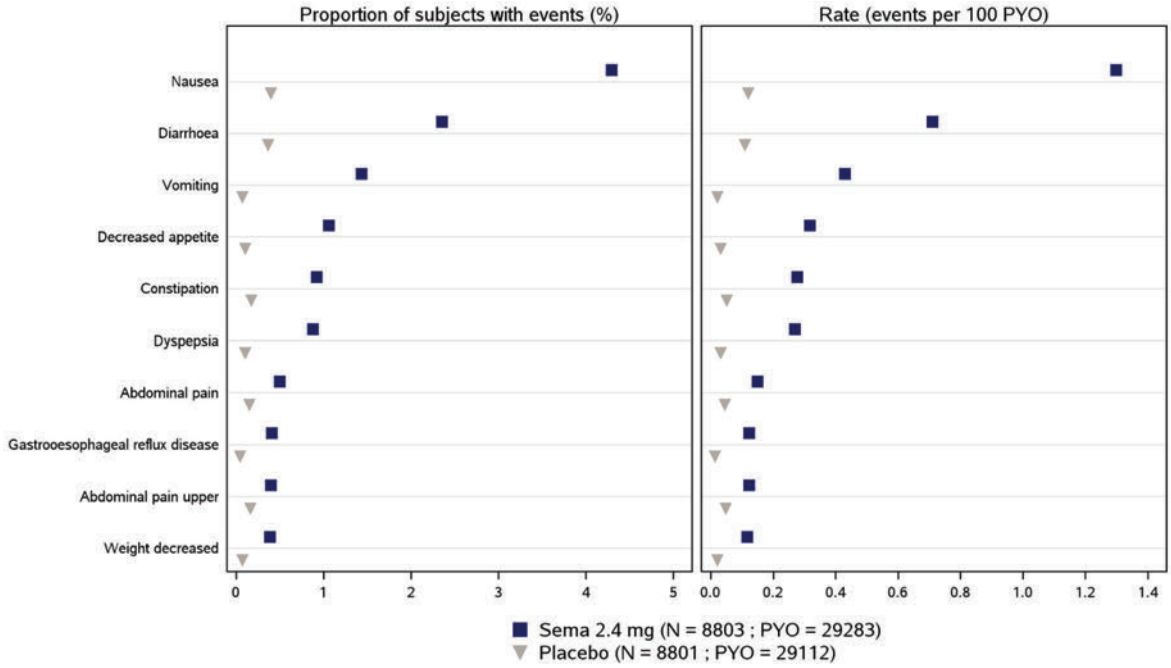
Metabolism and nutrition disorders	226 (2.6)	49 (0.6)
Decreased appetite	189 (2.2)	19 (0.2)
Dehydration	11 (0.1)	3 (<0.1)
Hypoglycemia	5 (0.1)	1 (<0.1)
Abnormal loss of weight	5 (0.1)	0
General disorders and administration site conditions	214 (2.4)	94 (1.1)
Asthenia	63 (0.7)	7 (0.1)
Fatigue	61 (0.7)	18 (0.2)
Malaise	25 (0.3)	9 (0.1)
Investigations	171 (1.9)	73 (0.8)
Weight decreased	77 (0.9)	10 (0.1)
Lipase increased	36 (0.4)	8 (0.1)
Amylase increased	16 (0.2)	4 (0.1)
Heart rate increased	5 (0.1)	1 (<0.1)
Psychiatric disorders	87 (1.0)	48 (0.6)
Depressed mood disorders and disturbances HGLT	29 (0.3)	15 (0.2)
Sleep disorders and disturbances	18 (0.2)	7 (0.1)
Anxiety disorders and symptoms	17 (0.2)	12 (0.1)
Mood disorders and disturbances NEC[a]	12 (0.1)	3 (<0.1)
Sexual dysfunctions, disturbances and gender identity disorders[b]	6 (0.1)	2 (<0.1)
Vascular disorders	63 (0.7)	47 (0.5)
Hypotension	16 (0.2)	7 (0.1)
Orthostatic hypotension	5 (0.1)	2 (<0.1)

a Includes PTs such as 'Irritability' and 'Anger'
b PTs 'Libido increased' and 'Loss of libido'

Source: SELECT CTR, Table 14.3.1.8

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 has not been resumed), was higher with semaglutide than with placebo (16.6% vs 8.2%). Similar to above, the excess of AEs leading to discontinuation were due to GI disorders (e.g., nausea, vomiting, diarrhea, constipation, dyspepsia, and gastroesophageal reflux disease), nervous system disorders (e.g., dizziness and headache), and metabolism and general disorders (e.g., decreased appetite, weight decreased, asthenia, and fatigue).

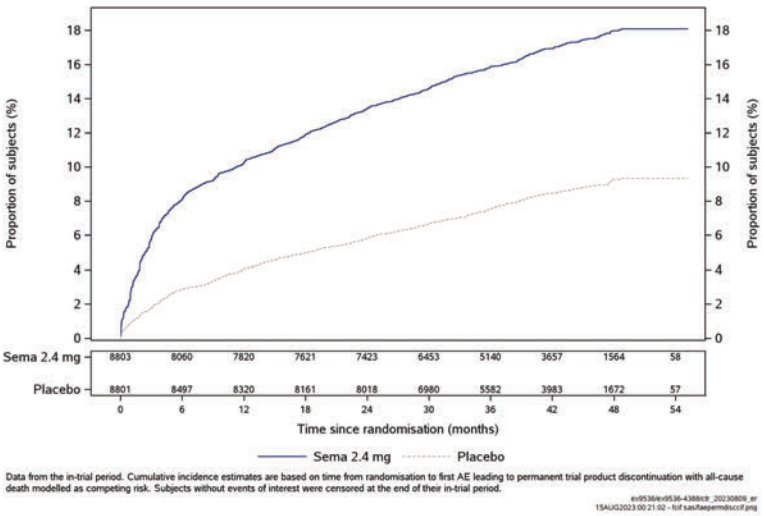
Figure 26. Adverse Events (PTs) Leading to Permanent Trial Product Discontinuation



Source: SELECT CTR, Figure 14.3.1.13

AEs leading to permanent discontinuation were particularly higher in the first 6 months of the trial for the semaglutide group (Figure 27).

Figure 27. AEs Leading to Permanent Discontinuation, Cumulative Incidence Plot



Source: SELECT CTR, Figure 14.3.1.11

8.4.4. Significant Adverse Events

Severe AEs (of any seriousness) are described in this section. A total of 1783 subjects (20.3%) randomized to semaglutide and 1824 (20.7%) randomized to placebo reported AEs as 'severe'. As shown in Table 43, most AEs considered severe were in the Cardiac disorders SOC, which is expected for a CVOT in a population at high risk for cardiovascular disorders. In most SOCs, there was not an excess of severe events in the semaglutide arm, with the exception of the Gastrointestinal disorders SOC (approximately twice as many severe events versus placebo). The most commonly reported severe events in the Gastrointestinal disorders SOC were nausea, diarrhea, vomiting, and constipation.

Table 43. Severe Adverse Events

	Semaglutide N=8803	Placebo N=8801
Cardiac disorders	526 (6.0)	626 (7.1)
Gastrointestinal disorders	329 (3.7)	157 (1.8)
Nausea	76	9
Diarrhea	46	14
Vomiting	45	8
Constipation	20	3
Abdominal pain upper	15	5
Dyspepsia	15	1
Abdominal pain	14	6
Gastrointestinal hemorrhage	11	6
Gastroesophageal reflux disease	11	5
Abdominal distension	11	0
Inguinal hernia	9	3
Infections and infestations	323 (3.7)	355 (4.0)
Nervous system disorders	230 (2.6)	288 (3.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	212 (2.4)	189 (2.1)
Surgical and medical procedures	210 (2.4)	268 (3.0)
Injury, poisoning and procedural complications	159 (1.8)	163 (1.9)
General disorders and administration site conditions	145 (1.6)	159 (1.8)
Respiratory, thoracic and mediastinal disorders	114 (1.3)	171 (1.9)
Vascular disorders	108 (1.2)	122 (1.4)
Musculoskeletal and connective tissue disorders	106 (1.2)	120 (1.4)
Renal and urinary disorders	91 (1.0)	75 (0.9)
Metabolism and nutrition disorders	64 (0.7)	31 (0.4)
Hepatobiliary disorders	51 (0.6)	64 (0.7)
Psychiatric disorders	39 (0.4)	42 (0.5)
Blood and lymphatic system disorders	39 (0.4)	31 (0.4)
Investigations	26 (0.3)	20 (0.2)
Eye disorders	14 (0.2)	16 (0.2)
Ear and labyrinth disorders	14 (0.2)	4 (<0.1)
Skin and subcutaneous tissue disorders	13 (0.1)	19 (0.2)

Reproductive system and breast disorders	13 (0.1)	15 (0.2)
Immune system disorders	8 (0.01)	9 (0.01)
Product issues	6 (0.01)	7 (0.01)
Endocrine disorders	4 (<0.01)	2 (<0.01)
Congenital, familial and genetic disorders	3 (<0.01)	3 (<0.01)

Source: Reviewer created from ADAE.xpt dataset

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

This is discussed in other sections of the review.

8.4.6. Laboratory Findings

Laboratory values as part of submission-specific safety issues are also addressed in relevant subsections in Section 8.5. A summary of biochemistry outliers is shown in Table 44, below. Overall, no new safety patterns for biochemistry were identified in SELECT.

APPEARS THIS WAY ON ORIGINAL

Table 44. Biochemistry – Categorical Summary of Maximum Post-Baseline Values

	Sema 2.4 mg N	(%)	Placebo N	(%)
Number of subjects	8803		8801	
Alanine Aminotransferase in Serum (U/L)				
N	8585	(97.5)	8579	(97.5)
Low (<LLN)	0		0	
Normal	7551	(85.8)	7452	(84.7)
High (>ULN)	1034	(11.7)	1127	(12.8)
>3x ULN	40	(0.5)	59	(0.7)
>5x ULN	8	(<.1)	16	(0.2)
>10x ULN	0		6	(<.1)
>20x ULN	0		1	(<.1)
Albumin in Serum (g/dL)				
N	8593	(97.6)	8591	(97.6)
Low (<LLN)	2	(<.1)	9	(0.1)
Normal	8391	(95.3)	8376	(95.2)
High (>ULN)	200	(2.3)	206	(2.3)
Alkaline Phosphatase in Serum (U/L)				
N	8593	(97.6)	8591	(97.6)
Low (<LLN)	48	(0.5)	44	(0.5)
Normal	8277	(94.0)	8230	(93.5)
High (>ULN)	268	(3.0)	317	(3.6)
>1.5x ULN	51	(0.6)	50	(0.6)
Amylase in Serum (U/L)				
N	2978	(33.8)	2997	(34.1)
Low (<LLN)	5	(<.1)	20	(0.2)
Normal	2665	(30.3)	2837	(32.2)
High (>ULN)	308	(3.5)	140	(1.6)
>3x ULN	7	(<.1)	6	(<.1)
Aspartate Aminotransferase in Serum (U/L)				
N	8588	(97.6)	8585	(97.5)
Low (<LLN)	0		0	
Normal	6841	(77.7)	6591	(74.9)
High (>ULN)	1747	(19.8)	1994	(22.7)
>3x ULN	78	(0.9)	109	(1.2)
>5x ULN	27	(0.3)	33	(0.4)
>10x ULN	0		6	(<.1)
>20x ULN	0		3	(<.1)
Bilirubin in Serum (umol/L)				
N	8585	(97.5)	8579	(97.5)
Low (<LLN)	0		0	
Normal	7171	(81.5)	7211	(81.9)
High (>ULN)	1414	(16.1)	1368	(15.5)
>1.5x ULN	430	(4.9)	389	(4.4)
>2x ULN	140	(1.6)	112	(1.3)
>3x ULN	30	(0.3)	14	(0.2)
>10x ULN	1	(<.1)	1	(<.1)
Calcium Albumin Corrected, Serum (mmol/L)				
N	8593	(97.6)	8591	(97.6)
Low (<LLN)	86	(1.0)	107	(1.2)
Normal	8223	(93.4)	8192	(93.1)
High (>ULN)	284	(3.2)	292	(3.3)
<1.5 mmol/L	0		0	
>3.4 mmol/L	1	(<.1)	0	

	Sema 2.4 mg N	(%)	Placebo N	(%)
Calcium in Serum (mmol/L)				
N	8593	(97.6)	8591	(97.6)
Low (<LLN)	56	(0.6)	74	(0.8)
Normal	7515	(85.4)	7542	(85.7)
High (>ULN)	1022	(11.6)	975	(11.1)
Creatine Kinase in Serum (U/L)				
N	1478	(16.8)	1481	(16.8)
Low (<LLN)	24	(0.3)	7	(<.1)
Normal	1121	(12.7)	1085	(12.3)
High (>ULN)	333	(3.8)	389	(4.4)
>5x ULN	8	(<.1)	8	(<.1)
>10x ULN	2	(<.1)	2	(<.1)
Creatinine in Serum (umol/L)				
N	8593	(97.6)	8591	(97.6)
Low (<LLN)	100	(1.1)	113	(1.3)
Normal	6167	(70.1)	6056	(68.8)
High (>ULN)	2326	(26.4)	2422	(27.5)
>1.5x baseline	321	(3.6)	363	(4.1)
>3x ULN	25	(0.3)	20	(0.2)
>6x ULN	1	(<.1)	2	(<.1)
GGT in Serum (U/L)				
N	8593	(97.6)	8591	(97.6)
Low (<LLN)	70	(0.8)	30	(0.3)
Normal	6760	(76.8)	6205	(70.5)
High (>ULN)	1763	(20.0)	2356	(26.8)
>5x ULN	111	(1.3)	158	(1.8)
High Sensitive C-Reactive Protein in Serum (mg/L)				
N	8593	(97.6)	8590	(97.6)
Low (<LLN)	0		0	
Normal	5515	(62.6)	4888	(55.5)
High (>ULN)	3078	(35.0)	3702	(42.1)
Lipase in Serum (U/L)				
N	2978	(33.8)	2997	(34.1)
Low (<LLN)	0		2	(<.1)
Normal	1856	(21.1)	2530	(28.7)
High (>ULN)	1122	(12.7)	465	(5.3)
>3x ULN	168	(1.9)	53	(0.6)
Potassium in Serum (mmol/L)				
N	8593	(97.6)	8590	(97.6)
Low (<LLN)	15	(0.2)	12	(0.1)
Normal	7446	(84.6)	7492	(85.1)
High (>ULN)	1132	(12.9)	1086	(12.3)
<2.5 mmol/L	0		0	
>7.0 mmol/L	24	(0.3)	23	(0.3)
Sodium in Serum (mmol/L)				
N	8593	(97.6)	8591	(97.6)
Low (<LLN)	43	(0.5)	29	(0.3)
Normal	7957	(90.4)	7953	(90.4)
High (>ULN)	593	(6.7)	609	(6.9)
<120 mmol/L	0		0	
>160 mmol/L	1	(<.1)	5	(<.1)

	Sema 2.4 mg N	(%)	Placebo N	(%)
Urea in Serum (mmol/L)				
N	8593	(97.6)	8591	(97.6)
Low (<LLN)	50	(0.6)	30	(0.3)
Normal	6911	(78.5)	6647	(75.5)
High (>ULN)	1632	(18.5)	1914	(21.7)

Data from the in-trial period. Both planned and unplanned assessments are included.
%: percentage of subjects in full analysis set, N: number of subjects contributing to the summary statistic

Source: SELECT CTR, Table 14.3.5.114

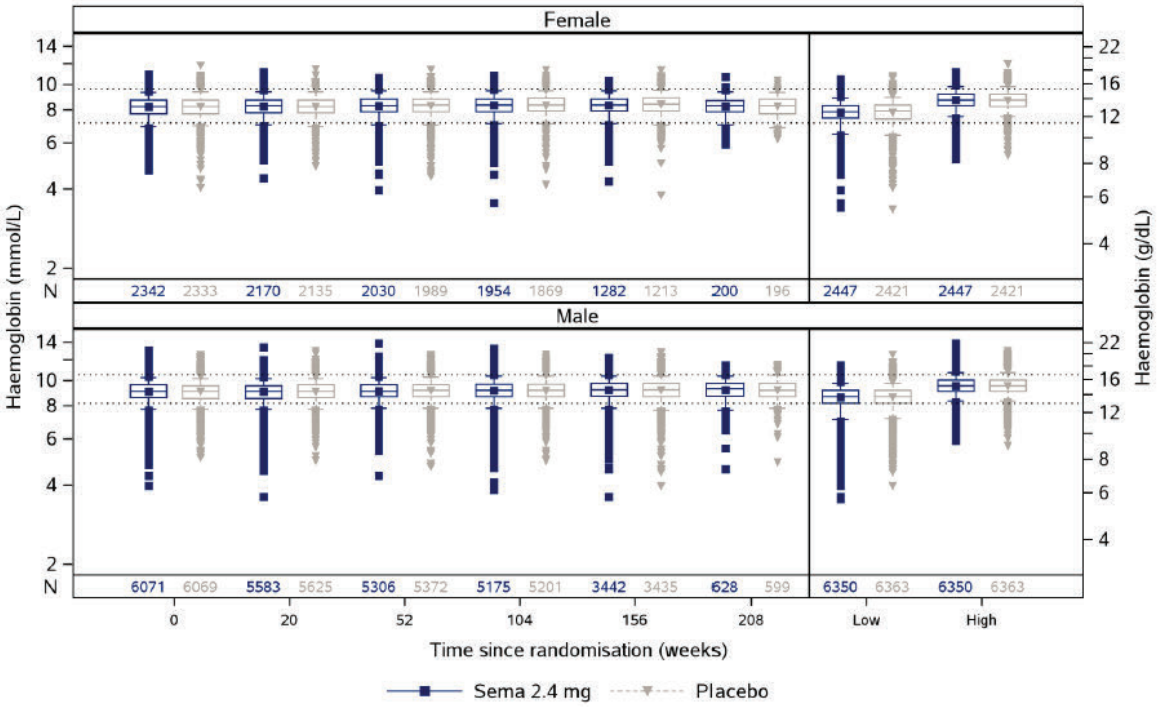
A selected number of boxplots that present outliers for hematology parameters are shown below in Figure 28, Figure 29, Figure 30, and Figure 31. Hematology is discussed further in Section 8.5.11.

Note that the leukocyte and lymphocyte high outliers were observed in a single semaglutide-treated subject – Subject ID (b) (6) – who had very abnormal values at baseline and an SAE of worsening chronic lymphocytic leukemia reported on study day 1439 (values circled in red in Figure 29 and Figure 30).

Four subjects on semaglutide and 3 on placebo reported very low platelet counts (< 25 x 10^9/L); none of the semaglutide subjects had related AEs and all had values that returned to normal or near baseline on subsequent testing. (One semaglutide subject – Subject ID (b) (6) – had a baseline value of 31 x 10^9/L.)

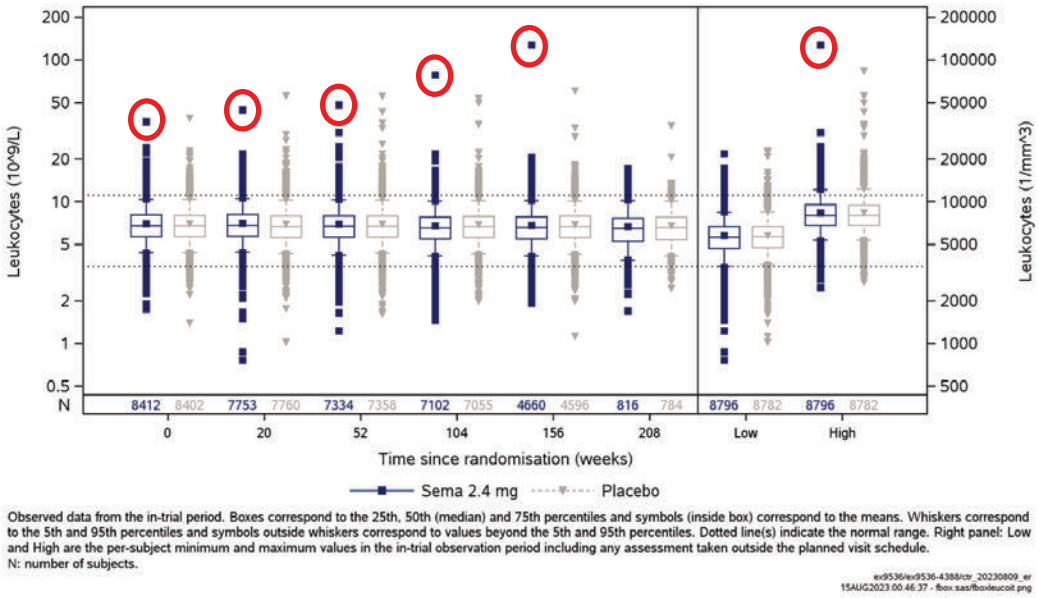
Overall, no new safety patterns for hematology were identified in SELECT.

Figure 28. Hemoglobin by Sex and Week



Source: SELECT CTR, Figure 14.3.5.80

Figure 29. Leukocytes by Week

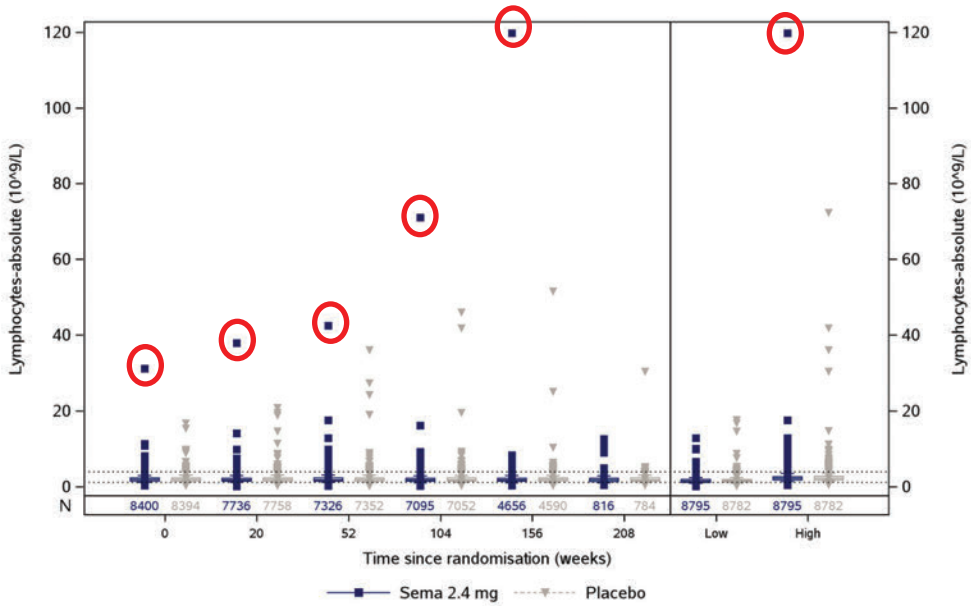


Observed data from the in-trial period. Boxes correspond to the 25th, 50th (median) and 75th percentiles and symbols (inside box) correspond to the means. Whiskers correspond to the 5th and 95th percentiles and symbols outside whiskers correspond to values beyond the 5th and 95th percentiles. Dotted line(s) indicate the normal range. Right panel: Low and High are the per-subject minimum and maximum values in the in-trial observation period including any assessment taken outside the planned visit schedule.
N: number of subjects.

ex9536/ex9536-4388/ctr_20230809_er
15AUG2023:00:46:37 - fbox.sas/fboxleucoit.png

Source: SELECT CTR, Figure 14.3.5.84

Figure 30. Lymphocytes by Week

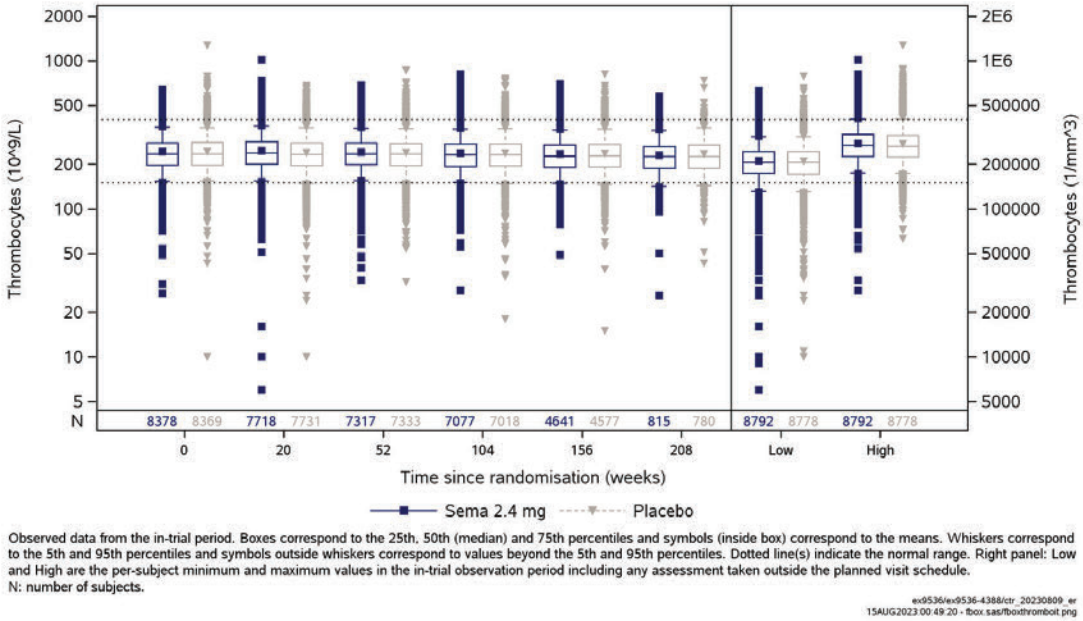


Observed data from the in-trial period. Boxes correspond to the 25th, 50th (median) and 75th percentiles and symbols (inside box) correspond to the means. Whiskers correspond to the 5th and 95th percentiles and symbols outside whiskers correspond to values beyond the 5th and 95th percentiles. Dotted line(s) indicate the normal range. Right panel: Low and High are the per-subject minimum and maximum values in the in-trial observation period including any assessment taken outside the planned visit schedule.
N: number of subjects.

ex9536/ex9536-4388/ctr_20230809_er
15AUG2023:00:57:17 - fbox.sas/fboxlymphoit.png

Source: SELECT CTR, Figure 14.3.5.108

Figure 31. Platelets by Week



Observed data from the in-trial period. Boxes correspond to the 25th, 50th (median) and 75th percentiles and symbols (inside box) correspond to the means. Whiskers correspond to the 5th and 95th percentiles and symbols outside whiskers correspond to values beyond the 5th and 95th percentiles. Dotted line(s) indicate the normal range. Right panel: Low and High are the per-subject minimum and maximum values in the in-trial observation period including any assessment taken outside the planned visit schedule.
N: number of subjects.

ex9536/ex9536-4388/ctr_20230809_er
15AUG2023 00:49:20 - fbox.sas/fboxthromboit.png

Source: SELECT CTR, Figure 14.3.5.88

8.4.7. Vital Signs

Clinically relevant changes in vital signs were evaluated for blood pressure and heart rate. These are discussed under Section 8.5.8, with AEs of tachyarrhythmias, hypotension, and syncope.

8.4.8. Electrocardiograms (ECGs)

ECGs were not routinely monitored in SELECT.

8.4.9. QT

QT was previously reviewed for semaglutide under the original NDAs. No events of torsade de pointes were reported in SELECT. The PT 'Electrocardiogram QT prolonged' was reported in 3 semaglutide-treated subjects and 2 placebo-treated subjects. No events were serious.

8.4.10. Immunogenicity

Anti-drug antibodies were not measured in this trial. See Section 8.5.13 for a discussion of allergy and other immune-related AEs.

8.5. Analysis of Submission-Specific Safety Issues

The applicant selected areas to focus on for the SELECT safety review, based on knowledge of GLP-1 RA safety and regulatory requests. Table 45 describes the safety focus areas and how they were evaluated in the clinical trial report (CTR).

Table 45. Overview of Safety Focus Areas in the SELECT CTR

Safety focus area	Adjudication/ Additional data collection	Basis for evaluation
Cardiovascular disorders	Yes/No	• Adjudication outcome • MedDRA search (SOC of Cardiac disorders) on SAEs • Blood pressure and heart rate
Gastrointestinal disorders	No/No	• MedDRA search (SOC of Gastrointestinal disorders) on SAEs
Gallbladder-related disorders	No/Yes (gallbladder disease)	• MedDRA search (gallbladder-related disorders) on AEs
Pancreatitis	Yes/Yes (pancreatitis)	• MedDRA search (pancreatitis) on AEs • Adjudication outcome (acute pancreatitis)
Kidney disorders	No/Yes (acute renal failure)	• MedDRA search (acute renal failure) on AEs • Laboratory assessment of kidney function parameters
Hepatic disorders	No/No	• MedDRA search (hepatic disorders) on SAEs • Laboratory assessment of liver function parameters
Appendicitis	No/No	• MedDRA search (appendicitis) on SAEs
Malignant neoplasms	No/Yes (malignant neoplasms)	• MedDRA search (malignant tumours) on AEs • Laboratory assessment of calcitonin
Eye disorders	No/No	• MedDRA search (SOC of Eye disorders) on SAEs
Hypoglycaemia	No/No	• MedDRA search (hypoglycaemia) on SAEs
Allergic reactions	No/No	• MedDRA search (allergic reactions) on SAEs
Medication errors	No/Yes (medication errors)	• MedDRA search (medication errors) on all AEs
Safety focus area	**Adjudication/ Additional data collection**	**Basis for evaluation**
Abuse or misuse	No/Yes (abuse or misuse)	• MedDRA search (abuse and misuse) AEs
Suicide/self-injury	No/No	• MedDRA search (suicide/self-injury) on SAEs
Rare events	No/No	• MedDRA search (rare events) on SAEs
Suspected transmission of an infectious agent via trial product	No/No	• MedDRA search (suspected transmission of an infectious agent via trial product) on SAEs[a]
COVID-19 events	No/No	• MedDRA search (COVID-19) on AEs

[a]Suspected transmission of an infectious agent via trial product was always to be considered a SAE per protocol.

Source: SELECT CTR, Table 12-2

The focus of my review included the applicant's presentations and additional safety issues based on ongoing postmarketing evaluations (e.g., psychiatric AEs, gastroparesis) and other areas of potential interest (e.g., tachyarrhythmias, bone, etc.).

8.5.1. Gastrointestinal Disorders

Gastrointestinal (GI) symptoms, such as nausea, vomiting, and diarrhea, are common adverse reactions of the GLP-1 RA class that are dose- and exposure-related. In general, GI disorders with semaglutide can be mitigated with slow dose-escalation. While they are associated with more treatment interruptions and permanent discontinuations (see Section 8.4.3), most events are non-serious.

However, significant GI symptoms can lead to volume depletion, dehydration, syncope, and renal insufficiency. Renal disorders are discussed in Section 8.5.8 and syncope is discussed in Section 8.5.9. These events are labeled in the Wegovy USPI.

Recently, the American Society of Anesthesiologists issued guidance on the risk of regurgitation and pulmonary aspiration of gastric contents during general anesthesia and deep sedation in patients on GLP-1 RAs.[53] (b) (5) (b) (5). This section evaluates these events as reported in SELECT; see below.

In SELECT, GI AEs were collected systematically when serious. The evaluation of GI safety was generally based on SAEs in the SOC 'Gastrointestinal disorders.' Overall, GI SAEs were only slightly higher in the semaglutide group vs. the placebo group (3.9% vs. 3.7%, respectively), with event rates of 1.55 vs. 1.38 events per 100 PYO.

The most common SAEs were in the MedDRA HLGT 'Abdominal hernias and other abdominal wall conditions,' with a numerical imbalance of 65 semaglutide-treated subjects (0.7%) vs. 46 placebo-treated subjects (0.5%). Most of this imbalance is driven by inguinal hernia (39 vs. 24) and incarcerated inguinal hernia (4 vs. 0). Men overwhelmingly made up these cases of inguinal hernia (64 M, 3 F) and the average age was 63.4 years. Interestingly, observational data, including the prospectively collected NHANES data, have shown a protective effect of obesity on inguinal hernia in men,[54,55] but no clear relationship with weight loss or weight gain.[54]

Other commonly reported GI SAEs by PT are shown in Table 46, with small imbalances noted

[53] https://www.asahq.org/about-asa/newsroom/news-releases/2023/06/american-society-of-anesthesiologists-consensus-based-guidance-on-preoperative Accessed 3 Jan 2024
[54] Ruhl CE and Everhart JE. Risk factors for inguinal hernia among adults in the US population. Am J Epidemiol. 2007 May;165(10):1154-61.
[55] www.uptodate.com, accessed Dec 15, 2023.

for diarrhea, gastrointestinal hemorrhage, vomiting, and colitis.

Although there is a small numerical imbalance in gastrointestinal hemorrhage, the outcome for all semaglutide-treated subjects was recovered/resolved. The 2 fatal events were in placebo-treated subjects.

More semaglutide-treated than placebo-treated subjects reported SAEs of vomiting (18 vs. 12) and Mallory-Weiss syndrome (6 vs. 0). All events were reported as recovered/resolved and none were fatal.

More semaglutide-treated than placebo-treated subjects reported SAEs of colitis (semaglutide 14 vs. placebo 10) and ischemic colitis (9 vs. 3). Using SAEs within the HLT 'Colitis (excl infective),' a total of 24 semaglutide-treated subjects vs. 15 placebo-treated subjects reported an event. Other infrequently reported preferred terms within this HLT included Crohn's disease, Terminal ileitis, and Colitis ulcerative. There was only 1 fatal event (ulcerative colitis) in a placebo-treated subject. Most events were reported as recovered/resolved, except for 4 events in 3 subjects: 1 event of ulcerative colitis in a placebo-treated subject, 1 event of colitis in a placebo-treated subject, and 1 event each of Crohn's disease and colitis in 1 semaglutide-treated subject.

Table 46. Most Frequent Serious Adverse Events of Gastrointestinal Disorders, By Preferred Term

Gastrointestinal SAEs, PT	Semaglutide N=8803	Placebo N=8801
Inguinal hernia	39 (0.4)	24 (0.3)
Diarrhea	23 (0.3)	16 (0.2)
Gastrointestinal hemorrhage	22 (0.2)	15 (0.2)
Vomiting	18 (0.2)	12 (0.1)
Gastritis	14 (0.2)	13 (0.1)
Colitis	14 (0.2)	10 (0.1)
Upper gastrointestinal hemorrhage	12 (0.1)	14 (0.2)
Gastroesophageal reflux disease	12 (0.1)	13 (0.1)
Nausea	12 (0.1)	8 (0.1)
Abdominal pain upper	11 (0.1)	12 (0.1)
Large intestine polyp	11 (0.1)	9 (0.1)
Intestinal obstruction	11 (0.1)	8 (0.1)
Small intestinal obstruction	10 (0.1)	10 (0.1)
Abdominal pain	9 (0.1)	18 (0.2)
Pancreatitis acute	9 (0.1)	14 (0.2)
Umbilical hernia	9 (0.1)	4 (<0.1)
Colitis ischemic	9 (0.1)	3 (<0.1)
Constipation	8 (0.1)	6 (0.1)
Diverticulum intestinal	7 (0.1)	2 (<0.1)

Abdominal adhesions	7 (0.1)	1 (<0.1)
Mallory-Weiss syndrome	6 (0.1)	0

Source: Reviewer created from ADAE.xpt dataset; cross-checked with SELECT CTR, Table 14.3.1.43

Gastroparesis/Impaired Gastric Emptying/Aspiration Pneumonia

Although Section 7 of the Wegovy USPI states that semaglutide causes a delay of gastric emptying, there have been a handful of post-marketing reports of gastroparesis that is prolonged or with significant sequelae, such as aspiration during anesthesia, with GLP-1 RA use.

(b) (5)

One event identified for 'pneumonia aspiration' in relation to a surgery occurred in a participant randomized to placebo. A second event occurred in the context of an upper endoscopy and was co-reported with a serious case of gastroparesis (Table 47, below).

(b) (5)

Table 47. Selected Case Details for Gastroparesis Events

Subj ID Age/Sex/BMI	PT	Medical history	Temporal relationship	Confounding factors	Reviewer summary of narrative	Applicant comment
(b) (6) 80/M/32.3	Impaired gastric emptying Pneumonia aspiration	Coronary heart disease Sleep apnea NYHA class I heart failure with preserved ejection fraction	1 month	Concomitant medications (amiodarone, antibiotics, gastrogel antacid, xylocaine viscous,	Patient admitted to the hospital for upper abdominal and lower chest pain. CT showed distended stomach and abnormal	Participant discontinued semaglutide and recovered from the event (positive dechallenge). Concomitant medications

[56] (b) (5)

[57] IR to applicant; DARRTS Ref ID 5221193

				pantoprazole, amlodipine) Procedure of upper endoscopy	thickening of the lower esophagus suggestive of gastric outlet obstruction (either mechanical or functional) and reflux esophagitis. After an appropriate period of fasting, the patient underwent an upper endoscopy. Despite fasting, there was still a large amount of material in the stomach, which lead to aspiration of gastric contents into the lungs. The patient was diagnosed with severe gastroparesis as well as aspiration pneumonia requiring ventilation in the intensive care unit. He eventually recovered with sequelae (deconditioned) and study product was discontinued. Of note, follow-up endoscopy was performed 2 months after the event/drug discontinuation (~6 weeks after discharged from the hospital). The conclusion from the study was gastritis and esophagitis with no evidence of	include agents that could indicate previous problems with gastric acid, infection, as well as several ion channel blockers, which may have contributed to the event. Predisposing factors for aspiration pneumonia includes mechanical disruption of the glottic closure or cardiac sphincter due to procedures such as upper endoscopy.

					gastric outlet obstruction.	
(b) (6) 77/F/29.3	Impaired gastric emptying	Abdominal pain Coronary heart disease Graves's disease Gastroesophageal reflux disease Small intestine ulceration H-pylori gastritis Hiatal hernia, vomiting (for 24 years) Nausea (for 16 years)	2 months	Long history of nausea and vomiting. Concomitant medication of Demerol (opioid analgesic).	Patient presented with worsening nausea and vomiting. A work-up showed reflux esophagitis, small hiatal hernia, and gastroparesis, and she was treated with IV hydration. A gastric emptying study showed significant delay in gastric emptying. Treatment with semaglutide was discontinued.	The participant experienced 2 episodes of gastroparesis. The first event of gastroparesis was considered serious, as the participant was hospitalized. The participant is reported to have recovered after therapy with metoclopramide and subsequently discharged from the hospital. Furthermore, it was reported that no change was taken to semaglutide at the time of the first event of gastroparesis. One month after discharge, the participant had a recurrent (nonserious) event of worsening of gastroparesis for which limited information is available. Concomitant medication of Demerol may have contributed to the event. Furthermore, the investigator highlights that the progression of gastroparesis actually started prior to treatment with semaglutide. The investigator evaluated the serious event as unlikely related to

						semaglutide.
[redacted] (b) (5)						

Reviewer comment: It appears plausible in both cases that semaglutide contributed to the event (or contributed to worsening of a chronic condition). The first case in particular demonstrates significant sequelae due to gastroparesis, likely caused from 1 month of treatment with semaglutide. No alternative etiology is as likely in this case. The second case is more confounded, but it is possible that semaglutide exacerbated a chronic condition.

For completeness, this reviewer separately conducted a MedDRA search in the SELECT database for SAEs related to aspiration pneumonia and gastroparesis/impaired gastric emptying.

Table 48. SAEs of Aspiration and Gastroparesis

	Semaglutide N=8803	**Placebo N=8801**
Aspiration-related SAEs[a]	9 (0.1%)	9 (0.1%)
Pneumonia aspiration	4	9
Pneumonitis aspiration	3	0
Aspiration	2	0
Gastroparesis-related SAEs[b]	5 (0.1%)	0
Impaired gastric emptying	4	0
Gastroparesis postoperative	1	0
a Using PT search containing 'aspiration' b Using PT search: Bezoar; Diabetic gastroparesis; Diabetic gastropathy; Endoscopy upper gastrointestinal tract; Endoscopy upper gastrointestinal tract abnormal; Gastric atony; Gastric emptying study; Gastric hypomotility; Gastric residual increased; Gastrointestinal hypomotility; Gastrointestinal motility disorder; Gastroparesis postoperative; Impaired gastric emptying; and Regurgitation		

Source: Reviewer created from ADAE.xpt dataset

In addition to the 2 cases identified above, brief narratives for the other gastroparesis events are provided here:

- Subject [redacted] (b) (6) (impaired gastric emptying) was a 55-year-old female who was treated with semaglutide for about 11 months when she was hospitalized due to syncope, worsening hypokalemia, and dehydration. Of note, she had previously been hospitalized for hypokalemia/dehydration after 3 months and 6 months into the trial. She had an upper endoscopy that showed esophagitis, polyps, and gastritis, and 12 days later (still hospitalized) was diagnosed with chronic gastroparesis based on a gastric emptying study. She was discharged 2 days later and was considered recovered from all events except chronic gastroparesis. She apparently stopped semaglutide temporarily during the events. The narrative is unclear, but she may have been treated chronically with a loop diuretic, which could have contributed to dehydration and hypokalemia.

- Subject (b) (6) (impaired gastric emptying) was a 78-year-old female who was treated with semaglutide for 8 months when she developed gastroparesis, acute pyelonephritis, hypokalemia, and sepsis. The time course of the event is unclear as the narrative says that the physician had sent the patient for a "colonoscopy" where they determined that "the stomach was not functioning properly and diagnosed it as gastroparesis". The "same day the patient was diagnosed with sepsis infection from acute pyelonephritis and hypokalemia." She was placed on a specific diet, reportedly recovered from all events, and continued in the trial.

- Subject (b) (6) (gastroparesis postoperative) was a 70-year-old male who was treated for about 3.5 months with semaglutide before "temporarily" discontinuing due to the events (apparently he discontinued treatment for ~20 months before restarting drug and completing the trial "on-treatment"). About 10 days prior to stopping drug, he had an event of worsening of hiatal hernia and vomiting. The subject was admitted to the hospital about 3 weeks later for "esophageal stricture following surgery" and then was readmitted about 1 week later. The patient had apparent "esophageal and gastric dysmotility, the etiology was uncertain but certainly appears to be exacerbated due to post-operatively-prolonged hospitalization." The patient required a gastro-jejunostomy placement for tube feeds.

Given the imbalance in gastroparesis-related SAEs above, non-serious AEs of gastroparesis were also searched (acknowledging the limitations in non-serious AE data collection in the SELECT trial). More events were observed in the semaglutide group vs. the placebo group. Most events were reported as recovered and did not lead to a dosage change.

Table 49. Gastroparesis, Summary of Serious and Non-Serious AEs

	Semaglutide N=8803	Placebo N=8801
Gastroparesis-related AEs[a]	34 (0.4)	11 (0.1)
Severe	5 (0.1)	1 (<0.1)
AEs leading to:		
Dose not changed	21 (0.2)	7 (0.1)
Drug interrupted	6 (0.1)	1 (<0.1)
Dose reduced	5 (0.1)	1 (<0.1)
Drug withdrawn	2 (<0.1)	2 (<0.1)
Not applicable	0	1 (<0.1)
AE outcome:		
Recovered/resolved	27 (0.3)	10 (0.1)
Not recovered/not resolved	6 (0.1)	3 (<0.1)
Recovered/resolved with sequelae	1 (<0.1)	0

PTs:		
Impaired gastric emptying	17 (0.2)	3 (<0.1)
Gastrointestinal motility disorder	9 (0.1)	2 (<0.1)
Regurgitation	4 (<0.1)	6 (0.1)
Gastrointestinal hypomotility	2 (<0.1)	0
Endoscopy upper gastrointestinal tract	1 (<0.1)	0
Gastroparesis postoperative	1 (<0.1)	0
a Using PT search: Bezoar; Diabetic gastroparesis; Diabetic gastropathy; Endoscopy upper gastrointestinal tract; Endoscopy upper gastrointestinal tract abnormal; Gastric atony; Gastric emptying study; Gastric hypomotility; Gastric residual increased; Gastrointestinal hypomotility; Gastrointestinal motility disorder; Gastroparesis postoperative; Impaired gastric emptying; and Regurgitation		

Source: Reviewer created from ADAE.xpt

Reviewer comment: Overall, more events of gastroparesis were reported; however, gastroparesis is an expected PD effect. (b) (5)

Appendicitis

Because a numerical imbalance of appendicitis in semaglutide-treated subjects was noted in the premarketing phase 3 trials, the applicant was asked to report events of appendicitis from SELECT. Appendicitis AEs were collected systematically when serious. The proportion of subjects with SAEs of appendicitis and the event rates were low and similar in the semaglutide and placebo groups (0.28% and 0.09 events per 100 PYO in both groups).

Ileus/Intestinal Obstruction

Postmarketing reports have indicated patients treated with GLP-1 RAs have developed ileus.[58] Wegovy and other drugs in the class have 'ileus' in the post-marketing reactions section of labeling.

A similar number of participants in each group reported these SAEs in SELECT (Table 50), although there were small numerical imbalances in various PTs (slightly more intestinal obstruction/large intestinal obstruction with semaglutide, more subileus (partial obstruction) with placebo). Mean and median study day for the start of the SAE was 770 and 845, respectively, in the semaglutide group, and 542 and 387, respectively, in the placebo group.

Three events were fatal in the semaglutide group (2 of 'Intestinal obstruction' and 1 of 'Large intestinal obstruction') and 2 in the placebo group (1 each of 'Ileus paralytic' and 'Intestinal pseudo-obstruction'). Both semaglutide fatalities due to 'intestinal obstruction' were related to

[58] FDA Pharmacovigilance Review, dated November 1, 2022 (signed Nov 8, 2022); DARRTS Ref ID 5074419

malignancy: renal non-small cell carcinoma and colon cancer. The fatality due to 'large intestinal obstruction' is described as follows:

- (b) (6) was a 62-year-old male who developed fecal impaction and constipation after 2.5 years in the trial on study drug. He also had gastric erosion and ulcers resulting in a GI bleed (made worse due to anticoagulation), hypotension, and aspiration pneumonia. He suffered 2 cardiac arrests before and after an esophagogastroduodenoscopy and died due to the event. No autopsy was performed to determine the underlying cause of the bowel obstruction.

Table 50. SAEs related to Ileus and Intestinal Obstruction

	Semaglutide N=8803	Placebo N=8801
Ileus/intestinal obstruction SAEs	26 (0.3)	27 (0.3)
Intestinal obstruction	11 (0.1)	8 (0.1)
Small intestinal obstruction	10 (0.1)	10 (0.1)
Ileus	3 (<0.1)	2 (<0.1)
Large intestinal obstruction	2 (<0.1)	0
Mechanical ileus	1 (<0.1)	0
Subileus	0	4 (<0.1)
Ileus paralytic	0	2 (<0.1)
Intestinal pseudo-obstruction	0	1 (<0.1)

Source: Reviewer created from ADAE.xpt dataset

8.5.2. Psychiatric Events, Including Suicidal Ideation and Behaviors

(b) (5)

Although suicidal behavior and ideation are labeled in the Warnings and Precautions section of the Saxenda (liraglutide for obesity) label partly because of an imbalance reported in the phase 3 trials, they are labeled in the Wegovy and Zepbound (tirzepatide for obesity) labels because of this precedent for labeling centrally acting obesity drugs, rather than a signal in the respective phase 3 chronic weight management programs.

(b) (5)

Suicidal ideation and behaviors recently (July 11, 2023) became a public safety issue for the GLP-1 RA class when the European Medicines Agency (EMA) issued a statement that they were reviewing data on the risk of suicidal thoughts and thoughts of self-harm with GLP-1 RAs. The review was triggered by the Icelandic Medicines Agency following reports of suicidal thoughts and self-injury in people using liraglutide and semaglutide. (b) (5)

(b) (5)

In SELECT, a small numerical imbalance in psychiatric SAEs was noted (semaglutide 59, 0.7% vs. placebo 49, 0.6%), of unclear significance as most of the events were distributed among terms. More subjects on semaglutide discontinued treatment due to psychiatric disorders, including mood disorders, sleep disorders, and anxiety disorders; discontinuations are discussed further below. Prospective psychiatric monitoring with mood and suicide questionnaires was not conducted in this trial. A small numerical imbalance was observed in SAEs of the HLGT 'Anxiety disorders and symptoms' (semaglutide 9 vs. placebo 4). SAEs for the HLGTs of 'Depressed mood and disturbances' and 'Suicidal and self-injurious behaviors' were similar between groups; these events are discussed further below. Psychiatric disorder SAEs are listed by HLGT in Table 51.

Table 51. Psychiatric Disorders SAEs, by HLGT

	Semaglutide N=8803 n (%)	**Placebo N=8801 n (%)**
All psychiatric disorders SAEs	59 (0.7)	49 (0.6)
Depressed mood disorders and disturbances	15 (0.2)	17 (0.2)
Psychiatric disorders NEC	12 (0.1)	10 (0.1)
Suicidal and self-injurious behaviors NEC	10 (0.1)	9 (0.1)
Anxiety disorders and symptoms	9 (0.1)	4 (<0.1)
Deliria (incl confusion)	5 (0.1)	7 (0.1)
Schizophrenia and other psychotic disorders	4 (<0.1)	2 (<0.1)
Manic and bipolar mood disorders and disturbances	4 (<0.1)	0
Dissociative disorders	2 (<0.1)	0
Changes in physical activity	1 (<0.1)	1 (<0.1)
Personality disorders and disturbances in behavior	1 (<0.1)	1 (<0.1)
Somatic symptom and related disorders	1 (<0.1)	1 (<0.1)
Disturbances in thinking and perception	1 (<0.1)	0
Sleep disorders and disturbances	1 (<0.1)	0
Adjustment disorders (incl subtypes)	0	1 (<0.1)
Psychiatric and behavioral symptoms NEC	0	1 (<0.1)

Source: Reviewer created from ADAE.xpt

Overall, slightly more subjects who lost at least 20% body weight experienced psychiatric SAEs than those who lost less than 20% body weight, with no difference overall between groups. However, given the relatively small number of events overall and the relatively greater number of subjects on semaglutide that lost this degree of weight during the trial, this finding should be interpreted with caution.

Table 52. Psychiatric Disorders SAEs and Most Common HLGTs by Maximum Weight Loss

	Semaglutide		Placebo		Total	
	n (%)	E (R)	n (%)	E (R)	n (%)	E (R)
Psychiatric disorders						
< 20%	46/7213 (0.64)	57 (0.24)	45/8560 (0.53)	55 (0.19)	91/15773 (0.58)	112 (0.21)
≥ 20%	13/1533 (0.85)	18 (0.34)	3/192 (1.56)	3 (0.45)	16/1725 (0.93)	21 (0.35)
Unclassified	0/57	0	1/49 (2.04)	1 (0.99)	1/106 (0.94)	1 (0.43)
Depressed mood disorders and disturbances						
< 20%	12 (0.17)	14 (0.06)	14 (0.16)	16 (0.06)	26 (0.16)	30 (0.06)
≥ 20%	3 (0.20)	3 (0.06)	2 (1.04)	2 (0.30)	5 (0.29)	5 (0.08)
Unclassified	0	0	1 (2.04)	14 (0.99)	1 (0.94)	1 (0.43)
Psychiatric disorders NEC						
< 20%	8 (0.11)	8 (0.03)	9 (0.11)	11 (0.04)	17 (0.11)	19 (0.04)
≥ 20%	4 (0.26)	4 (0.08)	1 (0.52)	1 (0.15)	5 (0.29)	5 (0.08)
Suicidal and self-injurious behaviors NEC						
< 20%	7 (0.10)	9 (0.04)	9 (0.11)	9 (0.03)	16 (0.10)	18 (0.03)
≥ 20%	3 (0.20)	3 (0.06)	0	0	3 (0.17)	3 (0.05)
Anxiety disorders and symptoms						
< 20%	7 (0.10)	10 (0.04)	4 (0.05)	4 (0.01)	11 (0.07)	14 (0.03)
≥ 20%	2 (0.13)	2 (0.04)	0	0	2 (0.12)	2 (0.03)

Source: SELECT CTR, Table 14.3.1.130

As discussed in Section 8.4.1, causes of non-CV death, including suicide, were adjudicated by the EAC. (Note that there were no psychiatrists on the EAC.) The EAC determined that 5 deaths in semaglutide-treated subjects and 3 deaths in placebo-treated subjects were completed suicides. One of the deaths the EAC adjudicated as "suicide" in the placebo group (preferred term: "hanging") leaves some uncertainty about intent. The EAC comments acknowledge the uncertainty. Brief completed suicide narratives by randomized group, including the death due to "hanging" are included below.

Completed Suicides (as adjudicated by EAC)

Semaglutide

- Subject (b) (6): This was a 49-year-old male on treatment for approximately 2.25 years. Past medical history included "depressive syndrome," other chronic medical conditions (hypergammaglobulinemia, coronary heart disease, asthma, heart failure with preserved ejection fraction NYHA class I), history of myocardial infarction, and stroke. Nine days after the last dose, the subject attempted suicide with a gunshot wound to head. He died (b) (6) (b) (6) later due to complications from the gunshot wound.

- Subject (b) (6): This was a 53-year-old male on treatment for approximately 1 year. Past medical history included tuberous sclerosis, thrombocytopenia, coronary heart disease, hypertension, irritable bowel disease, and history of myocardial infarction. At the time of drug discontinuation, the patient had complained of malaise, weakness, gastrointestinal side effects, excessive weight loss, and extreme loss of appetite. The subject and PI discussed symptoms and decided to put the patient on a treatment pause. Four days later, the patient phoned the site complaining still not feeling well. The PI suggested that subject come to site so that he can get admitted for diagnostic tests. The subject refused admission and told site that he would rather wait 2 more weeks to see if symptoms resolve. Four days later, the patient committed suicide by shooting himself in the head at home and died instantly.

  The patient did not have any medical history of mental illness, depression, anxiety, schizophrenia or prior suicidal attempts. No family history was available as the patient was adopted. The patient was not on any prior or current treatment with psychoactive drugs. Social or environmental circumstances which may have contributed to the event included that the patient was unemployed for 3 years and had part time work. It was reported that wife's income was enough to financially sustain them.

- Subject (b) (6): This was a 70-year-old male on treatment for approximately 10 months. Past medical history included visual impairment, gout, coronary heart disease, heart failure NYHA class I, history of prostate cancer with radical prostatectomy. Approximately 10 months into the trial the patient "committed suicide and died." Relevant historical information includes: 1) earlier that year the patient's (b) (6) died of suicide and 2) the (b) (6).

- Subject (b) (6): This was a 54-year-old male on treatment for approximately 7 months. Past medical history included COPD, dyscirculatory leukoencephalopathy, hypertensive heart, and NYHA class I heart failure. On (b) (6), the patient committed suicide by hanging, the event resulted in death. According to the son (phone contact), there were no

medical or family histories of mental illness, including depression, anxiety, schizophrenia, or previous suicidal ideation / attempts. The circumstances that could have caused / contributed to the events are unknown. According to the son, the patient did not have financial, psychological or other problems that could cause suicide.

- Subject (b) (6): This was a 54-year-old female on treatment for approximately 4 months. Past medical history included mild depression, myofascial back pain after motor vehicle accident, coronary heart disease / myocardial infarction, spontaneous cardiac artery dissection, retroperitoneal bleed, spinal fluid leak from nose, and cholelithiasis. Approximately 5 weeks after drug discontinuation the patient was found unresponsive by the patient's son with secretions and blood around mouth. It was last known by the family that the patient was awake at 23:30 previous night when the patient spoke on the telephone with her sister. She was resuscitated; in the ER, toxicology was positive for oxycodone, methadone, and tricyclics (not reported at screening/BL). The subject died 2 weeks later. The official cause of death was ruled as "Hypoxic encephalopathy, due to resuscitated cardiopulmonary arrest, due to oxycodone, methadone, and amitriptyline intoxication." According to the source documentation in the adjudication package, a suicide note was apparently found.

Placebo

- Subject (b) (6): This was a 59-year-old female who was on treatment for approximately 2 years and 3 months. Past medical history included paroxysmal atrial fibrillation, right eye vision loss, depression, neck pain, borderline personality disorder, alcohol abuse, history of stroke, and 2 prior suicide attempts. On (b) (6), the patient was found deceased. An autopsy was done and revealed death by suicide due to verapamil and ethanol toxicity. According to the source documentation in the adjudication package, a suicide note was found.

- Subject (b) (6): This was a 51-year-old male on treatment for 3 years and 9 months. Past medical history included depression, coronary heart disease, and myocardial infarction. At 3 years and 9 months of treatment in the trial the patient had a suicide attempt with salicylate, but survived. At 3 years and 11 months into the trial (2 months after discontinuation), he took an intentional overdose of 400 pills of aspirin 325 mg and died (cardiac arrest while on bedside dialysis in the ICU).

- Subject (b) (6): This was a 72-year-old male with a medical history of coronary heart disease, myocardial infarction, and hypertension. The patient was on treatment for over 3 years when he died due to “hanging.”

By report, the patient was not seen within 24hrs of death and there were no concerns when last seen. An autopsy was done; however, results were unavailable (not reported). The PI saw the coroner's report (death due to "hanging") but did not know if the event was a suicide or not.

AEs of suicide/self-injury were collected systematically when serious. The evaluation presented in Table 53 below is based on SAEs identified using the narrow SMQ for suicide/self-injury. Overall, a similar proportion of subjects reported SAEs of suicidal ideation or behavior in SELECT.

Table 53. Suicide/Self-Injury SMQ SAEs

	Semaglutide N=8803		Placebo N=8801	
	n (%)	E (R)	n (%)	E (R)
Suicide/self-injury SMQ SAEs	10 (0.1)	12 (0.04)	10 (0.1)	12 (0.04)
Completed suicide	5 (<0.1)	5 (0.02)	2 (<0.1)	2 (<0.01)
Suicidal ideation	4 (<0.1)	5 (0.02)	4 (<0.1)	4 (0.01)
Suicide attempt	1 (<0.1)	2 (<0.01)	3 (<0.1)	3 (0.01)
Intentional overdose	0	0	1 (<0.1)	2 (<0.01)
Depression suicidal	0	0	1 (<0.1)	1 (<0.01)
E=number of events; R=E/100 PYE)				

Source: SELECT CTR, Table 12-13

Of note, the 2 events of "intentional overdose" in the placebo subject were confirmed be suicidal behavior (aspirin overdose); 1 event was a suicide attempt and 1 event was a completed suicide (also captured in this table). Both events are described above in the brief narrative for subject (b) (6).

Table 54. Suicide/Self-Injury SMQ SAEs

Subj ID	Verbatim term	PT	Outcome	Action taken	Day	Duration	Sex	Age	BL BMI
Semaglutide									
(b) (6)	Suicide attempt	Suicide attempt	Recovered/resolved	Drug withdrawn	598	31	M	70	31.5
	Suicide attempt	Suicide attempt	Recovered/resolved	Not applicable	629	48			
	Completed suicide	Completed suicide	Fatal	Not applicable	829	31	M	46	38.4
	Suicide	Completed suicide	Fatal	Not applicable	375	1	M	52	36.8
	Death (suicide)	Completed suicide	Fatal	Dose not changed	306	1	M	69	34.7
	Suicide: hanging	Completed suicide	Fatal	Not applicable	225	1	M	53	30.0

(b) (6)	Suicidal ideations	Suicidal ideation	Recovered/resolved	Dose not changed	1070	4	M	64	32.9
	Suicide	Completed suicide	Fatal	Not applicable	179	15	F	54	42.4
	Suicidal ideation	Suicidal ideation	Recovered/resolved	Dose not changed	1173	6	F	54	33.6
	Suicidal ideation with plan	Suicidal ideation	Recovered/resolved	Drug interrupted	72	6	M	66	29.4
	Suicidal ideation with plan	Suicidal ideation	Recovered/resolved	Not applicable	104	9			
	Suicidal ideation	Suicidal ideation	Recovered/resolved	Dose not changed	76	2	F	56	31.1
Placebo									
(b) (6)	Suicide attempt	Suicide attempt	Recovered/resolved	Dose not changed	717	13	M	67	31.4
	Severe depression with suicidal thoughts.	Depression suicidal	Not recovered/not resolved	Dose not changed	441	–	M	56	40.7
	Suicide attempt	Suicide attempt	Recovered/resolved	Not applicable	956	30	M	64	28.7
	Acute suicidality	Suicidal ideation	Recovered/resolved	Dose not changed	234	22	M	50	40.5
	Suicidal ideation	Suicidal ideation	Recovered/resolved	Dose not changed	91	1	M	46	37.3
	Suicidal ideation	Suicidal ideation	Recovered/resolved	Drug interrupted	947	231	F	59	29.6
	Suicidal ideation due to major depressive disorder	Suicidal ideation	Recovered/resolved	Drug withdrawn	160	2	M	59	35.3
	Completed suicide	Completed suicide	Fatal	Not applicable	847	1	F	57	43.2
	Intentional aspirin overdose	Intentional overdose	Recovered/resolved	Dose not changed	1387	9	M	47	30.5
	Intentional aspirin overdose	Intentional overdose	Fatal	Dose not changed	1422	1			
	Suicide	Completed suicide	Fatal	Dose not changed	1422	1			
	Suicide attempt	Suicide attempt	Recovered/resolved	Not applicable	631	1	M	53	34.0

Source: Reviewer created from ADAE.xpt

In addition to SAEs reported by the applicant, a search was conducted to include non-serious AEs. Two additional subjects on semaglutide (1 suicidal ideation, 1 intentional overdose) and 4 additional subjects on placebo (1 suicidal ideation, 3 intentional overdose) reported AEs captured in the suicide and self-injury SMQ search. Further clarification regarding the non-serious intentional overdoses was requested by the applicant; these events were not considered to be events of suicidal behavior or self-harm.

SAEs of depression, excluding suicide and self-injury, were similar between groups (Table 55). However, as noted above, there was a slight numerical imbalance in psychiatric SAEs overall (semaglutide 59 (0.7%) vs. placebo 49 (0.6%)).

Table 55. Depression (excl suicide and self-injury) SMQ SAEs

	Semaglutide N=8803		Placebo N=8801	
	n (%)	E (R)	n (%)	E (R)
Depression (excl suicide and self-injury) SMQ SAEs	15 (0.2)	17 (0.06)	17 (0.2)	19 (0.06)
Depression	13 (0.1)	14 (0.05)	10 (0.1)	10 (0.03)
Major depression	2 (<0.1)	3 (0.01)	5 (<0.1)	5 (0.02)
Mixed anxiety and depressive disorder	0	0	2 (<0.1)	2 (0.01)
Adjustment disorder with depressed mood	0	0	1 (<0.1)	1 (<0.01)
Persistent depressive disorder	0	0	1 (<0.1)	1 (<0.01)
E=number of events; R=E/100 PYE)				

Source: Response to FDA information request; GLP-1 RA Products Assessment of Suicide/Self-Injury, dated 31 Aug 2023, Appendix 3K, Table 5

Permanent discontinuations due to SAEs in the psychiatric disorders SOC were infrequent and are listed below.

Table 56. Psychiatric SAEs Leading to Permanent Discontinuation

Subj ID	Verbatim Term	PT	Outcome	Day	Duration	Sex	Age	BL BMI
Semaglutide								
(b) (6)	Worsening of depression	Depression	Recovered/resolved	159	164	M	58	36.1
	Suicide attempt	Suicide attempt	Recovered/resolved	598	31	M	70	31.5
	Intermittent mild chronic confusion	Confusional state	Not recovered/not resolved	481	–	M	70	30.3
	Major depression	Major depression	Recovered/resolved	838	72	F	61	35.8
Placebo								
(b) (6)	Mental disorder	Mental disorder	Not recovered/not resolved	760	–	M	55	29.9
	Suicidal ideation due to major depressive disorder	Suicidal ideation	Recovered/resolved	160	2	M	59	35.3
	Altered mental status	Mental status changes	Fatal	679	1	F	61	32.4

Source: Reviewer created from ADAE.xpt

8.5.3. Malignant Neoplasms

Malignant neoplasms are of particular interest because of GLP-1 RA class concerns (pancreatic cancer,[60] medullary thyroid cancer [MTC][61]), as well as specific concerns raised in the Saxenda (liraglutide for weight management) program[62] (breast cancer, benign and malignant colorectal neoplasms, and melanoma and non-melanoma skin cancer). However, in the phase 3 weight management program for Wegovy, there was no evidence of an increased risk of malignancy overall with semaglutide, and there was no evidence of an increased risk of any individual malignancy, including malignancies classified as events of special interest. Likewise, the semaglutide for T2D program did not raise significant concerns regarding neoplasms.

Subjects were not eligible for inclusion if they had:

- Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma

- Presence or history of malignant neoplasms within the past 5 years prior to the day of screening (basal and squamous cell skin cancer and any carcinoma in-situ were allowed)

Although calcitonin was not included in screening, subjects were discontinued from study drug at any time in the event of calcitonin ≥ 100 ng/L.

Structured disease-specific forms collected history of certain neoplasms at baseline.

- History of colon neoplasms were reported in 5.8% of semaglutide-treated subjects and 5.9% of placebo-treated subjects; most were benign (5.3% overall).

- History of breast cancer was reported in 2.1% of female subjects in both groups, and history of carcinoma *in situ* of the breast was reported in 1.0% and 0.9% of semaglutide- and placebo-treated female subjects, respectively.

- History of skin cancer was reported in 5.1% of semaglutide- and 4.6% of placebo-treated subjects. Most skin cancer was basal cell carcinoma (semaglutide, n=302, 3.4%; placebo, n=274, 3.1%). There were numerically more subjects with melanoma history in the semaglutide group (n=54, 0.6%) vs. the placebo group (n=37, n=0.4%).

---

[60] Egan AG, et al. Pancreatic safety of incretin-based drugs – FDA and EMA assessment. N Engl J Med 2014; 370: 794-7.
[61] Parks M and Rosebraugh C. Weighing risks and benefits of liraglutide – the FDA's review of a new antidiabetic therapy. N Engl J Med 2010; 362: 774-7.
[62] Golden J, NDA 206321 FDA clinical review, dated October 18, 2014 (DARRTS Ref ID 3645293)

In SELECT, all AEs of malignant neoplasm were collected systematically, irrespective of seriousness. In addition, specific event forms with supplemental information were collected in the event of malignant neoplasms.

In a MedDRA search, malignant neoplasms were reported for a similar proportion of subjects with a similar event rate in the semaglutide group (4.79%, 1.77 events per 100 PYO) and the placebo group (4.75%, 1.73 events per 100 PYO), Table 57.

Malignancy AEs with a fatal outcome were reported in 0.7% of subjects in both treatment groups, with an event rate of 0.22 events per 100 PYO. The EAC adjudicated non-CV deaths as due to malignancies in 55 subjects in the semaglutide arm (0.6%) and 60 subjects in the placebo arm (0.7%); see Table 40 in Section 8.4.1. Similarly, malignancy adverse events by MedDRA search with outcome as 'fatal' were reported in 59 semaglutide-treated subjects and 60 placebo-treated subjects; see Table 57, below. Table 57 also highlights certain malignancies with imbalances unfavorable to semaglutide (bold font).

Table 57. Malignancies, MedDRA Search

	Semaglutide N=8803	**Placebo N=8801**
Malignancies, total	422 (4.79)	418 (4.75)
Female	81/2448 (3.31)	80/2424 (3.30)
Male	341/6355 (5.37)	338/6377 (5.30)
SAEs	358 (4.07)	354 (4.02)
Severe	201 (2.28)	177 (2.01)
AEs leading to fatal outcome	59 (0.67)	60 (0.68)
Skin neoplasms malignant and unspecified	96	106
HLT: Skin melanomas (excl ocular)	**24**	**15**
Reproductive neoplasms male malignant and unspecified	84	78
HLT: Prostatic neoplasms malignant[a]	**81**	**75**
Gastrointestinal neoplasms malignant and unspecified	69	68
HLT: Pancreatic neoplasms malignant (excl islet cell and carcinoid)	7	9
Renal and urinary tract neoplasms malignant and unspecified	49	41
HLT: Renal neoplasms malignant	**17**	**12**
HLT: Bladder neoplasms malignant	15	25
HLT: Urinary tract neoplasms malignant NEC	**13**	**2**
HLT: Renal pelvis and ureter neoplasms malignant	**6**	**2**
Respiratory and mediastinal neoplasms malignant and unspecified	48	46
Miscellaneous and site unspecified neoplasms malignant and unspecified	22	21
Breast neoplasms malignant and unspecified (incl nipple)	17	21
Endocrine neoplasms malignant and unspecified	14	8

HLT: Carcinoid tumors[b]	**4**	**0**
HLT: Thyroid neoplasms malignant[c]	5	6
PT: Medullary thyroid cancer	0	3
Hepatobiliary neoplasms malignant and unspecified	12	9
PT: Hepatocellular carcinoma	9	5
Lymphomas non-Hodgkin's B-cell	9	7
HLT: Mantle cell lymphomas	0	2
Plasma cell neoplasms	9	5
PT: Plasma cell myeloma	6	5
PT: Plasmacytoma	3	0
Metastases	8	11
Reproductive neoplasms female malignant and unspecified	7	10
Leukemias	7	7
Lymphomas NEC	2	2
Lymphomas non-Hodgkin's T-cell	2	1
Soft tissue neoplasms malignant and unspecified	1	3
Lymphomas Hodgkin's disease	1	1
Skeletal neoplasms malignant and unspecified	1	0
Mesotheliomas	0	2
Nervous system neoplasms malignant and unspecified NEC	0	2
Ocular neoplasms	0	2
Lymphomas non-Hodgkin's unspecified histology	0	1

a Includes PTs: prostate cancer, prostate cancer metastatic, prostate cancer recurrent, prostate cancer stage I, prostate cancer stage II, prostate cancer stage III, prostate cancer stage IV, neuroendocrine carcinoma of prostate
b includes PTs (1 each): carcinoid tumor, carcinoid tumor of the small bowel, carcinoid tumor pulmonary, carcinoid tumor of the gastrointestinal tract
c includes PTs: papillary thyroid cancer, medullary thyroid cancer, follicular thyroid cancer, thyroid cancer

Source: Reviewer created from ADAE.xpt dataset

Because of imbalances in melanomas, endocrine neoplasms, and renal and urinary tract cancers, some terms were expanded further for additional information. Although the PT 'Prostate cancer' was among the most frequently reported malignancies, with a slightly higher proportion in semaglutide-treated men (1.10% of men, 0.33 events per 100 PYO) vs. placebo (0.89% of men, 0.27 events per 100 PYO), evaluation by the HLT 'Prostatic neoplasms malignant' (indicating a more complete grouping of terms) as shown in Table 57 did not demonstrate a meaningful imbalance (semaglutide 1.27%, 0.38 events per 100 PYO vs. placebo (1.18%, 0.36 events per 100 PYO).

Melanoma

A small imbalance in skin melanomas was noted. Three of the semaglutide-treated subjects and 1 of the placebo-treated subjects who reported melanoma during the trial had a history of melanoma at baseline.

The imbalance in melanomas is primarily due to malignant melanoma *in situ* (semaglutide n=8 vs. placebo n=1, Table 58). Other melanoma preferred terms were balanced between groups. Two additional participants on placebo reported SAEs of ocular melanoma.

Table 58. Melanomas

	Semaglutide N=8803	Placebo N=8801
HLT: Skin melanomas (excl ocular)	24 (0.3)	15 (0.2)
SAEs	20	13
AEs leading to fatal outcome	2	1
Malignant melanoma	12	10
Malignant melanoma in situ	8	1
Metastatic malignant melanoma	2	3
Lentigo maligna	2	1
Melanoma recurrent	1	1
Superficial spreading melanoma stage I	1	0
HLT: Ocular neoplasms	0	2 (<0.1)
Choroid melanoma	0	2

Source: Reviewer created from ADAE.xpt dataset

Endocrine Cancers, Including MTC and Elevated Calcitonin

AEs in the HLGT 'Endocrine neoplasms malignant and unspecified' include a variety of thyroid cancers and neuroendocrine/carcinoid tumor PTs. In general, the numbers for any particular tumor listed are low, although there were 4 tumors in the semaglutide arm designated as 'carcinoid' and none in the placebo arm (also shown above in Table 57). As stated previously, no cases of medullary thyroid carcinoma were reported for any semaglutide-treated subject. Blood calcitonin, which is relevant to c-cell hyperplasia and MTC, is discussed below.

Table 59. Endocrine Cancers, Including Thyroid and Neuroendocrine Neoplasms

	Semaglutide N=8803	Placebo N=8801
HGLT: Endocrine neoplasms malignant and unspecified	14 (0.2)	8 (0.1)
SAEs	13 (0.1)	7 (0.1)
AEs leading to fatal outcome	1 (<0.1)	1 (<0.1)
Papillary thyroid cancer	4 (<0.1)	2 (<0.1)
Follicular thyroid cancer	2 (<0.1)	0
Pancreatic neuroendocrine tumor	2 (<0.1)	0
Neuroendocrine carcinoma metastatic	1 (<0.1)	1 (<0.1)
Adrenocortical carcinoma	1 (<0.1)	0
Carcinoid tumor	1 (<0.1)	0

Carcinoid tumor of the gastrointestinal tract	1 (<0.1)	0
Carcinoid tumor of the small bowel	1 (<0.1)	0
Carcinoid tumor pulmonary	1 (<0.1)	0
Neuroendocrine carcinoma	1 (<0.1)	0
Medullary thyroid cancer	0	3 (<0.1)
Small intestine neuroendocrine tumor	0	1 (<0.1)
Thyroid cancer	0	1 (<0.1)

Source: Reviewer created from ADAE.xpt dataset

Blood concentrations of calcitonin were monitored throughout the trial. All 3 events of MTC (all placebo subjects) were identified based on *baseline* calcitonin assessments.

A total of 19 subjects were reported to have calcitonin > 100 ng/L at least once. One subject (semaglutide) had a post-baseline value > 100 ng/L outside of the 'in-trial' period (Subject ID (b) (6), discussed further below). One subject (semaglutide) had 1 *baseline* value > 100 ng/L; all *post-baseline* values were < 100 ng/L.

The remaining 17 subjects had calcitonin > 100 ng/L post-baseline 'in-trial'. Of these, 5 subjects in the semaglutide group and 4 in the placebo group had calcitonin ≤ 100 ng/L at baseline that increased to > 100 ng/L post-baseline. These 5 semaglutide subjects, plus the 1 semaglutide subject with increase to > 100 ng/L outside the 'in-trial' period, are described further as follows:

- Subject (b) (6): This was a 54-year-old female who presented after ~13 months on treatment with calcitonin ~1100 pg/mL. Her thyroid gland was evaluated, and she was diagnosed with autoimmune thyroiditis (she apparently had a thyroid biopsy, but results were not provided). Additional testing demonstrated polycythemia and a lung neoplasm with mediastinal lymphadenopathy. Calcitonin was 3639 (no units provided). CT of the brain several months later showed metastases and she died about 1 month later prior to receiving treatment. Death and elevated calcitonin were attributed to a lung neoplasm with paraneoplastic activity, however there was no confirmatory diagnostic testing (no histopathology, no autopsy).

- Subject (b) (6): This was a 74-year-old male with a *baseline* calcitonin of 74.6 ng/L. Post-baseline values were: week 20 92.2, week 52 91.4, week 104 84.3, week 156 116, week 208 (off drug) 111, end-of-trial (off-drug) 73.3.

- Subject (b) (6): This was a 77-year-old female with a history of CHD and Sjogren's disease, who had a thyroid ultrasound about 2 years into the trial after the calcitonin level was found to be slightly elevated (6 ng/L [ULN 5.1 ng/L]). She was found to have a 1.7 cm nodule of the left lobe of the thyroid. Several months later, the central lab calcitonin was 97 ng/L; local lab 213 ng/L [ULN 20]) and biopsy revealed lymphocytic thyroiditis (Hashimoto). Carcinoembryonic antigen was 3.7 µg/L (ULN 5.0). She continued in the study

on drug. Additional calcitonin values were: 185 ng/L (day 1003), 79.8 ng/L (day 1098), and 131 ng/L (end-of-treatment (EOT)/day 1324).

- Subject (b) (6) This was a 76-year-old male with a baseline calcitonin of 13.8 ng/L (ULN 8.4). During the first 3 years in the trial, calcitonin ranged from 5.6-16.6. After 3 years and 9 months, at the EOT visit, the value was 150 ng/L. AEs (non-serious) reported at the time were painful leg and increased alkaline phosphatase. As per protocol, the site was advised that subject should be referred to a thyroid specialist and AEs monitored. Subsequent site response indicated that no abnormalities were found following examination by physician. No further information was provided.

- Subject (b) (6): This was a 66-year-old male with a baseline calcitonin of 10.7 ng/L (ULN 8.4). Calcitonin throughout the trial ranged from 8.6 (week 20) to 23.9 ng/L (EOT/day 1541; non-serious AE reported 'Blood calcitonin abnormal'). At a follow-up visit outside of the 'in-trial' period 50 days later, the subject had a value of 129 ng/L. No further information was provided.

- Subject (b) (6): This was a 74-year-old male with a baseline calcitonin of 13.1 ng/L (ULN 8.4). On day 113, the calcitonin increased to 38.3 ng/L and the drug was temporarily discontinued. After restarting, on day 379 the value was 21.1 and on day 730 the value was 16.9. On day 823, the value was 1207 ng/L. At a subsequent retest visit (trial day 862) calcitonin was 804 ng/L. There were no notable AEs reported near the time elevated calcitonin levels were recorded. As per protocol, the site was advised to refer the subject to a thyroid specialist. Subsequent site response indicated the subject was in referral with a specialist, however no diagnosis was reported at the time of correspondence.

The 4 placebo-treated subjects with baseline calcitonin < 100 that increased to ≥ 100 ng/L were as follows:

- Subject (b) (6): This was a 73-year-old male with a baseline calcitonin of 63.3 ng/L that increased to 101 ng/L at EOT (day 1590).

- Subject (b) (6): This was a 45-year-old female with a baseline calcitonin of 22.4 ng/L (ULN 5) that increased to 124 ng/L at EOT (day 1128). As per protocol, the site was advised to refer subject to thyroid specialist. Subsequent site response indicated subject was referred however no diagnosis at time of correspondence.

- Subject (b) (6): This was a 52-year-old female with a baseline calcitonin of 1 ng/L throughout the trial that increased to 142 ng/L at EOT (day 1434). AEs reported near time of elevated calcitonin levels included congenital/familial/genetic disorder, large lobulated right kidney and elevated alanine aminotransferase. As per protocol, the site was advised

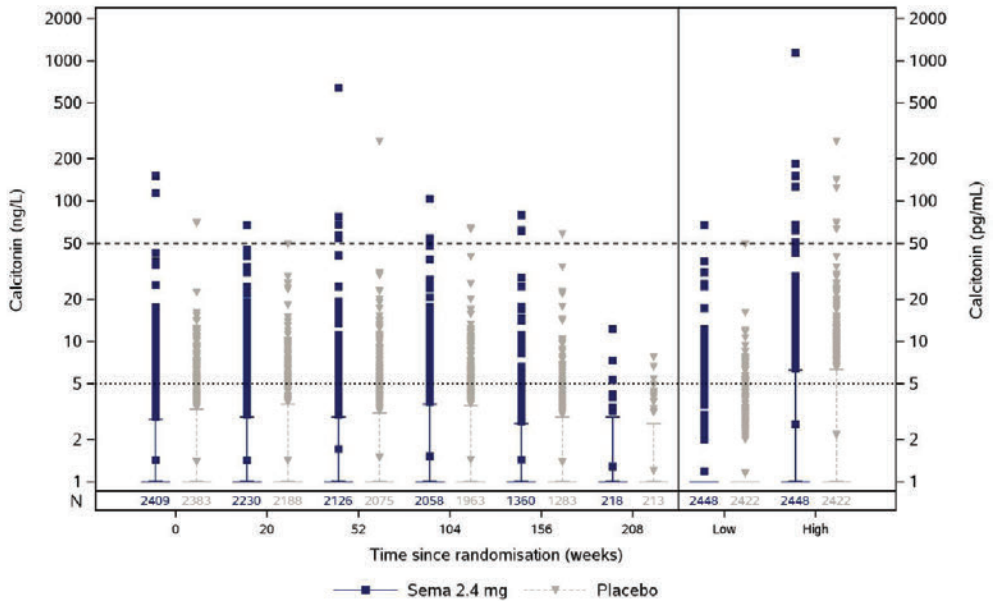
to refer the subject to a thyroid specialist. Subsequent site correspondence confirmed that repeated testing had been performed and that calcitonin levels were within normal ranges.

- Subject (b) (6): This was a 67-year-old female with a baseline calcitonin of 2.4 ng/L that increased to 266 ng/L at day 365 (treatment was withdrawn and no further measurements were recorded). Subsequent follow up by thyroid specialist reported small multinodular goiter via ultrasound, regarded as not clinically significant. The thyroid specialist suggested that potential cause for elevated calcitonin was due to beta blocker medication taken at the time. It was noted that subject was to have further follow up 6 months later.

'Blood calcitonin increased' was reported as an SAE in 2 semaglutide-treated subjects and 3 placebo-treated subjects. In 1 of the semaglutide-treated subjects (subject ID (b) (6)), baseline calcitonin was elevated at 24 ng/L, and ranged from 21.8 to 32.2 ng/L over the next 2 years. A stimulated calcitonin level was 458.0 ng/L. No diagnosis was made after a work-up which included a thyroid ultrasound and positron emission tomogram/computed tomography. The patient continued in the trial. In the second semaglutide-treated subject (subject ID (b) (6)), baseline calcitonin was elevated at 20.4 ng/L. Follow-up calcitonin 6 months later was 31 pg/mL. Work-up included biopsy, which showed chronic lymphocytic thyroiditis and thyroglossal duct cyst.

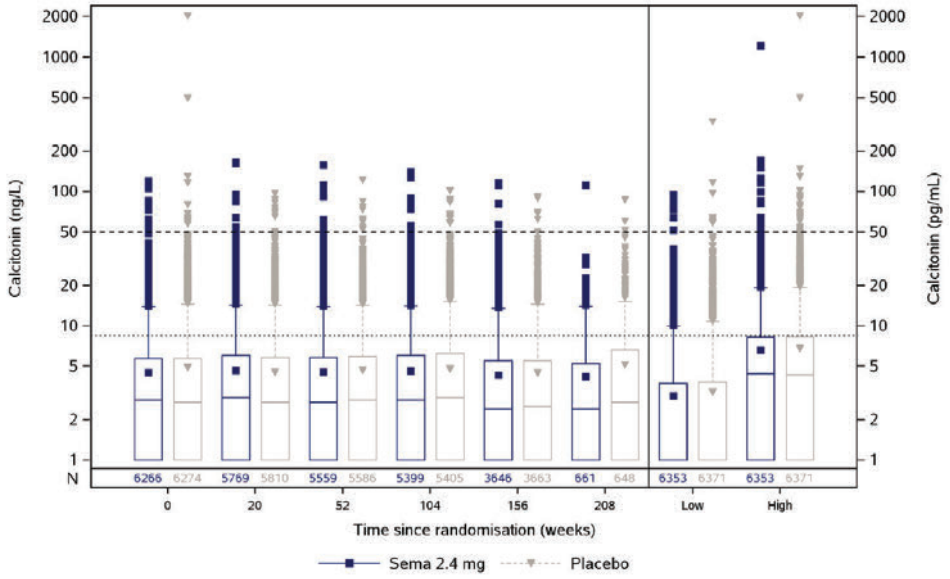
Box plots of calcitonin values are as follows:

Figure 32. Calcitonin by Week, Females



Source: SELECT CTR, Figure 14.3.5.31

Figure 33. Calcitonin by Week, Males



Source: SELECT CTR, Figure 14.3.5.32

Reviewer comment: Elevated calcitonin is suggestive of, but not diagnostic for c-cell hyperplasia or MTC. Similar numbers of patients in both groups had elevated calcitonin values with alternative diagnoses or no diagnosis reported. There were no reports of MTC in any semaglutide-treated participant, even after follow-up queries.

Cancer of the Bladder and Kidney

Cancers of the urinary system were reported in imbalanced numbers in both directions by HLT (Table 57, above) and by PT (Table 60, below). However, as there is no clear pattern to the imbalances, it seems likely to be due to chance. Furthermore, as the applicant noted in response to an information request, few bladder, ureter and kidney malignant neoplasms with no observed treatment differences were reported in the semaglutide cardiovascular outcome trials in patients with type 2 diabetes, SUSTAIN 6 and PIONEER 6.

Table 60. Renal and Urinary Tract Malignancies

	Semaglutide N=8803	Placebo N=8801
HLGTs Renal and urinary tract malignancies	49 (0.6)	41 (0.5)
SAEs	47 (0.5)	41 (0.5)
Fatal outcome	7 (0.1)	3 (<0.1)
Bladder transitional cell carcinoma	11 (0.1)	17 (0.2)
Transitional cell carcinoma	11 (0.1)	2 (<0.1)

Clear cell renal cell carcinoma	6 (0.1)	4 (<0.1)
Renal cell carcinoma	4 (<0.1)	5 (0.1)
Renal cancer metastatic	4 (<0.1)	0
Bladder cancer	3 (<0.1)	8 (0.1)
Renal cancer	2 (<0.1)	3 (<0.1)
Transitional cell cancer of the renal pelvis and ureter	2 (<0.1)	1 (<0.1)
Transitional cell cancer of renal pelvis and ureter metastatic	1 (<0.1)	1 (<0.1)
Bladder adenocarcinoma stage unspecified	1 (<0.1)	0
Malignant neoplasm of renal pelvis	1 (<0.1)	0
Papillary renal cell carcinoma	1 (<0.1)	0
Transitional cell cancer of the renal pelvis and ureter localized	1 (<0.1)	0
Transitional cell carcinoma metastatic	1 (<0.1)	0
Transitional cell carcinoma recurrent	1 (<0.1)	0
Ureteric cancer	1 (<0.1)	0
Bladder cancer recurrent	0	1 (<0.1)

Source: Reviewer created from ADAE.xpt dataset

Malignancy tissue of origin based on additional data collection

In addition to the MedDRA search, additional data regarding malignancies were collected on a specific form. A total of 431 (4.9%) subjects (535 events) in the semaglutide group and 429 (4.9%) subjects (516 events) in the placebo group had additional information collected on the form for malignant neoplasms. In general, data collected on the specific form corresponded to the AEs described via MedDRA search. [Note that the majority of events (93%) were captured by both MedDRA terms and additional data collection forms.]

Table 61. Tissue of Origin for Malignant Neoplasms Based on Additional Data Collection

	Sema 2.4 mg				Placebo			
	N	(%1)	E	(%2)	N	(%1)	E	(%2)
Number of subjects	8803				8801			
Female	2448				2424			
Male	6355				6377			
Events	431	(4.9)	535	(100)	429	(4.9)	516	(100)
Female	80	(3.3)	94	(100)	83	(3.4)	97	(100)
Male	351	(5.5)	441	(100)	346	(5.4)	419	(100)
Location of primary malignant neoplasm								
Skin	106	(1.2)	154	(28.8)	110	(1.2)	159	(30.8)
Male reproductive system (males only)	84	(1.3)	87	(19.7)	81	(1.3)	87	(20.8)
Lower gastrointestinal tract	46	(0.5)	51	(9.5)	35	(0.4)	37	(7.2)
Lower respiratory system	40	(0.5)	49	(9.2)	41	(0.5)	45	(8.7)
Bladder (urinary bladder, urethra)	24	(0.3)	26	(4.9)	29	(0.3)	32	(6.2)
Upper gastrointestinal tract	21	(0.2)	23	(4.3)	25	(0.3)	27	(5.2)
Kidney	19	(0.2)	21	(3.9)	14	(0.2)	14	(2.7)
Breast (females only)	17	(0.7)	17	(18.1)	20	(0.8)	23	(23.7)
Blood	15	(0.2)	15	(2.8)	13	(0.1)	14	(2.7)
Upper respiratory system	11	(0.1)	11	(2.1)	10	(0.1)	11	(2.1)
Other	11	(0.1)	18	(3.4)	8	(<.1)	8	(1.6)
Liver	9	(0.1)	10	(1.9)	6	(<.1)	6	(1.2)
Pancreas	8	(<.1)	9	(1.7)	11	(0.1)	12	(2.3)
Female reproductive system (females only)	8	(0.3)	8	(8.5)	11	(0.5)	11	(11.3)
Lymph node	8	(<.1)	8	(1.5)	7	(<.1)	7	(1.4)
Ureter	6	(<.1)	7	(1.3)	0			
Thyroid gland	6	(<.1)	7	(1.3)	8	(<.1)	8	(1.6)
Bone	4	(<.1)	4	(0.7)	5	(<.1)	5	(1.0)
Unknown	4	(<.1)	4	(0.7)	3	(<.1)	4	(0.8)
Gallbladder	3	(<.1)	4	(0.7)	2	(<.1)	2	(0.4)
Central nervous system	1	(<.1)	1	(0.2)	2	(<.1)	2	(0.4
Other endocrine glands	1	(<.1)	1	(0.2)	2	(<.1)	2	(0.4)

Sex-specific neoplasms are reported by sex using the sex-specific population to calculate percentage and rate. Gallbladder include extrahepatic bile ducts.
%1: percentage of subjects, %2: percentage of total number of events, E: number of events, N: number of subjects.
Source: SELECT CTR, Table 12-10

Reviewer comment: In summary, malignant neoplasms were reported for a similar proportion of subjects at a similar event rate. Small numerical imbalances were observed for melanoma in situ, various carcinoid/neuroendocrine tumors, and certain cancers of the urinary system. Other small imbalances were seen in other tissue types in both treatment groups, suggestive of chance findings. There were no reports of medullary thyroid cancer (MTC) in any semaglutide-treated subject, although some subjects had significant calcitonin elevations at the end of the trial without an available diagnosis.

8.5.4. Gallbladder-Related Disorders

Obesity and rapid weight loss are associated with an increased risk for gallstone formation.[63] In addition, GLP-1 receptor agonists decrease gallbladder emptying and the class has been associated with gallstone formation.[64] Acute gallbladder disease is a labeled warning (Section 5) in the Wegovy USPI.

In the SELECT trial, all AEs of gallbladder disease were collected systemically, irrespective of seriousness. The proportion of subjects with AEs of gallbladder-related disorders via MedDRA search and the event rate was higher in the semaglutide group than in the placebo group (2.79% vs 2.31% and 1.02 vs 0.85 events per 100 PYO).

Table 62. Gallbladder-Related Disorders

	Semaglutide N=8803		Placebo N=8801	
	n (%)	E (R)	n (%)	E (R)
Gallbladder-related disorders (MedDRA search)	246 (2.79)	300 (1.02)	203 (2.31)	246 (0.85)
Fatal	1 (0.01)	1 (<0.01)	3 (0.03)	6 (0.02)
SAEs	114 (1.30)	143 (0.49)	93 (1.06)	123 (0.42)
Severe	47 (0.53)	57 (0.19)	59 (0.67)	79 (0.27)
Drug withdrawn	6 (0.07)	6 (0.02)	11 (0.12)	14 (0.05)
E=number of events; R=E/100 PYE)				

Source: SELECT CTR, Table 14.3.1.24

As seen below in Table 63, the majority of events identified in the predefined MedDRA search, and the events driving the semaglutide numerical imbalance, were of the preferred term 'cholelithiasis.' A similar proportion of subjects in each group reported (acute) cholecystitis; there is a numerical imbalance not favoring semaglutide for chronic cholecystitis. Some events, such as 'jaundice' are not specific to the gallbladder. Hepatic events are discussed in Section 8.5.7.

Table 63. Gallbladder-Related Disorders Preferred Terms

	Semaglutide N=8803		Placebo N=8801	
	n	%	n	%
Cholelithiasis	123	1.4	100	1.1
Blood bilirubin increased	40	0.5	29	0.3
Cholecystitis acute	28	0.3	31	0.4
Cholecystitis	18	0.2	18	0.2
Bile duct stone	17	0.2	11	0.1

[63] Stinton LM, et al. Epidemiology of gallstones. Gastroenterol Clin North Am 2010 Jun; 39(2): 157-69, vii.
[64] FDA Pharmacovigilance Review, dated February 25, 2022. DARRTS Ref ID: 4943380

Cholecystitis chronic	16	0.2	6	0.1
Hyperbilirubinemia	7	0.1	2	0.0
Cholangitis	6	0.1	4	0.0
Obstructive pancreatitis	5	0.1	7	0.1
Cholecystitis infective	4	0.0	4	0.0
Sphincter of Oddi dysfunction	4	0.0	0	0.0
Biliary colic	3	0.0	6	0.1
Jaundice	3	0.0	0	0.0
Gallbladder disorder	2	0.0	4	0.0
Biliary dilatation	2	0.0	1	0.0
Cholangitis infective	2	0.0	1	0.0
Gallbladder rupture	2	0.0	1	0.0
Hyperplastic cholecystopathy	2	0.0	0	0.0
Jaundice cholestatic	1	0.0	2	0.0
Biliary obstruction	1	0.0	1	0.0
Cholangitis acute	1	0.0	1	0.0
Cholelithiasis obstructive	1	0.0	1	0.0
Bile duct stenosis	1	0.0	0	0.0
Cholelithiasis migration	1	0.0	0	0.0
Gallbladder cholesterolosis	1	0.0	0	0.0
Gallbladder enlargement	1	0.0	0	0.0
Gallbladder necrosis	1	0.0	0	0.0
Biliary dyskinesia	0	0.0	2	0.0
Portal hypertensive biliopathy	0	0.0	1	0.0
Post cholecystectomy syndrome	0	0.0	1	0.0

Source: Reviewer created from ADAE.xpt dataset

A total of 232 events in the semaglutide group (n=193, 2.2%) and 201 events in the placebo group (n=169, 1.9%) had additional information collected on the specific event form for gallbladder disease, defined in the protocol as biliary colic, cholecystitis and other forms of gallbladder disease (Table 64). A higher proportion of subjects on semaglutide who had additional data collection had a gallbladder event that led to cholecystectomy (semaglutide 38.9%, placebo 34.9%), antibiotics (28.0%, 21.9%), or endoscopic retrograde cholangiopancreatography (ERCP) (9.3%, 7.7%).

Table 64. Gallbladder Disease, Additional Data Collection

	Semaglutide N=8803 n (%)	**Placebo N=8801 n (%)**
Subjects with events with additional data collection	193 (2.2)	169 (1.9)
Signs/symptoms present during event	126 (65.3)	118 (69.8)
Imaging performed	189 (97.9)	161 (95.3)
Treatment	126 (65.3)	106 (62.7)
Cholecystectomy	75 (38.9)	59 (34.9)

Elective	48 (24.9)	33 (19.5)
Urgent	27 (14.0)	27 (16.0)
Antibiotics	54 (28.0)	37 (21.9)
Intravenous fluids	43 (22.3)	34 (20.1)
ERCP	18 (9.3)	13 (7.7)
Medication to dissolve stones	4 (2.1)	2 (1.2)
Shock wave lithotripsy	0	2 (1.2)
Other	23 (11.9)	22 (13.0)
History of rapid weight loss	23 (11.9)	3 (1.8)

Source: SELECT CTR, Table 14.3.1.110

8.5.5. **Pancreatitis**

Pancreas safety, including concerns about acute pancreatitis, has historically been an area of interest with incretin mimetics.[60] Post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis with GLP-1-based therapies, have led to warnings regarding acute pancreatitis in drug labeling for the class, including Wegovy (Wegovy USPI, Section 5.2).

In the Wegovy phase 3 clinical program, pancreatitis was reported infrequently. In approximately half of the cases, gallstones were observed in association with pancreatitis. As with other GLP-1 RAs, Wegovy is associated with elevations in pancreatic enzymes; however, these elevations were infrequently captured as pancreatitis events in the phase 3 program.

In SELECT, subjects were excluded with a history or presence of chronic pancreatitis, or presence of acute pancreatitis within the past 180 days prior to the day of screening.

All AEs of pancreatitis were collected systematically, irrespective of seriousness. In addition to a MedDRA search for events relevant to acute and chronic pancreatitis, the investigators were instructed to collect pancreatitis event information on a specific form, and the potential events of acute pancreatitis were sent for adjudication by the EAC and categorized according to severity using the Atlanta criteria.[65]

A similar proportion of participants in each arm had events of pancreatitis by MedDRA search, and the rate was low. Serious and severe events and events leading to withdrawal were similar between groups.

[65] Banks PA, et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-11.

Table 65. Pancreatitis Events

	Semaglutide N=8803		Placebo N=8801	
	n (%)	E (R)	n (%)	E (R)
Pancreatitis (MedDRA search)	29 (0.33)	33 (0.11)	30 (0.34)	33 (0.11)
Fatal	2 (0.02)	2 (<0.01)	1 (0.01)	1 (<0.01)
SAEs	19 (0.22)	23 (0.08)	25 (0.28)	28 (0.10)
Severe	12 (0.14)	15 (0.05)	14 (0.16)	15 (0.05)
Drug withdrawn	11 (0.12)	11 (0.04)	17 (0.19)	17 (0.06)
E=number of events; R=E/100 PYE)				

Source: SELECT CTR, Table 14.3.1.37

Table 66. Pancreatitis Preferred Terms

	Semaglutide N=8803		Placebo N=8801	
	n	%	N	%
Pancreatitis acute	12	0.1	15	0.2
Pancreatitis	7	0.1	6	0.1
Obstructive pancreatitis	5	0.1	7	0.1
Pancreatitis chronic	3	<0.1	1	<0.1
Edematous pancreatitis	1	<0.1	1	<0.1
Traumatic pancreatitis	1	<0.1	1	<0.1
Alcoholic pancreopathy	1	<0.1	0	<0.1
Pancreatitis relapsing	0	<0.1	1	<0.1

Source: Reviewer created from ADAE.xpt dataset

Additional data were collected via dedicated form in 39 events (34 subjects) in the semaglutide group and in 32 events (29 subjects) in the placebo group. In the semaglutide group, 12/39 events (30.8%) and in the placebo group 13/32 events (40.6%) had imaging consistent with the presence of gallstones. Imaging was consistent with acute pancreatitis in 19/39 events (48.7%) on semaglutide and 23/32 events (71.9%) on placebo, and with chronic pancreatitis in 5/39 (12.8%) and 3/32 (9.4%) events, respectively.

Adjudicated Acute Pancreatitis

A total of 69 subjects (35 in the semaglutide group and 34 in the placebo group) had a medical history of acute pancreatitis at screening. None of the subjects with a history of acute pancreatitis had EAC-confirmed events of acute pancreatitis during the in-trial period.

The EAC evaluated 87 events in 74 subjects and confirmed the diagnosis of acute pancreatitis in 46 events in 42 subjects. As shown in Table 67, semaglutide-treated subjects did not appear to demonstrate an excess of adjudicated pancreatitis in SELECT. Similar proportions of subjects in

both treatment groups had moderately severe and severe pancreatitis as judged by the Atlanta criteria.

Table 67. EAC-Confirmed Events of Acute Pancreatitis

	Semaglutide N=8803	Placebo N=8801
Acute pancreatitis	17 (0.2)	24 (0.3)
Severe acute upper abdominal pain	15 (0.2)	24 (0.3)
Elevated blood levels of pancreatic enzyme ≥ 3x ULN	13 (0.1)	18 (0.2)
Characteristic imaging findings	15 (0.2)	16 (0.2)
Severity		
Mild	9 (0.1)	18 (0.2)
Moderately severe	8 (0.1)	6 (0.1)
Severe	1 (<0.1)	3 (<0.1)
Cannot be determined	1 (<0.1)	0

Source: SELECT CTR, Table 12-3

8.5.6. **Hypoglycemia**

In SELECT, which excluded subjects with diabetes mellitus, hypoglycemia AEs were collected systematically when serious and were evaluated based on a predefined MedDRA search. Blood glucose was not routinely measured in SELECT.

SAEs of hypoglycemia were infrequent (3 events in 3 semaglutide-treated subjects vs. 1 event in 1 placebo-treated subject), and generally occurred in settings where there were contributing factors (other medication, bariatric surgery, fasting). Patients with a history of bariatric surgery (a risk factor for hypoglycemia) had more events of serious hypoglycemia while taking semaglutide (2.3%, 2/87) than placebo (0%, 0/97).

Table 68. Hypoglycemia SAEs

Subj ID Sex/Age/BMI	Verbatim	Seriousness/ Severity/ Outcome/ Action	Day	Details
Semaglutide				
(b) (6) F/55/39.6	Nocturnal hypoglycemia	Serious/ Severe/ Recovered/ Dose not changed	803	No blood glucose measurements at time of event; no concomitant glucose-lowering medication; prediabetic status at baseline and normoglycemic from day 463; alternative etiology suggested by investigator: concomitant medication of rifampicin

(b) (6) F/50/37.4	Hypoglycemia	Serious/ Mild/ Recovered/ Not applicable	1494	Blood glucose 46.8 mg/dL; no concomitant glucose-lowering medication; prediabetic status at baseline, the subject had fluctuations during the trial, normoglycemic at the end of trial; investigator's alternative etiology: Gastric sleeve surgery and partly fasting period due to Ramadan
(b) (6) M/53/34.4	Hypoglycemia	Serious/ Severe/ Recovered/ Dose not changed	730	Blood glucose 25.2 mg/dL; no concomitant glucose-lowering medication; prediabetic status at baseline and normoglycemic from day 474; alternative etiology of bariatric surgery in 2009 (medical history) with symptoms of 'dumping syndrome' after the procedure
Placebo				
(b) (6) M/59/46.2	Hypoglycemia	Serious/ Mild/ Recovered/ Dose not changed	558	Blood glucose 50 mg/dL; no concomitant glucose-lowering medication; alternative etiology: concomitant antibiotic (cefdinir); normoglycemic status at baseline and throughout the trial; had history of hypoglycemic events when treated with antibiotics

Source: SELECT CTR, Table 12-11

8.5.7. **Hepatic Disorders**

Drug-induced liver injury (DILI) for the GLP-1 RA class was evaluated under the NISS process (SSID 1004209) in 2021.[66] This evaluation did include semaglutide for obesity, which was under review at the time, and available data from SELECT, which was ongoing at the time. The evaluation did not support a direct mechanism for DILI with any GLP-1 RA, although the review concluded that there may be rare idiosyncratic reactions with the use of dulaglutide and liraglutide.

The Wegovy label includes description of liver enzyme increases in the pediatric population: *In a pediatric clinical trial, increases in alanine aminotransferase (ALT) greater than or equal to 5 times the upper limit of normal were observed in 4 (3%) WEGOVY-treated patients compared with 0% of placebo-treated patients. In some patients, increases in ALT and AST were associated with other confounding factors (such as gallstones).*

In the SELECT trial, SAEs of hepatic disorders by MedDRA search were uncommon and similar between groups. Overall, 36 subjects on semaglutide (0.41%) reported 45 events and 35 subjects on placebo (0.40%) reported 47 events. Events were fatal in 6 subjects on semaglutide and 11 subjects on placebo, and led to drug withdrawal in 1 and 2 subjects, respectively.

[66] See NISS Safety Lead Memorandum, dated October 15, 2021; DARRTS Reference ID: 4873151

Table 69. Potential Cases of DILI SAEs

Subj ID Sex/Age/BMI	PT/Verbatim term	AE Outcome/Action taken	Trial day of onset	Novo Nordisk case evaluation	Reviewer comment
Semaglutide					
(b) (6) F/45/27.9	Drug-induced liver injury/ Toxic or drug hepatitis	Recovered/ Drug interrupted	61	DILI which is likely to be related to paracetamol and not trial product as trial product has a negative rechallenge test.	Given the severity of this case (liver failure), the details are well-known to FDA. The case was previously reviewed by the NISS team[66,67] including Dr. Mark Avigan (hepatologist, OSE). The NISS team considered this a case of paracetamol-induced severe hepatotoxicity. However, it is unknown if weight loss leading to glutathione depletion may have been a contributing factor. Importantly, semaglutide was apparently restarted without recurrence.
(b) (6) M/50/28.3	Liver injury/ Self-limiting liver injury	Recovered/ Dose not changed	144	DILI which is unlikely to be related to trial product as improvement was seen when statin was stopped, and the participant continued on trial product.	
	Aspartate aminotransferase increased/ Elevated level of AST	Recovered/ Dose not changed	144		
	Blood bilirubin increased/ Elevated level of bilirubin	Recovered/ Dose not changed	144		
(b) (6) M/67/27.5	Drug-induced liver injury/ Drug-induced liver toxicity	Recovered/ Drug interrupted	593	This is a potential DILI case. It is unlikely to be caused by trial product as it has a negative	

[67] See DDLO NISS review (Dr. Tania Condarco), Table 14, dated July 15, 2021; DARRTS Reference ID: 4826614

				rechallenge test. Aspavor [atorvastatin] is the likely DILI agent.	
(b) (6) M/51/29.7	Suspected drug-induced liver injury/ Suspected DILI	Recovered/ Not applicable	1527	Potential DILI which is unlikely for trial product. More likely to be due to acetaminophen and/or ibuprofen as there is a temporal relationship and positive dechallenge test.	The patient's end-of-treatment ALT was 177 U/L (otherwise ranged from 27-35 U/L during the trial; ULN 55 U/L). He apparently had been taking cold medicine, including acetaminophen and ibuprofen for the previous 4 days. About 1 week later he returned for follow-up labs and ALT was 46 IU/L. Glutathione was also reported as 122 IU/L [reference range not reported, but suspected to be somewhat low].
(b) (6) M/68/30.2	Drug induced hepatitis/ Drug-induced liver injury	Recovered/ Drug interrupted	1078	Potential DILI which is likely related to Keflex due to an associative pattern.	
Placebo					
(b) (6) M/61/27.4	Drug-induced liver injury/ Drug-induced hepatitis	Recovered/ Dose not changed	299	DILI which is unlikely to be related to trial product as rechallenge test was negative. More likely related to ezetimibe with which there was a temporal association.	
(b) (6) F/69/35.9	Drug-induced liver injury/ Probable Atorvastatin hepatitis	Recovered/ Drug interrupted	96	Potential DILI which is likely related to Atorvastatin with a positive	
	Drug-induced liver injury/ Probable	Recovered/ Dose not changed	467		

	Atorvastatin hepatitis			dechallenge and rechallenge test.	

Source: Adapted from SELECT CTR, Table 12-4

Table 70. Cases of Other Liver Injury SAEs (not DILI)

Subj ID Sex/Age/BMI	PT/Verbatim term	AE Outcome/Action taken	Trial day of onset	Novo Nordisk case evaluation	Reviewer comment
Semaglutide					
(b) (6) M/77/39.9	Jaundice cholestatic/ Obstructive jaundice	Recovered/ Not applicable	546	Etiology is pancreatic cancer with metastasis	
(b) (6) M/57/28.7	Hepatitis acute/ Acute hepatitis	Recovered/ Not applicable	181	Etiology is heart failure with ischemic liver injury	As noted by adjudication committee: signs and symptoms of heart failure, elevated BNP, received IV furosemide, ejection fraction 17% [note: adjudicated as heart failure hospitalization]
(b) (6) M/64/38.6	Hyperbilirubinaemia/ Hyperbilirubinemia unconjugated type	Recovered/ Dose reduced	815	Etiology is heart failure with hemodialysis	This case was complicated, because hospitalized for hyperbilirubinemia 1 month prior to HF event (total bilirubin 2.3 mg/dL). Ultrasound showed small stones in the gallbladder with normal bile ducts; portal vein not dilated/no thrombus; spleen not enlarged. Diagnosis was "chronic liver disease". Readmitted 1 month later for HF and atrial

					fibrillation (note: do not see any discussion of hemodialysis), total bilirubin 3.6 mg/dL. Gi doctor thought evaluation for common bile duct obstruction could be done as an outpatient; bilirubin declined to 2.1 mg/dL after HF treatment. [note: adjudicated as heart failure hospitalization]
(b) (6) M/74/37.9	Ascites/ Moderate ascites	Not recovered/ Not applicable	414	Etiology is cholangiocarcinoma	
Placebo					
(b) (6) M/68/39.3	Hepatic failure/ Liver failure	Fatal/ Not applicable	1277	Etiology is worsening of end stage heart failure with decreasing ejection fraction.	[Note: adjudicated as 1) heart failure and 2) non-cardiovascular, non-renal death (*Patient with progressive liver failure, resulting in encephalopathy and death. Committee considered the possibility that heart failure was the proximate cause of the liver failure, but there was enough uncertainty to call the death liver failure as this was the clear immediate cause.*)]
(b) (6) M/57/40.0	Hepatic failure/ Liver failure	Fatal/ Not applicable	96	Etiology is sepsis due to choledocholithiasis and cholecystitis	
(b) (6) F/66/35.6	Ascites/ Ascites	Not recovered/ Dose not changed	1171	Etiology is volume depletion resulting in renal failure and	

				decompensated cirrhosis.	
(b) (6) M/59/28.7	Liver injury/ Acute liver injury	Fatal/ Not applicable	311	Etiology is heart failure with multiple organ dysfunction syndrome.	[Note: Adjudicated as cardiovascular death (heart failure)]
(b) (6) M/60/47.3	Jaundice cholestatic/ Mechanical jaundice	Recovered/ Dose not changed	190	Etiology is hepatocellular carcinoma	Common bile duct stent inserted for outflow of bile. Final diagnosis: hepatocellular cancer stage IV, grade 2 (patient had a history of hepatitis C). Died 5 months later. [Note: adjudicated as non-cardiovascular, non-renal death (malignancy)]
(b) (6) M/75/34.5	Alanine aminotransferase increased/ ALT>3 UNL	Fatal/ Drug withdrawn	112	Etiology is pancreatic cancer	Increased liver enzymes were found during protocol mandated blood sampling after the patient had been exposed to trial product for 3 months and 20 days. During further investigations to find the etiology for the reported events, CT-scan and ERCP showed suspected tumor in Papilla Vateri. The pathological anatomic diagnosis did not confirm malignant cells. Subsequently, the patient experienced renal failure and respiratory insufficiency with a fatal outcome. The cause of death is
	Blood bilirubin increased/ Bilirubin >2 UNL	Fatal/ Drug withdrawn	112		
	Hepatorenal syndrome/ Hepatorenal syndrome	Fatal/ Not applicable	142		

					reported as tumor in pancreas, which led to liver deficiency and renal deficiency and respiratory failure. [Note: adjudicated as non-cardiovascular, non-renal death (malignancy)]
(b) (6) M/64/38.5	Hepatitis acute/ Acute hepatitis	Recovered/ Not applicable	471	Etiology is COVID-19 and shock	
352104 F/65/43.3	Hepatic encephalopathy/ Hepatic encephalopathy	Recovered/ Dose not changed	961	Etiology is decompensated cirrhosis with ascites and hepatic encephalopathy due to gastrointestinal bleeding	
(b) (6) F/66/42.2	Hepatic encephalopathy/ Acute hepatic encephalopathy	Fatal/ not applicable	1030	Etiology is spontaneous decompensation of cirrhosis. [Note: adjudicated as non-cardiovascular, non-renal death (hepatobiliary causes)]	
(b) (6) M/69/31.8	Hepatitis acute/ Acute hepatitis	Recovered/ Not applicable	1258	Etiology is congestive heart failure in a subject with history of underlying heart disease complicated with congestive hepatitis.	

Source: Adapted from SELECT CTR, Table 12-4

In addition to the evaluation of hepatic disorder AEs, the hepatic biochemistry parameters alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (ALP) and γ-glutamyltransferase (GGT) were evaluated. Baseline ALT, AST, bilirubin, ALP and GGT levels were similar in the semaglutide and placebo groups. Mean ALP, ALT, bilirubin, and AST remained stable over time with no difference between treatments at week 104; mean GGT decreased with semaglutide at week 104 (ratio to baseline: 0.81 vs. 0.98 with placebo).

The proportion of subjects with hepatic parameters above the normal range and the proportion of subjects with outlier values (maximum post-baseline) were generally similar in the semaglutide and placebo groups, except for isolated bilirubin values > 3x ULN (Table 71); the statement: *increases in total bilirubin ≥ 3x ULN were observed in 0.3% (30/8585) of semaglutide-treated patients vs. 0.2% (14/8579) of placebo-treated patients* is recommended for Section 6.1 of the USPI. Hyperbilirubinemia has been reported with other GLP-1 RAs.[68]

Table 71. Hepatic Biochemistry Parameters, Maximum Post-Baseline

	Semaglutide	Placebo
ALT		
Baseline		
N	8557	8563
> ULN	428 (4.9)	418 (4.7)
> 5x ULN	2 (<0.1)	2 (<0.1)
Maximum post-baseline		
N	8585	8579
> ULN	1034 (11.7)	1127 (12.8)
> 5x ULN	8 (<0.1)	16 (0.2)
AST		
Baseline		
N	8614	8640
> ULN	731 (8.3)	752 (8.5)
> 5x ULN	6 (<0.1)	5 (<0.1)
Maximum post-baseline		
N	8588	8585
> ULN	1747 (19.8)	1994 (22.7)
> 5x ULN	27 (0.3)	33 (0.4)
Bilirubin		
Baseline		
N	8557	8563
> ULN	612 (7.0)	645 (7.3)
> 3x ULN	5 (<0.1)	1 (<0.1)
Maximum post-baseline		
N	8585	8579
> ULN	1414 (16.1)	1368 (15.5)
> 3x ULN	30 (0.3)	14 (0.2)
Alkaline phosphatase		
Baseline		
N	8726	8742
> ULN	140 (1.6)	124 (1.4)

[68] Saxenda USPI, Section 6.2

> 5x ULN	1 (<0.1)	0
Maximum post-baseline		
N	8593	8591
> ULN	268 (3.0)	317 (3.6)
> 5x ULN	1 (<0.1)	4 (<0.1)

Source: SELECT CTR, Table 12-7

Biochemical Hy's law (ALT or AST >3xULN and concurrent bilirubin >2xULN) were reported in 5 subjects in the semaglutide group and 5 subjects in the placebo group. One case in each group were also listed in Table 69 (semaglutide) and Table 70 (placebo). All cases had alternative etiologies.

Table 72. Cases with ALT or AST >3x ULN and Bilirubin >2x ULN

Subject ID Sex/Age/BMI	Trial day of measurement	On-treatment	Alternative etiology
Semaglutide			
(b) (6) M/61/29.3	726	Yes	Medical history of hemolytic anemia
(b) (6) M/50/28.3	144	Yes	Statin
(b) (6) M/58/29.1	153	Yes	Large alcohol consumption prior to the event
(b) (6) M/54/39.5	1	Yes	Hepatocellular carcinoma
(b) (6) M/49/29.0	723	No	Gilberts syndrome
Placebo			
(b) (6) M/62/29.9	129, 136	Yes	Choledocholithiasis
(b) (6) M/70/34.5	728, 735	Yes	Cholangiocarcinoma
(b) (6) F/48/32.4	161	Yes	Acute viral hepatitis A
(b) (6) M/75/34.5	112	Yes	Pancreatic cancer
(b) (6) M/61/28.4	1130	Yes	Hepatocellular carcinoma, history of hepatitis B and cirrhosis

Source: Adapted from SELECT CTR, Table 12-8

8.5.8. Renal disorders

GLP-1 RAs, including semaglutide, are labeled with a warning for acute kidney injury and worsening of chronic renal failure, as a result of dehydration/hypovolemia due to drug-related GI adverse effects (e.g., nausea, vomiting, diarrhea).

In the semaglutide weight management program there were small imbalances in renal adverse events, specifically acute kidney injury, associated with semaglutide. No events were associated with permanent treatment discontinuation.

In SELECT, all AEs of acute kidney failure were collected systematically, irrespective of seriousness. Acute kidney failure was evaluated based on a predefined MedDRA search (acute renal failure) supplemented with additional information collected on a specific event form and laboratory results. Acute renal failure as collected on the supplemental form was defined as an abrupt decrease in renal function, identified by 1 of the following:

- ≥0.3 mg/dL increase in serum creatinine within 48 hours
- ≥1.5 times increase in serum creatinine within 7 days
- urine volume <0.5 mL/kg/h for 6 hours

Table 73. Acute Renal Failure AEs

	Semaglutide N=8803	**Placebo N=8801**
Acute renal failure, sponsor custom search	**171 (1.9)**	**200 (2.3)**
Serious	88 (1.0)	113 (1.3)
Severe	45 (0.5)	50 (0.6)
Fatal	6 (0.1)	6 (0.1)
Drug interrupted	38 (0.4)	26 (0.3)
Drug permanently discontinued	3 (<0.1)	3 (<0.1)
Preferred terms:		
Acute kidney injury	124 (1.4)	146 (1.7)
Renal impairment	29 (0.3)	37 (0.4)
Renal failure	16 (0.2)	19 (0.2)
Prerenal failure	3 (<0.1)	1 (<0.1)
Anuria	3 (<0.1)	0
Oliguria	1 (<0.1)	2 (<0.1)
Nephropathy toxic	0	1 (<0.1)

Source: SELECT CTR, Table 14.3.1.20 and reviewer created from ADAE.xpt dataset

The proportions of subjects with additional data collection were semaglutide 1.5% and placebo 1.7%. The majority of events in both groups fulfilled criteria for acute kidney injury and had evidence of conditions contributing to event, including volume depletion.

Table 74. Acute Renal Failure, Additional Data Collection

	Sema 2.4 mg				Placebo			
	N	(%1)	E	(%2)	N	(%1)	E	(%2)
Number of subjects	8803				8801			
Events	132	(1.5)	149	(100)	150	(1.7)	170	(100)
Event present itself								
Acute kidney injury (AKI)	88	(1.0)	98	(65.8)	84	(1.0)	94	(55.3)
>= 0.3 mg/dL (>=26.5 µmol/l) increase in serum creatinine within 48 hours	63	(0.7)	71	(47.7)	64	(0.7)	71	(41.8)
Increase in serum creatinine to >= 1.5 times baseline within 7 days	33	(0.4)	33	(22.1)	32	(0.4)	32	(18.8)
Urine volume < 0.5mL/kg/h for 6 hours	5	(<.1)	5	(3.4)	8	(<.1)	8	(4.7)
An abrupt or rapid decline in renal filtration function not fulfilling criteria for AKI	20	(0.2)	21	(14.1)	27	(0.3)	28	(16.5)
Other	28	(0.3)	30	(20.1)	46	(0.5)	48	(28.2)
Nephrotoxic agents within last 3 months								
No	90	(1.0)	95	(63.8)	91	(1.0)	97	(57.1)
Yes	39	(0.4)	44	(29.5)	52	(0.6)	65	(38.2)
Aminoglycoside(s)					3	(<.1)	3	(1.8)
Nonsteroidal anti-inflammatory drug(s) (NSAIDs)	15	(0.2)	18	(12.1)	17	(0.2)	19	(11.2)
IV contrast	9	(0.1)	9	(6.0)	8	(<.1)	8	(4.7)
Initiation of a RAS blockade	6	(<.1)	6	(4.0)	14	(0.2)	19	(11.2)
Other drug(s) potentially affecting urinary protein excretion or renal function	18	(0.2)	20	(13.4)	27	(0.3)	36	(21.2)
Unknown	10	(0.1)	10	(6.7)	8	(<.1)	8	(4.7)
Evidence or suspicion of conditions explaining or contributing to event								
No	20	(0.2)	20	(13.4)	21	(0.2)	21	(12.4)
Yes	106	(1.2)	115	(77.2)	121	(1.4)	137	(80.6)
Volume depletion due to gastrointestinal symptoms	24	(0.3)	26	(17.4)	24	(0.3)	24	(14.1)
Volume depletion due to reason(s) other than gastrointestinal symptoms	15	(0.2)	16	(10.7)	25	(0.3)	30	(17.6)
Acute urinary tract infection	17	(0.2)	18	(12.1)	11	(0.1)	11	(6.5)
Chronic urinary tract infection	3	(<.1)	3	(2.0)	2	(<.1)	2	(1.2)
Post-renal obstructive disease	8	(<.1)	8	(5.4)	9	(0.1)	10	(5.9)
Hypertension	8	(<.1)	8	(5.4)	9	(0.1)	9	(5.3)
Recent decrease in renal perfusion due to volume depletion, decreased cardiac output or hypotension	24	(0.3)	25	(16.8)	22	(0.2)	24	(14.1)
Progression of chronic renal impairment/nephropathy	6	(<.1)	6	(4.0)	13	(0.1)	14	(8.2)
Primary glomerulonephritis					1	(<.1)	1	(0.6)
Systemic autoimmune disease					4	(<.1)	6	(3.5)

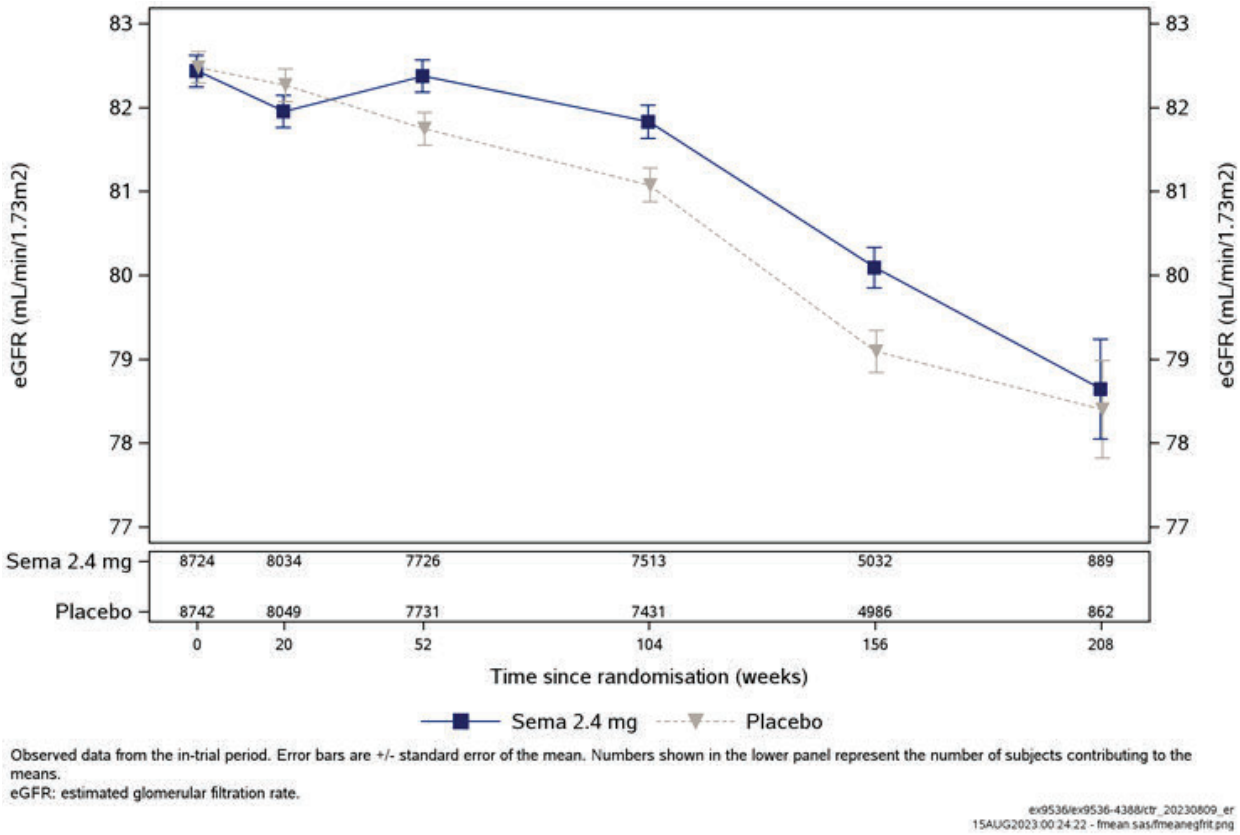
%1: percentage of subjects, %2: percentage of total number of events, E: number of events, N: number of subjects

Source: SELECT CTR, Table 14.3.1.112

Kidney Function Parameters

In both treatment groups, there was a decline from baseline in eGFR (Figure 34) over the course of the trial. At week 104 (the timepoint of data collection for selected efficacy and safety endpoints), the mean change from baseline was -0.84 mL/min/1.73 m^2 in the semaglutide group and -1.66 mL/min/1.73 m^2 in the placebo group.

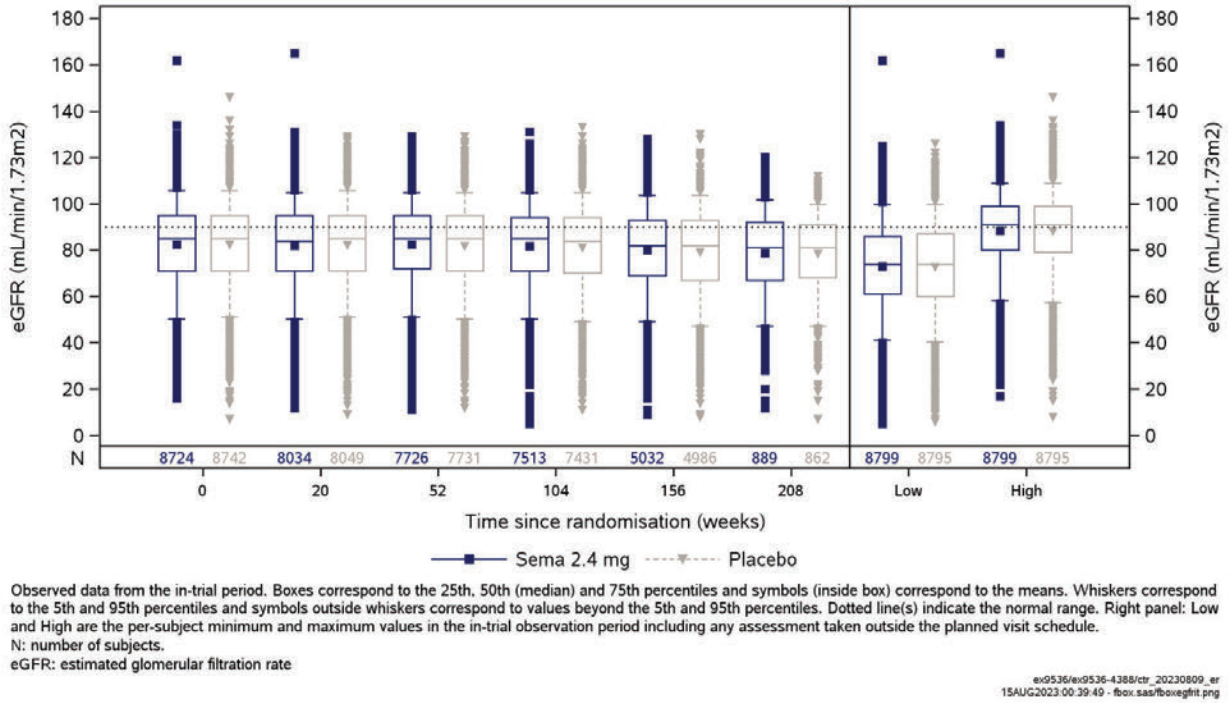
Figure 34. Mean eGFR by Week



Source: SELECT CTR, Figure 12-15

A box plot of eGFR by week did not indicate substantial differences in outliers between the groups (Figure 35).

Figure 35. eGFR by Week, Box Plot



Observed data from the in-trial period. Boxes correspond to the 25th, 50th (median) and 75th percentiles and symbols (inside box) correspond to the means. Whiskers correspond to the 5th and 95th percentiles and symbols outside whiskers correspond to values beyond the 5th and 95th percentiles. Dotted line(s) indicate the normal range. Right panel: Low and High are the per-subject minimum and maximum values in the in-trial observation period including any assessment taken outside the planned visit schedule.
N: number of subjects.
eGFR: estimated glomerular filtration rate

ex9536/ex9536-4388/ctr_20230809_er
15AUG2023:00:39:49 - fbox.sas/fboxegfrit.png

Source: SELECT CTR, Figure 14.3.5.112

The proportions of subjects with serum creatinine > ULN and > 3x ULN were generally similar, with small numerical imbalances noted at weeks 20 and 208 (> ULN) and week 104 (>3x ULN).

Table 75. Serum Creatinine, Categorical Summary by Week

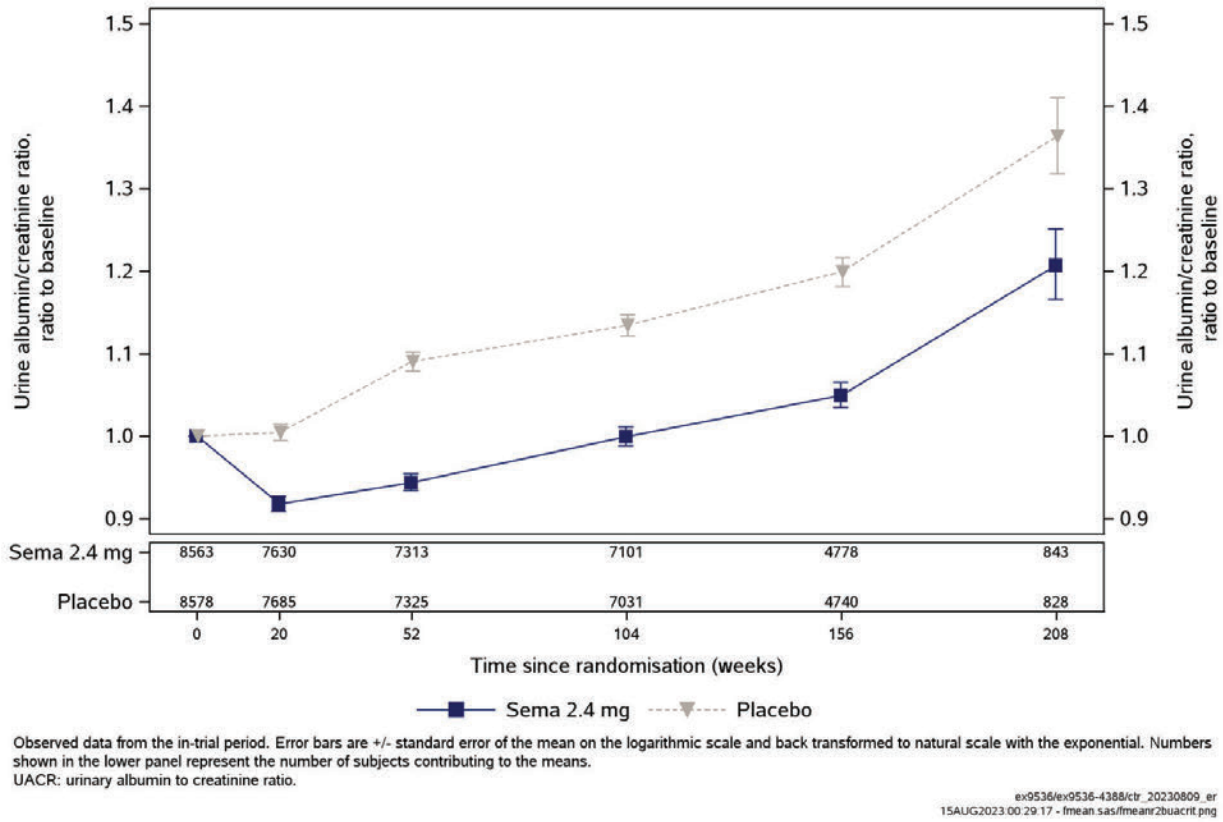
	Semaglutide	Placebo
Baseline, N	8726	8742
High (> ULN)	1247 (14.3)	1255 (14.4)
>3x ULN	2 (<0.1)	5 (0.1)
Week 20, N	8035	8050
High (> ULN)	1197 (14.9)	1169 (14.5)
>3x ULN	4 (<0.1)	5 (0.1)
Week 52, N	7728	7734
High (> ULN)	1018 (13.2)	1129 (14.6)
>3x ULN	9 (0.1)	6 (0.1)
Week 104, N	7515	7431
High (> ULN)	1018 (13.5)	1160 (15.6)
>3x ULN	8 (0.1)	4 (0.1)
Week 156, N	5032	4986
High (> ULN)	740 (14.7)	847 (17.0)
>3x ULN	3 (0.4)	5 (0.6)
Week 208, N	889	863

High (> ULN)	151 (17.0)	132 (15.3)
>3x ULN	2 (0.2)	2 (0.2)
End of Treatment, N	7254	7092
High (> ULN)	1175 (16.2)	1239 (17.5)
>3x ULN	8 (0.1)	9 (0.1)

Source: SELECT CTR, Table 14.3.5.51 and reviewer calculated

As described in the efficacy Section 6.1.2, the proportions of subjects on semaglutide with macroalbuminuria was lower than those on placebo, and this drove the lower proportion of subjects on semaglutide with first composite nephropathy event. Albuminuria was also an exploratory endpoint in the phase 3 trial in patients with obesity and type 2 diabetes, with some improvement indicated for semaglutide vs. placebo. Consistent with these observations, the geometric mean ratio to baseline in the urine albumin to creatinine ratio (UACR) was slightly lower over time in the semaglutide group vs. placebo: at week 104, UACR was 1.00 in the semaglutide group and 1.13 in the placebo group.

Figure 36. UACR Ratio-to-Baseline by Week



Source: SELECT CTR, Figure 14.3.5.118

8.5.9. Cardiovascular disorders, including tachyarrhythmias, hypotension, and syncope

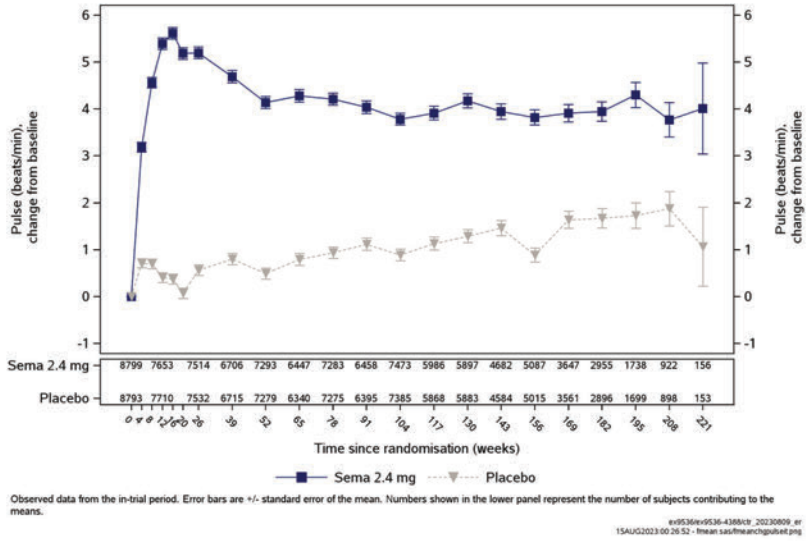
Atherosclerotic and heart failure events were efficacy endpoints and are discussed in Section 6. However, as described in the Wegovy USPI, semaglutide is associated with increases in heart rate (HR) of 1 to 4 bpm and decreases in systolic blood pressure (SBP) of 3 to 5 mmHg versus placebo, and therefore adverse events specifically related to these drug effects are of interest. Vital signs (HR and BP) were measured at each visit.

Overall, the proportion of subjects with CV SAEs, including fatal events, were lower in semaglutide-treated subjects as compared to placebo-treated subjects. In addition, the proportions of subjects with MACE were lower in the semaglutide group, regardless of categorical increases in HR or decreases in BP during the trial, as discussed below.

Heart Rate and Related Events

At baseline, mean observed HR was similar across the 2 treatment groups. The treatment difference for HR change from baseline at week 104 was +3.10 bpm (95% CI 2.80, 3.39). Figure 37 demonstrates that the largest effect was seen around week 20, with some attenuation and stabilization over time.

Figure 37. Heart Rate Change from Baseline Over Time



Source: SELECT CTR, Figure 14.2.144

More subjects in the semaglutide group as compared to those in the placebo group experienced a maximum HR increase from baseline ≥ 20 bpm: 35.3% versus 24.7%, respectively. In both groups, subjects with the lowest baseline HR experienced maximum HR increases ≥ 20

bpm more frequently [i.e., in patients with baseline HR < 60 bpm, maximum HR increases ≥ 20 bpm was observed in 67.3% of semaglutide-treated subjects and 45.8% of placebo-treated subjects].

The sponsor evaluated SAEs and first MACE by maximum increase in HR (Table 76 and Table 77). Overall, events were lower for semaglutide vs. placebo across all HR groups.

Table 76. SAEs by Maximum Increase in HR

	Sema 2.4 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects by maximum increase in heart rate								
< 10 bpm	2362	(100)			3307	(100)		
10 bpm <= to < 20 bpm	3275	(100)			3265	(100)		
20 bpm <=	3106	(100)			2174	(100)		
Not reported	60	(100)			55	(100)		
Observation time (year) by maximum increase in heart rate								
< 10 bpm	7683				10556			
10 bpm <= to < 20 bpm	10845				10943			
20 bpm	10616				7494			
Not reported	139				119			
Events by maximum increase in heart rate								
< 10 bpm	720	(30.48)	1612	20.98	1126	(34.05)	2550	24.16
10 bpm <= to < 20 bpm	1062	(32.43)	2335	21.53	1159	(35.50)	2622	23.96
20 bpm <=	1139	(36.67)	2644	24.91	905	(41.63)	2302	30.72
Not reported	20	(33.33)	31	22.31	14	(25.45)	33	27.81

Subgroups are defined by maximum heart rate increase (beats/min) from baseline during the trial.
%: percentage of subjects per subgroup, E: number of events, N: number of subjects, R: events per 100 years of observation

Source: SELECT CTR, Table 12-22

Table 77. First MACE by Maximum Increase in HR

	Sema 2.4 mg			Placebo		
	N	E	(%)	N	E	(%)
Number of subjects	8803			8801		
Maximum heart rate increase from baseline (bpm)	8743			8746		
< 10 bpm	2362	170	(7.2)	3307	268	(8.1)
10 <= to < 20 bpm	3275	196	(6.0)	3265	242	(7.4)
20 <= bpm	3106	196	(6.3)	2174	183	(8.4)

Subgroups are defined by maximum heart rate increase (beats/min) from baseline during Trial 4388. Data from the in-trial period.
E: number of subjects with a first MACE, (%): percentage of subjects with a first MACE,
N: number of subjects in group.
EAC: event adjudication committee, MACE: major adverse cardiovascular event.

Source: SELECT CTR, Table 12-23

Overall, SAEs of tachyarrhythmias[69] were not seen more frequently in the semaglutide group; however, there were more reports of PT: 'Supraventricular tachycardia' in the semaglutide group (Table 78). Increases in this SAE were seen in the semaglutide group regardless of maximum HR increases in the trial (Table 79).

Table 78. Tachyarrhythmia SAEs

	Semaglutide N=8803	Placebo N=8801
Tachyarrhythmia SAEs	**226 (2.6)**	**239 (2.7)**
Atrial fibrillation	127 (1.4)	152 (1.7)
Ventricular tachycardia	36 (0.4)	38 (0.4)
Atrial flutter	23 (0.3)	22 (0.3)
Supraventricular tachycardia	***18 (0.2)***	***7 (0.1)***
Ventricular extrasystoles	12 (0.1)	9 (0.1)
Ventricular fibrillation	7 (0.1)	11 (0.1)
Arrhythmia	7 (0.1)	7 (0.1)
Tachycardia	4 (<0.1)	5 (0.1)
Ventricular arrhythmia	4 (<0.1)	4 (<0.1)
Atrial tachycardia	2 (<0.1)	6 (0.1)
Tachyarrhythmia	2 (<0.1)	0
Arrhythmic storm	1 (<0.1)	1 (<0.1)
Tachycardia induced cardiomyopathy	1 (<0.1)	0
Ventricular tachyarrhythmia	1 (<0.1)	0
Arrhythmia supraventricular	0	1 (<0.1)
Supraventricular extrasystoles	0	1 (<0.1)

Source: Reviewer created from ADAE.xpt

Table 79. Supraventricular Tachycardia SAEs, by Maximum Increase in HR

	Semaglutide	Placebo
	n (%)	n (%)
Supraventricular tachycardia SAEs, overall	18/8803 (0.20)	7/8801 (0.08)
< 10 bpm	3/2362 (0.13)	2/3307 (0.06)
10 to < 20 bpm	8/3275 (0.24)	2/3265 (0.06)
≥ 20 bpm	7/3106 (0.23)	3/2174 (0.14)

Source: SELECT CTR, Table 14.3.1.116

Blood Pressure and Related Events

At baseline, mean observed SBP and diastolic blood pressure (DBP) were similar across the 2 treatment groups. As described as an efficacy endpoint in Section 6.1.2, at week 104 larger

[69] Reviewer selected relevant PTs from SMQs: Supraventricular tachyarrhythmias, Tachyarrhythmia terms, nonspecific, and Ventricular tachyarrhythmias, and FMQ Arrhythmias

reductions in SBP and DBP were observed in semaglutide-treated subjects versus placebo-treated subjects.

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 2 treatment groups, regardless of baseline blood pressure group (Table 80); acknowledging the limitations of a post-randomization analysis.

Subjects on semaglutide tended to experience categorical SBP decreases from baseline of either -20 or -10 mmHg regardless of baseline SBP (Table 80); however, a similar pattern was not observed with DBP.

Table 80. Post-Baseline Hypotension and Categorical Decreases in Blood Pressure by Baseline Blood Pressure

	Semaglutide N=8803	Placebo N=8801
Subjects with post-baseline hypotension*		
All subjects	1369/8744 (15.7)	1388/8747 (15.9)
Subjects with baseline SBP < 120 or DBP < 80 mmHg	1100/4407 (25.0)	1122/4507 (24.9)
Subjects with baseline SBP ≥ 120 and DBP ≥ 80 mmHg	212/3050 (7.0)	221/3118 (7.1)
Subjects with baseline SBP ≥ 130 and DBP ≥ 90 mmHg	57/1287 (4.4)	45/1122 (4.0)
Maximum SBP change < -20 mmHg from baseline		
All subjects	4051/8744 (46.3)	3221/8747 (36.8)
Subjects with baseline SBP < 110	21/642 (3.3)	21/599 (3.5)
Subjects with baseline SBP ≥ 110 to < 130	856/3327 (25.7)	506/3419 (14.8)
Subjects with baseline SBP ≥ 130	3174/4775 (66.5)	2694/4729 (57.0)
Maximum SBP change ≥ -20 to < -10 mmHg from baseline		
All subjects	2555/8744 (29.2)	2657/8747 (30.4)
Subjects with baseline SBP < 110	162/642 (25.2)	89/599 (14.9)
Subjects with baseline SBP ≥ 110 to < 130	1236/3327 (37.2)	1164/3419 (34.0)
Subjects with baseline SBP ≥ 130	1157/4775 (24.2)	1404/4729 (29.7)
* defined as non-missing minimum SBP < 90 mmHg or minimum DBP < 60 mmHg		

Source: SELECT CTR, Table 14.3.1.126

SAEs related to hypotension and decreased blood pressure were similar between groups (semaglutide n=38, 0.4%; placebo n=33, 0.4%), however non-serious AEs were more frequently reported in the semaglutide group. As shown in Table 81, serious and non-serious AEs related to hypotension and decreased BP were reported in 2.9% of semaglutide-treated subjects vs. 1.5% of placebo-treated subjects.

Table 81. Hypotension AEs (serious and non-serious)

	Semaglutide N=8803	Placebo N=8801
Hypotension FMQ	258 (2.9)	129 (1.5)
Hypotension	189 (2.1)	96 (1.1)
Orthostatic hypotension	63 (0.7)	31 (0.4)
Blood pressure decreased	12 (0.1)	4 (<0.1)
Procedural hypotension	0	1 (<0.1)

Source: Reviewer created from ADAE.xpt, using 'Hypotension' FMQ

SAEs of 'Syncope'[70] were reported in 65 (0.7%) semaglutide-treated subjects vs. 55 (0.6%) placebo-treated subjects. Syncope is labeled in the Wegovy USPI.

SAEs of PT 'Shock' were reported in 7 semaglutide-treated subjects vs. 2 placebo-treated subjects, Table 82. Most semaglutide events can be attributed to other causes, although it is unknown if 'malnutrition' in subject ID (b) (6) could have been a contributing factor.

Table 82. SAEs of Shock

Subj ID Sex/Age/BMI	Verbatim term	Severity	Outcome	Study day	Comments
Semagutide					
(b) (6) F/67/41.5	Hypotensive shock	Severe	Recovered/resolved	1513	2 days prior to the event, the subject had a total hip replacement; hypotension was thought secondary to hypovolemia and blood loss during surgery
(b) (6) F/74/49.5	Shock	Severe	Fatal	1411	The event of shock was co-existent with events of heart failure, renal failure, COVID-19, pleural effusions, malnutrition, and hypothermia. It appears that the event of heart failure preceded the other events, but the time course and the potential relationship of these events to drug (e.g., "malnutrition" after being on drug for almost 4 years) is unclear.
(b) (6) F/59/38.2	Shock	Severe	Fatal	683	The patient was diagnosed with non-small cell lung cancer 6 mos prior to the event; an

[70] Search='Syncope' FMQ narrow, although PT 'Syncope' was the only match in the SAE dataset

					ambulance was called due to experiencing worsening dyspnea at home, it was reported that the patient required CPR for 20-30 min due to pulseless electrical activity – resuscitated, but continued to be profoundly hypotensive. Diagnosed with acute respiratory distress syndrome, pneumonia in the setting of stage III lung cancer.
(b) (6) M/84/36.5	Shock	Severe	Fatal	556	2 mos prior to the event, patient had exacerbation of congestive heart failure. The subject was in rehab at the time of this event with increased confusion, then developed tachypnea, hypoxia, and became unconscious. Unclear if shock was septic vs. cardiogenic.
(b) (6) F/78/32.1	Mixed shock (septic and pulmonary)	Severe	Recovered/resolved	851	Patient was only treated with semaglutide for 4 months; was off drug for almost 2 years at the time of the event. Several weeks prior to the event, the patient was hospitalized with COVID-19, atrial fibrillation, and acute myocardial infarction. At the time of the event, she was reported to have presented with cardiogenic pulmonary edema and sepsis.
(b) (6) M/53/58.6	Undifferentiated shock	Severe	Recovered/resolved	1200	The patient was on semaglutide for 2 years, but had discontinued for approximately 1 year at the time of the event. He presented with hypotension, diarrhea, acute kidney injury, and positive blood cultures approximately 2 months after being treated for cellulitis.
(b) (6) F/72/35.3	Hypotensive shock	Moderate	Recovered/resolved	737	This event of hypotensive shock was reported in association with acute on chronic heart failure, paroxysmal atrial

					fibrillation, lactic acidosis, and overdiuresis.
Placebo					
(b) (6) M/70/34.5	Vascular shock	Severe	Fatal	765	This event occurred in the setting of pancreatic carcinoma vs, cholangiocarcinoma, with renal failure, obstipation, and cholangitis.
(b) (6) M/69/50.1	Undifferentiated shock	Severe	Fatal	1443	This subject died due to multiple events: undifferentiated shock, COVID-19, and widely metastatic disease, unknown primary.

Source: Reviewer created from narratives and ADAE.xpt

8.5.10. **Bone safety**

Intentional diet-induced weight loss in individuals with obesity has been associated with bone loss in interventional studies,[71] and in observational studies, small body size[72] and weight loss[73] are associated with fracture in older women. It is unknown how a longer duration of weight loss with semaglutide would impact bone in a population of older adults with cardiovascular disease. In an exploratory analysis of SELECT, a numerical imbalance of hip fracture SAEs (11 semaglutide vs. 3 placebo) was noted, and the applicant was asked to query the SELECT database for fracture SAEs overall, and by sex, baseline age group, and post-baseline maximum weight loss (<20% or ≥20%).

As shown in Table 83, overall fracture events were similar between groups (in fact, numerically greater with placebo). In addition to a hip fracture imbalance, other fracture sites that were reported as SAEs more frequently in the semaglutide group include femur fracture (13 vs. 11), femoral neck fracture (11 vs. 9), pelvic fracture (8 vs. 5), and spinal compression fracture (8 vs. 5). Notably, the differences of the number of events were very small for any single bone site; however, it is of interest that these numerical imbalances appear only in female patients (see Table 84) and patients 75 years and older (see Table 85). Imbalances were not seen based on the post-randomization weight loss groups (<20% or ≥20%).

[71] Pritchard JE, Nowson CA, Wark JD. Bone loss accompanying diet-induced or exercise-induced weight loss: a randomised controlled study. Int J Obes Relat Metab Disord. 1996 Jun;20(6):513-20.
[72] Ensrud
[73] Langlois

Table 83. Fracture FMQ SAEs

System organ class High level group term Preferred term	Sema 2.4 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	8803				8801			
Observation time (year)	29283				29112			
Events	108	(1.23)	127	0.43	139	(1.58)	158	0.54
Injury, poisoning and procedural complications	107	(1.22)	126	0.43	136	(1.55)	155	0.53
Bone and joint injuries	107	(1.22)	126	0.43	135	(1.53)	154	0.53
Rib fracture	15	(0.17)	16	0.05	21	(0.24)	21	0.07
Femur fracture	13	(0.15)	13	0.04	11	(0.12)	11	0.04
Femoral neck fracture	11	(0.12)	11	0.04	9	(0.10)	9	0.03
Hip fracture	11	(0.12)	11	0.04	3	(0.03)	3	0.01
Pelvic fracture	8	(0.09)	8	0.03	5	(0.06)	5	0.02
Spinal compression fracture	8	(0.09)	9	0.03	5	(0.06)	5	0.02
Humerus fracture	7	(0.08)	8	0.03	11	(0.12)	11	0.04
Ankle fracture	5	(0.06)	5	0.02	12	(0.14)	12	0.04
Foot fracture	5	(0.06)	5	0.02	6	(0.07)	6	0.02
Thoracic vertebral fracture	5	(0.06)	5	0.02	4	(0.05)	4	0.01
Radius fracture	4	(0.05)	4	0.01	6	(0.07)	6	0.02
Lumbar vertebral fracture	3	(0.03)	3	0.01	5	(0.06)	5	0.02
Wrist fracture	3	(0.03)	3	0.01	4	(0.05)	5	0.02
Patella fracture	3	(0.03)	3	0.01	3	(0.03)	3	0.01
Fibula fracture	3	(0.03)	3	0.01	2	(0.02)	2	<.01
Lower limb fracture	3	(0.03)	3	0.01	1	(0.01)	1	<.01
Tibia fracture	2	(0.02)	2	<.01	9	(0.10)	9	0.03
Facial bones fracture	2	(0.02)	2	<.01	4	(0.05)	4	0.01
Hand fracture	2	(0.02)	2	<.01	2	(0.02)	2	<.01
Jaw fracture	2	(0.02)	2	<.01	2	(0.02)	2	<.01
Ulna fracture	2	(0.02)	2	<.01	2	(0.02)	2	<.01
Spinal fracture	2	(0.02)	2	<.01	1	(0.01)	1	<.01
Upper limb fracture	1	(0.01)	1	<.01	4	(0.05)	4	0.01
Sternal fracture	1	(0.01)	1	<.01	2	(0.02)	2	<.01
Skull fracture	1	(0.01)	1	<.01	1	(0.01)	1	<.01
Skull fractured base	1	(0.01)	1	<.01	0			
Clavicle fracture	0				8	(0.09)	8	0.03
Forearm fracture	0				3	(0.03)	3	0.01
Cervical vertebral fracture	0				2	(0.02)	2	<.01
Scapula fracture	0				2	(0.02)	2	<.01
Acetabulum fracture	0				1	(0.01)	1	<.01
Lisfranc fracture	0				1	(0.01)	1	<.01
Maisonneuve fracture	0				1	(0.01)	1	<.01
Procedural related injuries and complications NEC	0				1	(0.01)	1	<.01
Periprosthetic fracture	0				1	(0.01)	1	<.01
Musculoskeletal and connective tissue disorders	1	(0.01)	1	<.01	3	(0.03)	3	0.01
Fractures	1	(0.01)	1	<.01	3	(0.03)	3	0.01
Pathological fracture	1	(0.01)	1	<.01	2	(0.02)	2	<.01
Osteoporotic fracture	0				1	(0.01)	1	<.01

Source: Response to FDA Information Request dated December 15, 2023, Table 48

Table 84. Fracture FMQ SAEs by Sex, Selected Events

System organ class High level group term Preferred term	Sema 2.4 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects								
Female	2448				2424			
Male	6355				6377			
Observation time (year)								
Female	8095				7995			
Male	21188				21117			
Events								
Female	43	(1.76)	49	0.61	39	(1.61)	42	0.53
Male	65	(1.02)	78	0.37	100	(1.57)	116	0.55
Injury, poisoning and procedural complications								
Female	43	(1.76)	49	0.61	39	(1.61)	42	0.53
Male	64	(1.01)	77	0.36	97	(1.52)	113	0.54
Bone and joint injuries								
Female	43	(1.76)	49	0.61	39	(1.61)	42	0.53
Male	64	(1.01)	77	0.36	96	(1.51)	112	0.53
Rib fracture								
Female	1	(0.04)	1	0.01	1	(0.04)	1	0.01
Male	14	(0.22)	15	0.07	20	(0.31)	20	0.09
Femur fracture								
Female	6	(0.25)	6	0.07	1	(0.04)	1	0.01
Male	7	(0.11)	7	0.03	10	(0.16)	10	0.05
Femoral neck fracture								
Female	6	(0.25)	6	0.07	3	(0.12)	3	0.04
Male	5	(0.08)	5	0.02	6	(0.09)	6	0.03
Hip fracture								
Female	7	(0.29)	7	0.09	0			
Male	4	(0.06)	4	0.02	3	(0.05)	3	0.01
Pelvic fracture								
Female	7	(0.29)	7	0.09	1	(0.04)	1	0.01
Male	1	(0.02)	1	<.01	4	(0.06)	4	0.02
Spinal compression fracture								
Female	2	(0.08)	2	0.02	0			
Male	6	(0.09)	7	0.03	5	(0.08)	5	0.02
Humerus fracture								
Female	3	(0.12)	3	0.04	5	(0.21)	5	0.06
Male	4	(0.06)	5	0.02	6	(0.09)	6	0.03
Ankle fracture								
Female	3	(0.12)	3	0.04	6	(0.25)	6	0.08
Male	2	(0.03)	2	<.01	6	(0.09)	6	0.03
Foot fracture								
Female	1	(0.04)	1	0.01	3	(0.12)	3	0.04
Male	4	(0.06)	4	0.02	3	(0.05)	3	0.01
Thoracic vertebral fracture								
Female	1	(0.04)	1	0.01	2	(0.08)	2	0.03
Male	4	(0.06)	4	0.02	2	(0.03)	2	<.01
Radius fracture								
Female	1	(0.04)	1	0.01	3	(0.12)	3	0.04
Male	3	(0.05)	3	0.01	3	(0.05)	3	0.01
Lumbar vertebral fracture								
Female	0				1	(0.04)	1	0.01
Male	3	(0.05)	3	0.01	4	(0.06)	4	0.02
Wrist fracture								
Female	1	(0.04)	1	0.01	3	(0.12)	4	0.05
Male	2	(0.03)	2	<.01	1	(0.02)	1	<.01
Patella fracture								
Female	0				1	(0.04)	1	0.01
Male	3	(0.05)	3	0.01	2	(0.03)	2	<.01
Fibula fracture								
Female	1	(0.04)	1	0.01	0			
Male	2	(0.03)	2	<.01	2	(0.03)	2	<.01
Lower limb fracture								
Female	2	(0.08)	2	0.02	1	(0.04)	1	0.01
Male	1	(0.02)	1	<.01	0			
Tibia fracture								
Female	2	(0.08)	2	0.02	2	(0.08)	2	0.03
Male	0				7	(0.11)	7	0.03
Facial bones fracture								
Female	0				0			

Source: Response to FDA Information Request dated December 15, 2023, Table 49

Table 85. Fracture FMQ by Age Group, Selected Events

System organ class High level group term Preferred term	Sema 2.4 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects								
< 55	2057				2094			
55 <= to < 65	3387				3338			
65 <= to < 75	2656				2706			
75 <=	703				663			
Observation time (year)								
< 55	6818				6885			
55 <= to < 65	11267				11068			
65 <= to < 75	8866				8991			
75 <=	2333				2168			
Events								
< 55	13	(0.63)	17	0.25	28	(1.34)	32	0.46
55 <= to < 65	23	(0.68)	25	0.22	41	(1.23)	44	0.40
65 <= to < 75	43	(1.62)	49	0.55	49	(1.81)	56	0.62
75 <=	29	(4.13)	36	1.54	21	(3.17)	26	1.20
Injury, poisoning and procedural complications								
< 55	13	(0.63)	17	0.25	28	(1.34)	32	0.46
55 <= to < 65	23	(0.68)	25	0.22	41	(1.23)	44	0.40
65 <= to < 75	42	(1.58)	48	0.54	48	(1.77)	55	0.61
75 <=	29	(4.13)	36	1.54	19	(2.87)	24	1.11
Bone and joint injuries								
< 55	13	(0.63)	17	0.25	28	(1.34)	32	0.46
55 <= to < 65	23	(0.68)	25	0.22	40	(1.20)	43	0.39
65 <= to < 75	42	(1.58)	48	0.54	48	(1.77)	55	0.61
75 <=	29	(4.13)	36	1.54	19	(2.87)	24	1.11
Rib fracture								
< 55	4	(0.19)	4	0.06	3	(0.14)	3	0.04
55 <= to < 65	2	(0.06)	2	0.02	4	(0.12)	4	0.04
65 <= to < 75	5	(0.19)	5	0.06	11	(0.41)	11	0.12
75 <=	4	(0.57)	5	0.21	3	(0.45)	3	0.14
Femur fracture								
< 55	1	(0.05)	1	0.01	2	(0.10)	2	0.03
55 <= to < 65	2	(0.06)	2	0.02	3	(0.09)	3	0.03
65 <= to < 75	6	(0.23)	6	0.07	4	(0.15)	4	0.04
75 <=	4	(0.57)	4	0.17	2	(0.30)	2	0.09
Femoral neck fracture								
< 55	0				0			
55 <= to < 65	4	(0.12)	4	0.04	4	(0.12)	4	0.04
65 <= to < 75	3	(0.11)	3	0.03	4	(0.15)	4	0.04
75 <=	4	(0.57)	4	0.17	1	(0.15)	1	0.05
Hip fracture								
< 55	0				0			
55 <= to < 65	1	(0.03)	1	<.01	1	(0.03)	1	<.01
65 <= to < 75	1	(0.04)	1	0.01	1	(0.04)	1	0.01
75 <=	9	(1.28)	9	0.39	1	(0.15)	1	0.05
Pelvic fracture								
< 55	1	(0.05)	1	0.01	2	(0.10)	2	0.03
55 <= to < 65	0				0			
65 <= to < 75	4	(0.15)	4	0.05	3	(0.11)	3	0.03
75 <=	3	(0.43)	3	0.13	0			
Spinal compression fracture								
< 55	1	(0.05)	1	0.01	1	(0.05)	1	0.01
55 <= to < 65	3	(0.09)	3	0.03	1	(0.03)	1	<.01
65 <= to < 75	4	(0.15)	5	0.06	1	(0.04)	1	0.01
75 <=	0				2	(0.30)	2	0.09
Humerus fracture								
< 55	2	(0.10)	3	0.04	0			
55 <= to < 65	1	(0.03)	1	<.01	1	(0.03)	1	<.01
65 <= to < 75	3	(0.11)	3	0.03	4	(0.15)	4	0.04
75 <=	1	(0.14)	1	0.04	6	(0.90)	6	0.28
Ankle fracture								
< 55	1	(0.05)	1	0.01	4	(0.19)	4	0.06
55 <= to < 65	1	(0.03)	1	<.01	4	(0.12)	4	0.04
65 <= to < 75	3	(0.11)	3	0.03	4	(0.15)	4	0.04
75 <=	0				0			

Source: Response to FDA Information Request dated December 15, 2023, Table 50

Reviewer comment: Given the biological plausibility, I would recommend labeling that more fractures of the hip (including femur and femoral neck), and pelvis were reported in women (24/2448 [1.0%] vs. 5/2424 [0.2%]) and in those over the age of 75 years (17/703 [2.4%] vs. 4/663 [0.6%]) in patients randomized to semaglutide vs. placebo.

8.5.11. Hematologic Disorders

A small imbalance was noted in the overall review of serious adverse events for the 'Blood and lymphatic system disorders' SOC (Section 8.4.2).

Table 86. Blood and Lymphatic System Disorders SAEs

	Semaglutide N=8803	Placebo N=8801
Blood and lymphatic system disorders SOC	83 (0.9)	62 (0.7)
HLGT		
Anemias nonhemolytic and marrow depression	59 (0.7)	48 (0.5)
Anemia	36	30
White blood cell disorders	11 (0.1)	4 (<0.1)
Spleen, lymphatic and reticuloendothelial system disorders	8 (0.1)	4 (<0.1)
Platelet disorders	6 (0.1)	2 (<0.1)
Coagulopathies and bleeding diatheses (excl thrombocytopenic)	1 (<0.1)	4 (<0.1)
Red blood cell disorders	1 (<0.1)	1 (<0.1)
Hematological disorders NEC	1 (<0.1)	0
Hemolyses and related conditions	1 (<0.1)	0

Source: Reviewer created from ADAE.xpt dataset

A number of these events were cytopenias, identified by the applicant in their review of "rare" events. An imbalance was noted – 16 semaglutide subjects (with 17 events, 1 subject had 2 separate events of neutropenic fever) vs. 3 placebo subjects. Although these were notable imbalances, review of the narratives shows alternative etiologies in most cases.

Table 87. Cytopenias SAEs

	Semaglutide N=8803	Placebo N=8801
Cytopenia events	16 (0.2)	3 (<0.1)
Thrombocytopenia	6 (0.1)	1 (<0.1)
Febrile neutropenia	4 (<0.1)	0
Pancytopenia	2 (<0.1)	1 (<0.1)
Leukopenia	2 (<0.1)	0
Neutropenia	2 (<0.1)	0
Agranulocytosis	0	1 (<0.1)

Source: Reviewer created from ADAE.xpt dataset

Thrombocytopenia – semaglutide-treated subjects

- Subject ID (b) (6): attributed to amiodarone, furosemide
- Subject ID (b) (6): history of metastatic urothelial carcinoma, attributed to chemotherapy, subarachnoid hemorrhage

- Subject ID (b) (6): on treatment for ~1 year at time of event; unclear from narrative if immune mediated vs. artifact (platelet clumping); patient recovered off drug
- Subject ID (b) (6): attributed to chemotherapy for small cell lung cancer, complicated by COVID-19 hypoxemic respiratory failure (later died)
- Subject ID (b) (6): attributed to Bactrim (recent sinus infection), recovered on drug
- Subject ID (b) (6): on drug for 28 months, attributed to sepsis (likely urinary source)

Febrile neutropenia/neutropenia – semaglutide-treated subjects

- Subject ID (b) (6): history of metastatic testicular cancer, attributed to chemotherapy
- Subject ID (b) (6): history of diffuse large B-cell lymphoma, attributed to malignancy and chemotherapy (later died)
- Subject ID (b) (6): history of lung adenocarcinoma, attributed to chemotherapy (later died)
- Subject ID (b) (6): history of gastric cancer, attributed to chemotherapy
- Subject ID (b) (6): history of esophageal carcinoma, attributed to chemotherapy
- Subject ID (b) (6): history of myeloid leukemia, attributed to chemotherapy

8.5.12. Excessive Weight Loss

Historically, excessive weight loss has not been a significant safety concern in obesity trials given the relatively young and healthy populations studied in development programs and limited weight loss efficacy. SELECT is a novel trial, given that participants are older and at high risk for cardiovascular and other serious events, it is of longer duration than most weight loss trials, and semaglutide has demonstrated potent weight loss effects.

The effects of excessive weight loss in SELECT were evaluated in several ways: SAEs based on MedDRA search and an evaluation of SAEs in patients who lost at least 20% body weight vs. patients who loss less than that amount; acknowledging the limitations of a post-randomization analysis.

The following is an exploratory search of the SAE dataset in SELECT for the following MedDRA preferred terms potentially related to excess weight loss or malnutrition: “Abnormal loss of weight,” “Weight decreased,” “Underweight,” “Cachexia,” “Malnutrition,” and “Malnutrition-inflammation-atherosclerosis syndrome.” Four subjects were identified; 3 semaglutide and 1 placebo (Table 88).

Table 88. Weight Loss/Malnutrition SAEs, Exploratory Search

Subj ID Sex/Age BMI	PT	Severity	Outcome	Action	Study day	Duration (days)	Body weight change[a] (Percent body weight change)[b]
Semaglutide							
(b) (6) F/74/49.5	Malnutrition	Severe	Fatal	Not applicable	1411	9	-29.1 kg (-22.8%)
(b) (6) F/67/34.4	Weight decreased	Severe	Recovered/ resolved	Drug interrupted	1237	172	-37.9 kg (-42.0%)
(b) (6) M/66/28.3	Malnutrition	Moderate	Recovered/ resolved	Not applicable	369	13	-14.4 kg (-18.5%)
Placebo							
(b) (6) M/77/27.4	Weight decreased	Severe	Not recovered/ not resolved	Drug interrupted	996	NA	-8.4 kg (-10.6%)
a Weight change from ADVS dataset used from visit closest to reported SAE b % calculated as (change / baseline body weight) * 100 (ADVS dataset)							

Source: Reviewer created from ADAE.xpt and ADVS.xpt

Brief narratives for the semaglutide subjects are as follows:

- Subject (b) (6): This subject had a baseline BMI of 49.5 kg/m^2 ((b) (6)), and a history of atrial fibrillation, sleep apnea, hypertension, and ischemic stroke. Her last recorded study values were (b) (6), including a final study BMI of 38.2 kg/m^2. About a week before hospitalization, the subject had heart failure symptoms. She was admitted to the hospital on (b) (6), which was the reported onset date for events of acute renal failure, pleural effusions, hypothermia, shock, and malnutrition. She was admitted to intensive care for sepsis, pericarditis, heart failure, and acute renal failure. On (b) (6) she was diagnosed with COVID-19. Renal function rapidly declined. The patient died in the hospital on (b) (6). No autopsy was done. Reasons of death according to the death certificate were: severe right heart failure, hypothermic shock, severe acute renal failure, COVID-19, and denutrition (malnutrition).

Reviewer comment: It is unknown to what extent the weight loss (-23% from baseline) the patient experienced over the 3 years and 10 months she was in the trial contributed to this acute illness. It should be noted that despite -23% weight loss, her BMI at time of death would still be categorized as obesity (approximately 38 kg/m^2 [Class 2 obesity], decreased from baseline BMI 50). Laboratory values to support the diagnosis of malnutrition are difficult to interpret in the setting of acute renal and heart failure. It may be that chronic underlying illness contributed to malnutrition (i.e., bi-directional cause and effect).

- Subject (b) (6): This subject had a history of dyslipidemia, sleep apnea, hypertension, head trauma, renal artery angioplasty, ischemic stroke, and heart disease. The narrative also references a parathyroid adenoma. During the course of the trial, the subject lost considerable weight – in the first 4 months, she lost about 17 kg and the drug was temporarily stopped (maximum dose reached was 1 mg weekly). Over the next year and 5 months, she regained about 8 kg and the drug was restarted at a dose of 0.24 mg weekly (not escalated). Over the next year and 7 months she gradually lost almost 30 kg, at which point she stopped treatment (total weight loss ~42% of baseline). At that time, she had symptoms of sudden asthenia, weakness of lower limbs, and aphasia. The symptoms persisted for 15-20 minutes and then stopped after bilious vomiting. She was admitted and diagnosed with "suspected transient ischemic attack on hypertensive peak." It was reported that there was no etiology for the bilious vomiting. One month after discharge (off drug), she regained about 3 kg.

Reviewer comment: It is plausible that semaglutide treatment led to excessive weight loss in this apparently highly sensitive subject. It is unknown how the substantial weight loss relates to the presumed TIA. It seems that there were other medical conditions ongoing, such as a new parathyroid adenoma and bilious vomiting of unclear etiology.

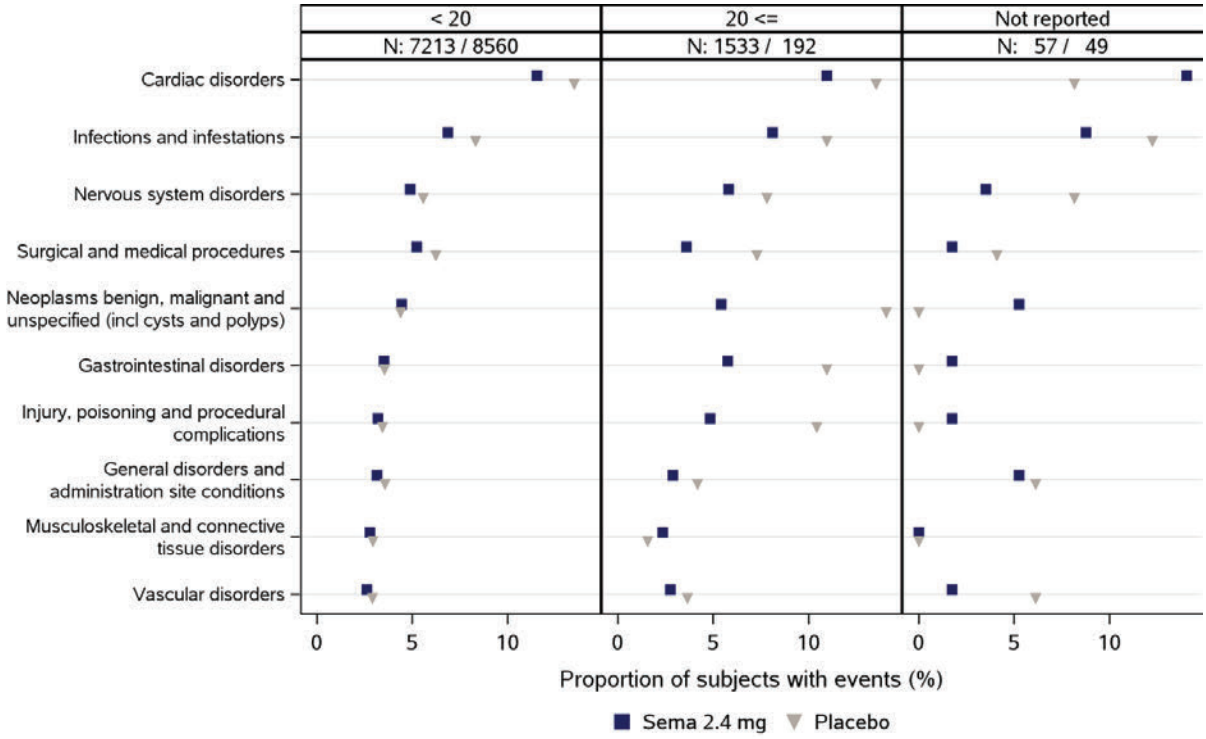
- Subject (b) (6): This subject had a history of primary adrenocortical insufficiency, hypertensive heart disease without heart failure, mixed hyperlipidemia, peptic ulcer, pituitary microadenoma, non-alcoholic fatty liver, coronary heart disease, and hypertension. He was treated with the study drug for 3 months ((b) (6)) and then permanently discontinued. The SAE of hypotension was reported about 9 months after stopping drug ((b) (6)). Despite drug discontinuation, the patient had complained about intermittent post-prandial nausea and vomiting for at least 6 months prior to the event. The patient also complained of burning sensation over epigastrium and abdominal distension. He also reported unintentional body weight loss (80 kg to 40 kg in 1 year) and general weakness [It is noted that actual weight reported was 78 kg at baseline ((b) (6) (b) (6)), 74.6 kg around the time of drug discontinuation ((b) (6)), and 63.6 kg at the last recorded study visit ((b) (6)).] On presentation ((b) (6)), by report he had hyponatremia, hypokalemia, hypophosphatemia, hypomagnesemia, hypocalcemia, and hypoalbuminemia. He was given the tentative diagnosis of malnutrition and ileus (GI dysfunction due to atherosclerosis of abdominal aorta and branches).

Reviewer comment: This case appears more likely due to mesenteric ischemia with GI symptoms, hypotension, and malnutrition, than semaglutide.

Figure 38 below summarizes SAEs by SOC for those subjects who lost more or less than 20% of body weight during the trial. Within the semaglutide group, SAEs were reported by similar

proportions of subjects and with similar rates for subjects with maximum weight loss ≥ 20% vs. < 20%. In subjects treated with placebo, SAEs were reported more frequently and at a higher rate by subjects with maximum weight loss ≥ 20% vs. < 20%, suggesting that the cause of excess weight loss in the placebo subjects may be associated with (confounded by) disease (notably, neoplastic disease).

Figure 38. SAEs by Maximum Weight Loss



Source: SELECT CTR, Figure 14.3.1.131

The proportions of participants with maximum weight loss ≥ 40% was 0.4% for semaglutide (N=35; all were female) vs. <0.1% for placebo (N=4; 2 male and 2 female).

A total of 20 subjects developed a BMI ≤ 18.5 kg/m^2 during the trial; 16 semaglutide-treated participants (15 female and 1 male) vs. 4 placebo-treated participants (1 female and 3 male). All except for 3 semaglutide-treated participants had a baseline BMI < 30 kg/m^2. Of the semaglutide-treated subjects: 2 discontinued due to weight loss, 1 had the dose of semaglutide reduced, 2 had cancer, and 1 died during the trial of unknown causes but had a history of HIV, heart failure, stroke, and atrial fibrillation, and been recently hospitalized for acute decompensated heart failure and stroke.

Reviewer comment: As perhaps expected from administration of a drug that promotes weight loss in a population of older adults with chronic illness (history of atherosclerotic cardiovascular disease), a small number of "malnutrition" SAEs or cases of underweight BMI with semaglutide were reported. However, cases are few in number, and lacked sufficient detail on how or why malnutrition was diagnosed, limiting conclusions that can be drawn. It may be that certain patients with frailty may be more sensitive to and at risk from substantial weight loss with semaglutide, but there is insufficient information to support labeling at this time.

8.5.13. **Allergy**

No imbalance was observed in SAEs in the SOC 'Immune system disorders' (semaglutide n=11, placebo n=14), including the HLGT 'Allergic conditions' (semaglutide n=7, placebo n=12).

The sponsor conducted a pre-defined MedDRA search of PTs related to allergic reactions. Similarly, no increase overall was noted (semaglutide n=26 vs. placebo n=24). Although there were numerically more events of 'Shock,' these were reviewed and determined unlikely to be allergy-related (see Table 82 in Section 8.5.9).

Table 89. Allergy SAEs, Sponsor Custom Search

	Semaglutide N=8803	Placebo N=8801
Allergy, sponsor custom search	**26 (0.3)**	**24 (0.3)**
Shock	7 (0.1)	2 (<0.1)
Drug hypersensitivity	4 (<0.1)	3 (<0.1)
Circulatory collapse	3 (<0.1)	3 (<0.1)
Anaphylactic reaction	2 (<0.1)	4 (<0.1)
Angioedema	2 (<0.1)	2 (<0.1)
Urticaria	2 (<0.1)	2 (<0.1)
Dermatitis	2 (<0.1)	0
Bronchospasm	1 (<0.1)	0
Contrast media allergy	1 (<0.1)	0
Drug reaction with eosinophilia and systemic symptoms	1 (<0.1)	0
Laryngospasm	1 (<0.1)	0
Edema mouth	1 (<0.1)	0
Dermatitis contact	0	2 (<0.1)
Anaphylactic shock	0	1 (<0.1)
Anti-neutrophil cytoplasmic antibody positive vasculitis	0	1 (<0.1)
Eczema nummular	0	1 (<0.1)
Hypersensitivity	0	1 (<0.1)

Hypersensitivity pneumonitis	0	1 (<0.1)
Rash	0	1 (<0.1)

Source: Reviewer created from ADAE.xpt

Events of drug hypersensitivity and angioedema were rare and similar between treatment groups.

The 2 cases of anaphylaxis in semaglutide-treated subjects were considered unlikely due to drug: 1 event was due to a wasp bite, and 1 event occurred in a subject who had past history of drug allergy (lisinopril), was treated with Losartan and Tylenol prior to the event (Tylenol thought to be source of drug allergy), and developed hypotension. Of note, he had been on study drug for 1 year and continued on semaglutide after the event.

One SAE of drug rash with eosinophilia and systemic symptoms (DRESS) in a semaglutide-treated subject was thought to be due to the COVID vaccine; the subject continued on treatment with semaglutide.

More subjects on semaglutide discontinued drug due to allergic conditions (semaglutide n=9 vs. placebo=4); PTs were 'Hypersensitivity' (semaglutide n=8, placebo n=2) and 'Drug hypersensitivity' (semaglutide n=1, placebo n=2).

8.5.14. **COVID-19**

The COVID-19 pandemic occurred during the conduct of the SELECT trial (October 2018 to June 2023). AEs of COVID-19 were collected systematically, regardless of seriousness. COVID-19 AEs were evaluated based on a predefined MedDRA search among all AEs. Based on the predefined MedDRA search, COVID-19 AEs were reported for a similar proportion of subjects with a similar event rate in the semaglutide group and the placebo group (24.0% vs. 24.4% and 8.86 vs. 9.08 events per 100 PYO, respectively). Approximately 10% of COVID-19 events in both groups were SAEs, with somewhat better outcomes in the semaglutide group (fewer fatal outcomes, severe presentations, and hospitalizations; Table 90).

Table 90. COVID-19 SAEs

	Sema 2.4 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	8803				8801			
Observation time (year)	26223				26056			
Events	232	(2.64)	249	0.95	277	(3.15)	293	1.12
Severity								
Severe	111	(1.26)	118	0.45	123	(1.40)	130	0.50
Moderate	89	(1.01)	95	0.36	127	(1.44)	133	0.51
Mild	35	(0.40)	36	0.14	30	(0.34)	30	0.12
Hospitalization/prolongation of hospitalization								
Yes	222	(2.52)	238	0.91	255	(2.90)	270	1.04
No	10	(0.11)	11	0.04	22	(0.25)	23	0.09
Relationship to trial product								
Probable	0				0			
Possible	1	(0.01)	1	<.01	0			
Unlikely	231	(2.62)	248	0.95	277	(3.15)	293	1.12
Outcome								
Fatal	43	(0.49)	46	0.18	65	(0.74)	66	0.25
Not recovered	1	(0.01)	1	<.01	3	(0.03)	3	0.01
Recovered with sequelae	3	(0.03)	4	0.02	6	(0.07)	6	0.02
Recovering	0				0			
Recovered	184	(2.09)	197	0.75	205	(2.33)	218	0.84
Unknown	1	(0.01)	1	<.01	0			
Action taken								
Drug withdrawn	5	(0.06)	5	0.02	12	(0.14)	12	0.05
Drug interrupted	63	(0.72)	66	0.25	81	(0.92)	82	0.31
Dose reduced	0				0			
Dose increased	0				0			
Dose not changed	110	(1.25)	117	0.45	142	(1.61)	150	0.58
Unknown	0				2	(0.02)	2	<.01
Not applicable	58	(0.66)	61	0.23	45	(0.51)	47	0.18

Source: SELECT CTR, Table 14.3.1.50

(b) (5)

(b) (5)

This reviewer conducted an exploratory review of the SELECT AE database (serious and non-serious; acknowledging that non-serious AEs were not systematically collected) for MedDRA PTs: allodynia, burning sensation, dysesthesia, hyperesthesia, hyperpathia, pain of skin, sensitive skin, skin burning sensation, skin discomfort, and skin sensitization.

A total of 88 events were reported in 76 subjects, 68 (0.8%) on semaglutide and 8 (0.1%) on placebo. None of the events was serious. Details are as follows:

Table 91. Dysesthesia AEs

	Semaglutide N=8803	**Placebo N=8801**
Dysesthesia AEs	68 (0.8)	8 (0.1)
Severity:		
Severe	1	0
Moderate	19	1
Mild	49	7
PTs:		
Hyperesthesia	18	0
Sensitive skin	16	1
Pain of skin	10	1
Skin burning sensation	8	1
Dysesthesia	7	0
Burning sensation	4	5
Allodynia	4	0
Skin discomfort	1	0

Source: Reviewer created from ADAE.xpt dataset

Reviewer comment: (b) (5) (b) (5) *it may be appropriate to descriptively label dysesthesia in Section 6.1 of the Wegovy label until more information is available.*

(b) (5)

8.5.16. Other Adverse Events

A number of other explorations of the safety data were undertaken, evaluating serious and non-serious AEs. Although non-serious AEs were generally not systematically collected in SELECT, some AEs that were biologically plausibly linked to semaglutide are of interest and are summarized below.

Urolithiases

A small imbalance in urolithiases was noted in SELECT, with SAEs of the HLGT 'Urolithiases' reported in 55 (0.6%) semaglutide subjects and 39 (0.4%) placebo subjects. An exploratory review of all AEs (serious and non-serious) showed that the overall imbalance persisted, including an imbalance for the PT 'nephrolithiasis'.

Table 92. 'Urolithiases' HLGT AEs

	Semaglutide N=8803	**Placebo N=8801**
Urolithiasis SAEs	55 (0.6%)	39 (0.4%)
Nephrolithiasis	25	24
Ureterolithiasis	20	10
Calculus urinary	7	4
Calculus bladder	3	1
Calculus urethral	1	0
Urolithiasis AEs – serious and non-serious	102 (1.2%)	69 (0.8%)
Nephrolithiasis	65	46
Ureterolithiasis	23	15
Calculus urinary	11	7
Calculus bladder	5	3
Calculus urethral	1	0
Nephrocalcinosis	1	0

Source: Reviewer created from ADAE.xpt dataset

Reviewer comment: It is recommended that urolithiases be described in Section 6.1 of labeling.

Hiccups

None of the AE reports of PT 'hiccups' in SELECT were serious. Nevertheless, there were 21 AEs reported in 20 subjects on semaglutide versus 1 AE in 1 subject on placebo. All events were mild or moderate. In the semaglutide subjects, the median event duration was 115 days, ranging from 2 days to 1182 days. The duration was 10 days in the placebo-treated subject. In the semaglutide group, 5 subjects interrupted drug and 1 subject withdrew drug due to the AE. Four additional subjects – in whom dose was not changed – were reported to have not

recovered from the event. In the rest of the events, the AE resolved. The dose was not changed in the placebo-treated subject, and the event resolved. Hiccups can be related to gastric distension and/or effects on the vagus nerve,[76] and therefore it appears plausibly due to semaglutide.

Hair Loss

Hair loss is mentioned in Section 6.1 in Wegovy, as it was observed in the phase 3 chronic weight management program. Hair loss with the GLP-1 RAs has received media attention due to post-marketing reports,[77] (b) (5) (b) (5).

None of the AE reports of PT 'alopecia' in SELECT was serious. A total of 41 semaglutide-treated subjects and 19 placebo-treated subjects reported AEs of 'alopecia'. All events were considered mild or moderate. In the majority of the events in either arm, dose did not change. A total of 6 semaglutide- and 3 placebo-treated subjects interrupted drug, 2 semaglutide- and 1 placebo-treated subjects reduced the dose, and 2 semaglutide-treated subjects withdrew drug due to the alopecia.

Hair loss has been reported in relation to bariatric surgery and has been postulated to be associated with weight loss or nutritional deficiencies.[78] It is plausible that treatment with semaglutide could be related to hair loss.

Falls

A slightly greater number of subjects reported SAEs of falls (PT: 'Fall') on semaglutide (51, 0.6%) vs. placebo (35, 0.4%). However, a similar number of subjects reported AEs of falls – serious and non-serious: 132 semaglutide vs. 130 placebo. The increase in SAE reporting could plausibly be associated with increased fragility (see discussion of hypotension/syncope in Section 8.5.9, bone safety in Section 8.5.10, and excessive weight loss in Section 8.5.12).

[76] www.uptodate.com, accessed February 3, 2024.
[77] https://www.nbcnews.com/health/health-news/weight-loss-drugs-and-hair-loss-rcna79798, accessed February 3, 2024.
[78] Cohen-Kurzrock RA, Cohen PR. Bariatric Surgery-Induced Telogen Effluvium (Bar SITE): Case Report and a Review of Hair Loss Following Weight Loss Surgery. Cureus. 2021;13(4).

8.6. Safety Analyses by Demographic Subgroups

The following factors (demographic and disease related) were prespecified for the safety evaluation:

- Sex
- Baseline age
- Race
- Ethnic origin
- Baseline BMI
- Baseline kidney function
- Baseline HbA1c
- Baseline chronic heart failure status
- Baseline CV disease status
- Region

Table 93. SAEs Overall by Subgroups

	Semaglutide	Placebo
Sex		
Female	765/2448 (31.3)	787/2424 (32.5)
Male	2176/6355 (34.2)	2417/6377 (37.9)
Age		
< 55 yrs	554/2057 (26.9)	607/2094 (29.0)
55-<65 yrs	1022/3387 (30.2)	1115/3338 (33.4)
65-<75 yrs	1028/2656 (38.7)	1144/2706 (42.3)
≥75 yrs	337/703 (48.0)	338/663 (51.0)
Race		
Asian	202/720 (28.1)	228/727 (31.4)
Black or African American	130/348 (37.4)	113/323 (35.0)
White	2489/7387 (33.7)	2745/7404 (37.1)
Other	85/253 (33.6)	84/273 (30.8)
Not reported	35/95 (36.8)	34/74 (46.0)
Ethnic origin		
Hispanic/Latino	230/914 (25.2)	268/908 (29.3)
Not Hispanic/Latino	2676/7794 (34.3)	2902/7817 (37.1)
Not reported	35/95 (36.8)	36/76 (47.4)
BMI		
<30	820/2555 (32.1)	897/2469 (36.3)
30-<35	1241/3693 (33.6)	1346/3781 (35.6)
35-<40	577/1687 (34.2)	607/1659 (36.6)
40-<45	201/579 (34.7)	226/595 (38.0)
≥45	102/289 (35.3)	128/297 (43.1)
Kidney function		
<60	420/963 (43.6)	464/935 (49.6)

≥60	2496/7761 (32.2)	2727/7807 (34.9)
Not reported	25/79 (31.7)	13/59 (22.0)
Glycemic status		
<5.7	940/2925 (32.1)	1051/2980 (35.3)
≥5.7	2001/5877 (34.1)	2151/5819 (37.0)
Not reported	0/1 (0)	2/2 (100)
Chronic heart failure status		
Yes	792/2155 (36.8)	893/2131 (41.9)
No	2149/6647 (32.3)	2310/6667 (34.7)
Not reported	0/1 (0)	1/3 (33.3)
CV disease		
Only MI	1945/5962 (32.6)	2100/5944 (35.3)
Only stroke	485/1578 (30.7)	518/1556 (33.3)
Only PAD	112/376 (29.8)	136/401 (33.9)
≥2 CVD	335/718 (46.7)	379/719 (52.7)
Not reported	64/169 (37.9)	71/181 (39.2)
Region		
Europe	1155/3326 (34.7)	1217/3366 (36.2)
North America	797/2200 (36.2)	835/2201 (40.7)
U.S.	703/1821 (38.6)	788/1831 (43.0)
Asia	387/1100 (35.2)	420/1101 (38.2)
Other (Africa, South America, and 'Other')	602/2177 (27.7)	672/2133 (31.5)

Source: SELECT CTR, Tables 12-25 to 12-34; Applicability of non-US data for US population, Table 2-6

Because the Black/African American and Other race subgroups were the only notable exception to semaglutide being associated with unfavorable SAE proportions, additional information is provided for safety by race. (See section 8.5.10 for a separate discussion of bone safety in women and patients 75 years and older.) As discussed in Section 6.1.2 and shown in Figure 11, there was no interaction by race for the primary MACE endpoint. Formal interaction testing was not conducted for safety. An overview of SAEs by race is presented in Table 94. It is noted that subjects in the Black/African American race in both treatment arms reported more events with fatal outcome, more severe events, and more discontinuation of drug than other subgroups.

Table 94. SAEs by Race

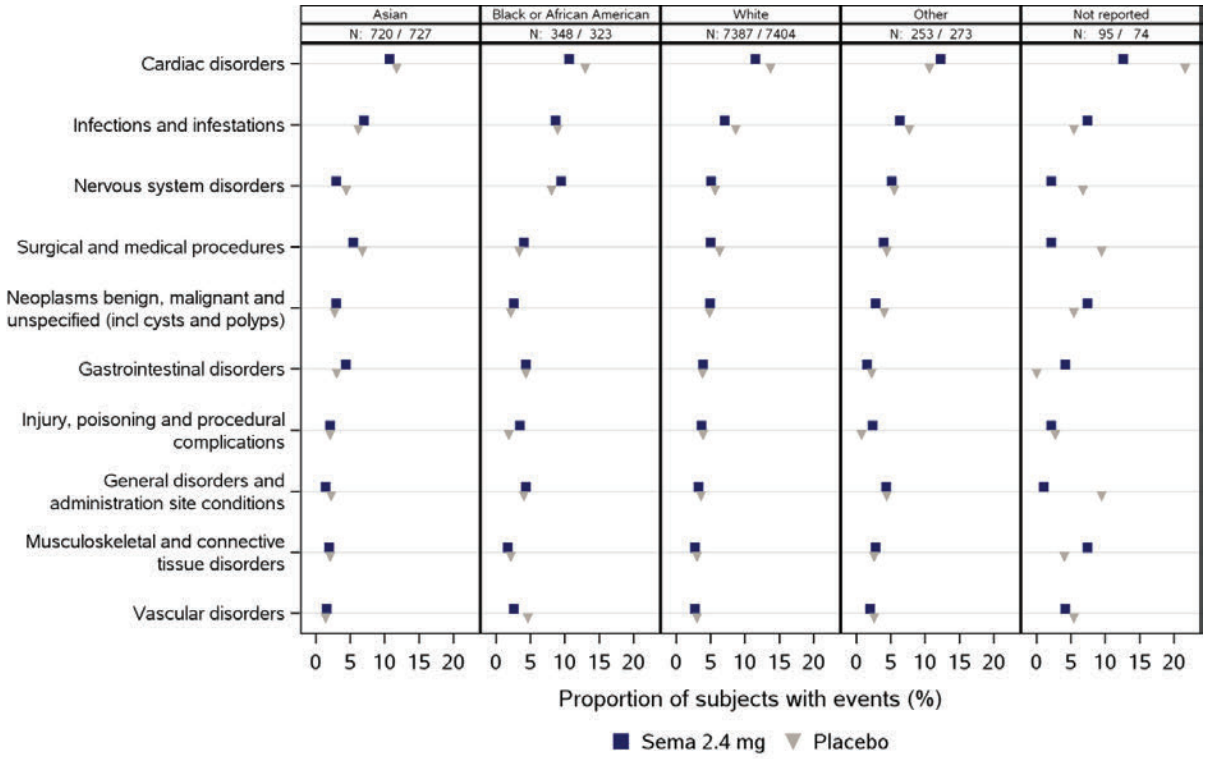
	Semaglutide	**Placebo**
N		
Asian	720	727
Black or African American	348	323
White	7387	7404
Other	253	273
Not reported	95	74
Fatal outcome		
Asian	21 (2.9)	36 (5.0)
Black or African American	26 (7.5)	26 (8.1)

White	305 (4.1)	375 (5.1)
Other	16 (6.3)	19 (7.0)
Not reported	3 (3.2)	4 (5.4)
Severe		
Asian	102 (14.2)	101 (13.9)
Black or African American	86 (24.7)	73 (22.6)
White	1285 (17.4)	1453 (19.6)
Other	51 (20.2)	55 (20.2)
Not reported	16 (16.8)	15 (20.3)
Drug withdrawn		
Asian	8 (1.1)	3 (0.4)
Black or African American	11 (3.2)	5 (1.6)
White	153 (2.1)	162 (2.2)
Other	3 (1.2)	5 (1.8)
Not reported	2 (2.1)	1 (1.4)

Source: SELECT CTR, Table 14.3.1.141

Figure 39 and Figure 40 present most frequent SAEs by race by SOC and PT, respectively. No significant pattern emerged for any 1 type of event, despite some individual differences.

Figure 39. Most Frequent SAEs by SOC by Race

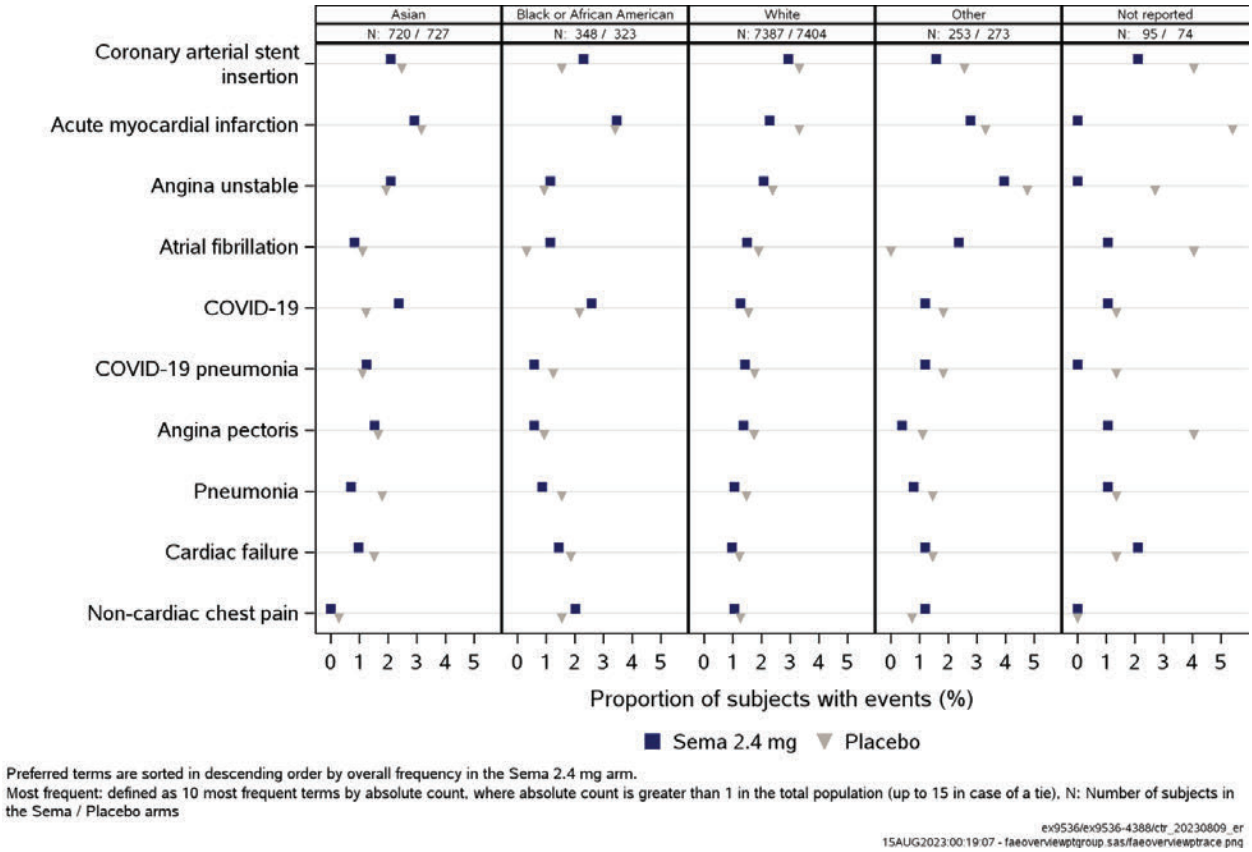


System organ classes are sorted in descending order by overall frequency in the Sema 2.4 mg arm.
Most frequent: defined as 10 most frequent terms by absolute count, where absolute count is greater than 1 in the total population (up to 15 in case of a tie). N: Number of subjects in the Sema / Placebo arms

ex9536/ex9536-4388/ctr_20230809_er
15AUG2023:00:19:08 - faeoverviewsocgroup.sas/faeoverviewsocrace.png

Source: SELECT CTR, Figure 14.3.1.143

Figure 40. Most Frequent SAEs by PT by Race



Source: SELECT CTR, Figure 14.3.1.144

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Malignant neoplasms are discussed in Section 8.5.3.

8.8.2. Human Reproduction and Pregnancy

No pregnancies were reported in the trial.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable; children were not enrolled in this trial.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

AEs of potential abuse and misuse were collected systematically, irrespective of seriousness, and evaluated based on a predefined MedDRA search. AEs of potential abuse or misuse were reported for a similar proportion of subjects and with a similar event rate in the semaglutide group and the placebo group (0.11% vs 0.14% and 0.04 vs 0.06 events per 100 PYO). SAEs specifically related to suicidality are discussed in Section 8.5.2.

SELECT was not designed to evaluate withdrawal or rebound, but these events are addressed in the clinical review of the phase 3 trials supporting original approval of Wegovy.

8.9. Safety in the Postmarket Setting

(b) (5)

Dysgeusia is already labeled in the Wegovy USPI.

(b) (5)

(b) (5) Hair loss is already labeled in the Wegovy USPI, and is discussed in Section 8.5.16.

8.9.2. Expectations on Safety in the Postmarket Setting

Semaglutide has been widely used since approval, particularly in recent years, both for indicated conditions as well as likely substantial off-label use. Safety concerns, while generally well-understood for semaglutide and other drugs of this class, have become more recognized given the wide postmarketing use. (b) (5)
.

Semaglutide is approved for cardiovascular weight reduction in a population of patients with type 2 diabetes, so notwithstanding the somewhat higher dosage for the obesity population, I would anticipate that similar safety concerns in this vulnerable population could arise for this approval: e.g., volume depletion, tachyarrhythmias, gastroparesis. However, it is important to note that on balance, patients on semaglutide had fewer MACE vs. placebo, as well as numerically (although not statistically confirmed) fewer deaths and serious adverse events.

8.9.3. Additional Safety Issues From Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

In general, the safety profile of semaglutide as evaluated in SELECT is consistent with known safety issues with semaglutide in other clinical settings and trials. The most commonly reported SAEs in this trial were cardiovascular-related, although most CV events were less frequently reported in semaglutide-treated subjects, consistent with the primary efficacy endpoint result.

Gastrointestinal (GI) disorders are the most frequently reported AEs in most clinical trials of semaglutide; in SELECT, GI SAEs were the most frequently reported with an unfavorable imbalance.

The proportion of subjects with AEs leading to discontinuation of trial product was higher with semaglutide than with placebo (16.6% vs 8.2%), primarily due to GI disorders (e.g., nausea, vomiting, diarrhea, constipation, dyspepsia, and gastroesophageal reflux disease), nervous system disorders (e.g., dizziness and headache), and metabolism and general disorders (e.g., decreased appetite, weight decreased, asthenia, and fatigue).

Adverse events of interest with semaglutide/the GLP-1 RA class, or with unfavorable imbalances observed in SELECT included the following:

- Gastrointestinal disorders: The most common SAEs in the Gastrointestinal disorders system organ class were due to abdominal wall hernias, with 65 semaglutide-treated subjects (0.7%) vs. 46 placebo-treated subjects (0.5%). Most events were inguinal hernias. Small imbalances were noted for diarrhea, gastrointestinal hemorrhage, vomiting, and colitis. Gastroparesis was reported rarely, but events are consistent with postmarketing reports. In particular, one subject had significant aspiration pneumonia that was likely due to semaglutide-induced gastroparesis after being on drug for 1 month. (b) (5) (b) (5).

- Psychiatric disorders, including suicidal ideation and behaviors: A small numerical imbalance in psychiatric SAEs was noted (semaglutide 0.7% vs. placebo 0.6%), of unclear significance as most of the events were distributed among terms. Overall, depression SAEs and suicide and self-injury SAEs were similar between treatment groups. More subjects on semaglutide discontinued treatment due to psychiatric disorders, including mood disorders, sleep disorders, and anxiety disorders. The EAC classified 5 deaths in semaglutide-treated subjects and 3 deaths in placebo-treated subjects as completed suicides, although it should be noted that the EAC did not include any psychiatrists. (b) (5) Suicidal ideation and behaviors are currently labeled in the Warnings and Precautions of the Wegovy USPI.

- Malignant neoplasms: Overall, malignant neoplasms were reported for a similar proportion of subjects at a similar event rate. Small numerical imbalances were observed for melanoma *in situ*, various carcinoid/neuroendocrine tumors, and certain cancers of the urinary system. Other small imbalances were seen in other tissue types in both treatment groups, suggestive of a chance finding. There were no reports of medullary thyroid cancer (MTC) in any semaglutide-treated subject, although some subjects had significant calcitonin elevations at the end of the trial without an available diagnosis.

- Gallbladder disorders: The proportion of subjects with and the event rate of AEs of gallbladder-related disorders was higher in the semaglutide group than in the placebo group. A slightly higher proportion of subjects on semaglutide vs. placebo had a gallbladder event that led to cholecystectomy, use of antibiotics, or endoscopic retrograde cholangiopancreatography (ERCP). Gallbladder disorders are labeled in the Warnings and Precautions section of the Wegovy USPI.

- Pancreatitis: A similar proportion of subjects in each treatment arm had events of pancreatitis as reported by investigators, and the rate was low. Serious and severe events and events leading to withdrawal were similar between groups. Pancreatitis was also an adjudicated event, and semaglutide-treated subjects did not appear to demonstrate an excess of pancreatitis confirmed by the EAC in SELECT. Similar proportions of subjects in both treatment groups had moderately severe and severe pancreatitis as judged by the Atlanta criteria. Acute pancreatitis is labeled in the Warnings and Precautions section of the Wegovy USPI.

- Hypoglycemia: SAEs of hypoglycemia were infrequent (3 events in 3 semaglutide-treated subjects vs. 1 event in 1 placebo-treated subject), and generally occurred in settings where there were contributing factors (other medication, bariatric surgery, fasting). Semaglutide may predispose patients to hypoglycemia in these settings.

- Hepatic disorders: In the SELECT trial, SAEs of hepatic disorders, including events considered drug-induced liver injury (DILI), were uncommon and similar between groups. The proportion of subjects with hepatic parameters above the normal range and the proportion of subjects with outlier values (maximum post-baseline) were generally similar in the semaglutide and placebo groups, except for isolated bilirubin values > 3x ULN. Hyperbilirubinemia has been reported with other GLP-1 RAs. Biochemical Hy's law (ALT or AST >3xULN and concurrent bilirubin >2xULN) were reported in 5 subjects in the semaglutide group and 5 subjects in the placebo group. All cases had alternative etiologies.

- Renal disorders: There was not an excess of acute kidney injury (AKI) with semaglutide in SELECT. In both treatment groups, there was a decline from baseline in estimated glomerular filtration rate (eGFR) over the course of the trial. Semaglutide was not associated with significant outliers in renal parameters. AKI is labeled in the Warnings and Precautions section of the Wegovy USPI.

- Heart rate increases: The treatment difference for HR change from baseline at week 104 was +3.10 bpm. More subjects in the semaglutide group as compared to those in the placebo group experienced a maximum HR increase from baseline ≥ 20 bpm. Overall, SAEs of tachyarrhythmias were not seen more frequently in the semaglutide group; however, there were more reports of PT: 'Supraventricular tachycardia' in the semaglutide group. Heart rate increase is labeled in the Warnings and Precautions section of the Wegovy USPI.

- Hypotension and syncope: SAEs related to hypotension and decreased blood pressure were similar between groups, however, non-serious AEs were more frequently reported. A small numeric imbalance in syncope was noted. Hypotension and syncope are labeled in Section 6.1 of the Wegovy USPI.

- Fractures: Overall fracture events were similar between groups (in fact, numerically greater with placebo). However, certain important fracture sites were reported as SAEs more frequently in the semaglutide group vs. the placebo group, including hip fracture, femur/femoral neck fracture, pelvic fracture, and spinal compression fracture. Although the differences of the number of events were very small for any single bone site, it is of interest that these numerical imbalances appear only in female patients and patients 75 years and older, suggesting they may be more at risk for bone loss with semaglutide-induced weight loss.

- Cytopenias: A small imbalance was noted in the overall review of serious adverse events for the 'Blood and lymphatic system disorders' SOC. Specifically, an imbalance in various types of cytopenias was noted: 16 semaglutide subjects vs. 3 placebo subjects. Review of the

narratives identified alternative etiologies in most cases, suggesting the imbalances may be due to chance.

- Hypersensitivity: Overall, events of drug hypersensitivity and angioedema were rare and similar between treatment groups. The 2 cases of anaphylaxis in semaglutide-treated subjects were considered unlikely due to semaglutide. More subjects on semaglutide discontinued drug due to allergic conditions ('hypersensitivity' and 'drug hypersensitivity'), but the numbers were small.

- Others: A small number of malnutrition SAEs or cases of underweight body mass index (BMI) with semaglutide were reported, limiting conclusions that can be drawn. It may be that certain patients with frailty may be more sensitive to and at risk from substantial weight loss with semaglutide. Small imbalances were noted for serious and non-serious urolithiases; adding this to Section 6.1 of the Wegovy USPI is recommended given biological plausibility. A small imbalance was observed for SAEs of falls, but not for non-serious AEs. Non-serious AEs were reported for dysesthesia, hiccups, and hair loss. Dysesthesia and hiccups are recommended for Section 6.1. (b) (5) (b) (5) Hair loss is currently in Section 6.1.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

This section includes a summary of major changes to proposed labeling (listed below); refer to the label upon approval for final modifications.

The Division of Medication Error Prevention and Analysis 1 (DMEPA) in the Office of Surveillance and Epidemiology (OSE) reviewed[79] the Wegovy PI and Medication Guide (MG) and did not identify areas of vulnerability that may lead to medication errors. DMEPA had no recommendations.

[79] DARRTS Reference ID: 5290657

The Office of Prescription Drug Promotion (OPDP) had concerns in their review[80] that the use of "long term" in the weight reduction indication may overstate efficacy. However, DDLO ultimately determined that the weight results of the SELECT trial support the concept that with Wegovy treatment, weight is reduced and then maintained long term.

- Added a new indication: Wegovy is indicated in combination with a reduced calorie diet and increased physical activity to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight.
- New language for the chronic weight management indication is proposed: Wegovy is indicated in combination with a reduced calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term in:
    - Adults and pediatric patients aged 12 years and older with obesity
    - Adults with overweight in the presence of at least one weight-related comorbid condition.
- Limitations of Use regarding combination with other products for weight reduction and a history of pancreatitis were removed.
- Removed reference to BMI criteria and calculation from Sections 1 and 2.
- The statement that the 0.25 mg, 0.5 mg, and 1 mg once-weekly dosages are initiation and escalation dosages and are not approved as maintenance dosages for chronic weight management has been removed from Section 2.
- Revised Section 5.2 (Acute Pancreatitis) from "Wegovy has not been studied in patients with a history of pancreatitis" to state that there is limited experience from clinical trials with Wegovy in patient with pancreatitis.
- Revised Section 5.4 (Hypoglycemia) to state that Wegovy in T1D has not been evaluated.
- A description of SELECT was added to Section 6.1.
- Dysesthesia, Fractures, Urolithiasis, severe Gastrointestinal Adverse Reactions, and Hiccups were added to Section 6.1.
- A description of hypoglycemia in patients with a history of bariatric surgery and without T2D was described in Section 6.1.
- A description of bilirubin increases was added to Laboratory Abnormalities (Liver Enzymes) in Section 6.1.
- A description of SELECT, including an increase in fractures, was added to Section 8.5 (Geriatric Use).
- A statement that the mechanism of CV risk reduction has not been established was added to Section 12.1 (Mechanism of Action).
- A statement that Wegovy delays gastric emptying was added to Section 12.2 (Pharmacodynamics). Body composition information was also included in Section 12.2.

[80] DARRTS Reference ID: 5337115

- Clinical data from SELECT was added to Section 14.1, including the primary composite endpoint, key secondary endpoints of CV death and all-cause death, and fatal and non-fatal MI, and fatal and non-fatal stroke.
  - (b) (4)
  - Standard anthropometry and cardiometabolic parameters were included.
  - (b) (4) (b) (4)
- The Medication Guide was updated to reflect changes to the PI. The collaborative review[81] from the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) outlines recommended changes such as description of the indications [What is WEGOVY?], removal of limitations of use, updates to information about hypoglycemia to reflect potential use in patients with T1D, and the revision of common side effects. There was some discussion about the use of the phrase "excess weight"; ultimately DDLO determined that only "overweight" would be retained to be consistent with the PI language.

[81] DARRTS Reference ID: 5337975

11. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

12. Postmarketing Requirements and Commitments

No new PMRs or PMCs are recommended. The SELECT trial fulfills PMR 4081-6.

13. Appendices

13.1. References

ACS Definition References:

1. Karen A. Hicks, Kenneth W. Mahaffey, Roxana Mehran, Steven E. Nissen, Stephen D. Wiviott, Billy Dunn, Scott D. Solomon, John R. Marler, John R. Teerlink, Andrew Farb, David A. Morrow, Shari L. Targum, Cathy A. Sila, Mary T. Thanh Hai, Michael R. Jaff, Hylton V. Joffe, Donald E. Cutlip, Akshay S. Desai, Eldrin F. Lewis, C. Michael Gibson, Martin J. Landray, A. Michael Lincoff, Christopher J. White, Steven S. Brooks, Kenneth Rosenfield, Michael J. Domanski, Alexandra J. Lansky, John J.V. McMurray, James E. Tcheng, Steven R. Steinhubl, Paul Burton, Laura Mauri, Christopher M. O'Connor, Marc A. Pfeffer, H.M. James Hung, Norman L. Stockbridge, Bernard R. Chaitman, Robert J. Temple and on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI). 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation. 2018;137:961-972.

2. Thygesen, Kristian, Alpert JS, Jaffe AS, Chaitman BR, and Bax JJ, Morrow DA, White HD on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction, Fourth Universal Definition of Myocardial Infarction. Circulation, 2018, 138:618-651

Acute Pancreatitis Definition References:

1. Classification of acute pancreatitis – 2012: revision of the Atlanta classification and definitions by international consensus. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS; Acute Pancreatitis Classification Working Group. Gut. 2013 Jan;62(1):102-11

Coronary Artery Revascularisation Definition References:

1. Karen A. Hicks, Kenneth W. Mahaffey, Roxana Mehran, Steven E. Nissen, Stephen D. Wiviott, Billy Dunn, Scott D. Solomon, John R. Marler, John R. Teerlink, Andrew Farb, David A. Morrow, Shari L. Targum, Cathy A. Sila, Mary T. Thanh Hai, Michael R. Jaff, Hylton V. Joffe, Donald E. Cutlip, Akshay S. Desai, Eldrin F. Lewis, C. Michael Gibson, Martin J. Landray, A. Michael Lincoff, Christopher J. White, Steven S. Brooks, Kenneth Rosenfield, Michael J. Domanski, Alexandra J. Lansky, John J.V. McMurray, James E. Tcheng, Steven R. Steinhubl, Paul Burton, Laura Mauri, Christopher M. O'Connor, Marc A. Pfeffer, H.M. James Hung, Norman L. Stockbridge, Bernard R. Chaitman, Robert J. Temple and on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI). 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation. 2018;137:961-972. Originally published February 26, 2018

Death Definition References

1. Karen A. Hicks, Kenneth W. Mahaffey, Roxana Mehran, Steven E. Nissen, Stephen D. Wiviott, Billy Dunn, Scott D. Solomon, John R. Marler, John R. Teerlink, Andrew Farb, David A. Morrow, Shari L. Targum, Cathy A. Sila, Mary T. Thanh Hai, Michael R. Jaff, Hylton V. Joffe, Donald E. Cutlip, Akshay S. Desai, Eldrin F. Lewis, C. Michael Gibson, Martin J. Landray, A. Michael Lincoff, Christopher J. White, Steven S. Brooks, Kenneth Rosenfield, Michael J. Domanski, Alexandra J. Lansky, John J.V. McMurray, James E. Tcheng, Steven R. Steinhubl, Paul Burton, Laura Mauri, Christopher M. O'Connor, Marc A. Pfeffer, H.M. James Hung, Norman L. Stockbridge, Bernard R. Chaitman, Robert J. Temple and on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI). 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation. 2018;137:961-972

Heart Failure Definition References:

1. Karen A. Hicks, Kenneth W. Mahaffey, Roxana Mehran, Steven E. Nissen, Stephen D. Wiviott, Billy Dunn, Scott D. Solomon, John R. Marler, John R. Teerlink, Andrew Farb, David A. Morrow, Shari L. Targum, Cathy A. Sila, Mary T. Thanh Hai, Michael R. Jaff, Hylton V. Joffe, Donald E. Cutlip, Akshay S. Desai, Eldrin F. Lewis, C. Michael Gibson, Martin J. Landray, A. Michael Lincoff, Christopher J. White, Steven S. Brooks, Kenneth Rosenfield, Michael J. Domanski, Alexandra J. Lansky, John J.V. McMurray, James E. Tcheng, Steven R. Steinhubl, Paul Burton, Laura Mauri, Christopher M. O'Connor, Marc A. Pfeffer, H.M. James Hung, Norman L. Stockbridge, Bernard R. Chaitman, Robert J. Temple and on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI). 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation. 2018;137:961-972.

2. Ponikowski P et al. Eur Heart J (2016) 37:2129-2200

3. Nagueh SF et al. J Am Soc Echocardiogr 2016;29:277-314.

Stroke Definition References:

1. Karen A. Hicks, Kenneth W. Mahaffey, Roxana Mehran, Steven E. Nissen, Stephen D. Wiviott, Billy Dunn, Scott D. Solomon, John R. Marler, John R. Teerlink, Andrew Farb, David A. Morrow, Shari L. Targum, Cathy A. Sila, Mary T. Thanh Hai, Michael R. Jaff, Hylton V. Joffe, Donald E. Cutlip, Akshay S. Desai, Eldrin F. Lewis, C. Michael Gibson, Martin J. Landray, A. Michael Lincoff, Christopher J. White, Steven S. Brooks, Kenneth Rosenfield, Michael J. Domanski, Alexandra J. Lansky, John J.V. McMurray, James E. Tcheng, Steven R. Steinhubl, Paul Burton, Laura Mauri, Christopher M. O'Connor, Marc A. Pfeffer, H.M. James Hung, Norman L. Stockbridge, Bernard R. Chaitman, Robert J. Temple and on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI). 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation. 2018;137:961-972.

2. Adams HP, Bendixen BH, Kappelle LJ et-al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24 (1): 35-41.

3. Goldstein LB, Jones MR, Matchar DB et-al. Improving the reliability of stroke subgroup classification using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. Stroke. 2001;32 (5): 1091-8.

4. Radu RA et al. Etiologic classification of ischemic stroke: Where do we stand. Clinical neurology and neurosurgery 2017;159:93-106

Nephropathy Definition References

1. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. http://www.kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf

2. Guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency, Committee for Medicinal Products for Human Use (CHMP) EMA/CHMP/355988/2014 2, 16 June 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500169469.pdf

3. KDIGO Clinical Practice Guideline for Acute Kidney Injury, Volume 2, Issue 1, March 2012. http://www.kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf

4. Common Terminology Criteria for Adverse Events (CTCAE), U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute Version 4, Published: May 28, 2009 (v4.03:June 14, 2010). https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf

5. Defining end stage renal disease in clinical trials, a framework for adjudication. Agerwal, Nephrol Dial Transplant (2016) 31:864-867

13.2. Financial Disclosure

The applicant provided financial disclosure information as outlined below. It should be noted that out of 4714 investigators at 804 sites, only 61 (1.3%) had disclosable financial interests.

Covered Clinical Study (Name and/or Number): SELECT / EX9536-4388

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4714		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 61		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 61 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 7		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JULIE K GOLDEN
03/07/2024 09:50:16 PM

LAURA B HIGGINBOTHAM
03/07/2024 09:54:25 PM

JOHN M SHARRETTS
03/07/2024 10:34:02 PM
I concur with the analyses and conclusions in this review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215256Orig1s011

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	215256
Supplement #:	11
Drug Name:	Semaglutide injection
Indications:	(b) (4) [redacted]
Applicant:	Novo Nordisk Inc.
Dates:	Stamp date: 09/08/2023 PDUFA date: 03/08/2024
Review Priority:	Priority
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Satyajit Ghosh, Ph.D.
Concurring Reviewers:	Feng Li, Ph.D., Team Leader
Medical Division:	Division of Diabetes, Lipid Disorders, and Obesity Product
Clinical Team:	Julie Golden, M.D., Reviewer Laura Higginbotham, M.D., Team Leader
Project Manager:	Martin White

Keywords: NDA review, Cardiovascular Outcomes Trial.

Table of Contents

1 LIST OF TABLES

2 LIST OF FIGURES

1 EXECUTIVE SUMMARY

Novo Nordisk submitted a supplemental new drug application (sNDA) to expand the indication of semaglutide (marketed as Wegovy) (b) (4) To support the claim and update the product label, the submission included the results of one large cardiovascular outcomes trial (SELECT – Semaglutide effects on cardiovascular outcomes in people with overweight or obesity). The primary objective of this study was to assess the effect of treatment with semaglutide 2.4 mg compared to placebo for approximately 5 years (59 months) on the incidence of CV events in adults with established CV disease and overweight or obesity.

The primary endpoint was time to first MACE, which consisted of three components: cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke. The superiority of semaglutide 2.4 mg compared to placebo was established in this study with a hazard ratio and 95% confidence interval of 0.80 (0.72, 0.90) for the primary endpoint. About 3% of the randomized subjects were lost to follow up (missing data). Sensitivity analyses based on retrieved dropouts produced similar results.

The prespecified key secondary endpoints tested sequentially included time to CV death, time to first occurrence of a composite heart failure (HF) endpoint, and time from randomization to all-cause death. The hazard ratio and its 95% confidence intervals for each of the key secondary endpoint was 0.85 (0.71, 1.01), 0.82 (0.71, 0.96), and 0.81 (0.71, 0.93), respectively. Because the time to CV death failed to achieve statistically significance at one-sided level 0.025, time to HF and time to all-cause death could not be claimed statistically significant based on the prespecified testing order.

There was no statistical issue identified during the review. Overall, the study showed a treatment benefit of Wegovy in reducing risk of MACE for adults with obesity and established CV disease.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Semaglutide is a potent GLP-1 analogue with a high degree of homology to human GLP-1. In addition to the pancreas and the brain, GLP-1 receptors are also expressed in the heart, blood vessels, cells of the immune system and the kidney and may mediate macro- and micro-vascular effects. Semaglutide 2.4 mg has been approved under the trade name Wegovy for weight management in adults and pediatric patients (aged 12 years and older). It is a once weekly subcutaneous (s.c.) administration as an adjunct to reduced calorie diet and increased physical activity. On September 08, 2023, the applicant submitted this supplementary NDA for approval of semaglutide injection for lowering risk of cardiovascular events in adults.

2.1.2 History of Drug Development

Semaglutide 1 mg injection was first approved as a treatment for type 2 diabetes in 2017. It (2.4 mg once weekly) was subsequently approved for weight management in 2021. The 2021 approval letter included the postmarking requirement PMR 4081-6:

"Complete the ongoing randomized, double-blind, parallel-group, placebo-controlled trial in approximately 17,500 patients with established CV disease and overweight or obesity (randomized 1:1 to semaglutide 2.4 mg and placebo) to evaluate the long-term effects of semaglutide 2.4 mg on pancreatitis, gallbladder disorders, renal safety, serious hepatic events, malignant neoplasms, serious hypoglycemia, and serious gastrointestinal disorders."

This submission included the results from the CV outcome trial, SELECT, to fulfill PMR 4081-6 and update the label with a new indication.

2.2 Data Sources

The study reports, protocol, statistical analysis plan, and all referenced literature were submitted by the applicant to the Agency. The data and final study report for the electronic submission were archived under the network path \\CDSESUB1\evsprod\NDA215256\0431\. Information necessary for this review was contained in Module 1, and Module 5.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted data are acceptable in terms of quality. I was able to reproduce the primary and secondary endpoint analyses for the clinical study submitted.

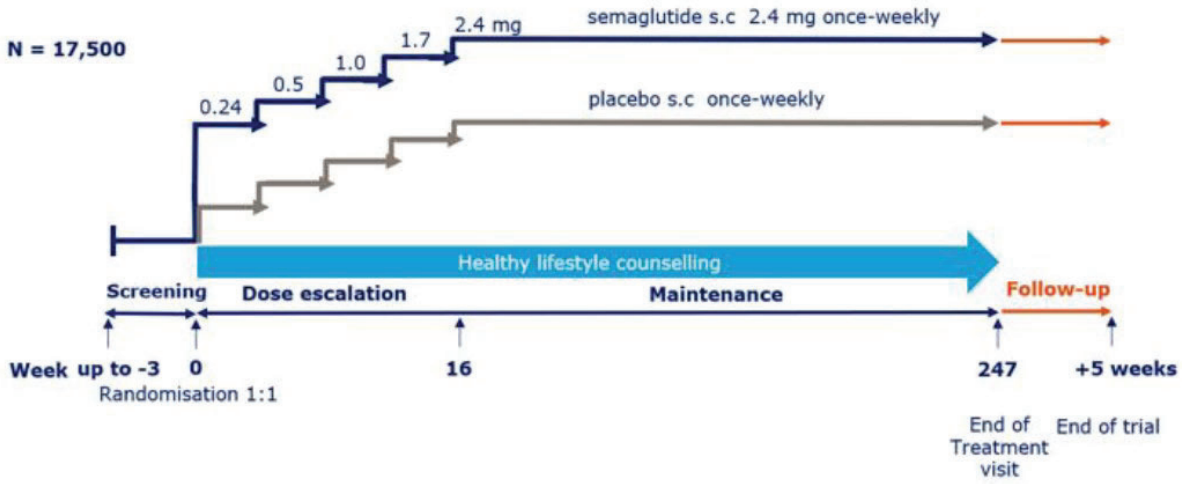
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study design

SELECT was a multinational, multicenter, randomized, double-blind, parallel group, placebo-controlled trial comparing semaglutide 2.4 mg with placebo both administered s.c. once weekly in subjects with established CV disease and overweight or obesity. 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 (1225) of primary endpoint events was reached. A total of 17,500 adults with established CV disease and overweight or obesity were planned to be randomized 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: Study Design for SELECT



Source: CSR page 50, Figure 9-1.

The assessments for evaluation of CV endpoints in this trial comprised all-cause death, acute coronary syndrome, stroke, coronary artery revascularization, and heart failure (HF) events. These events underwent adjudication by the event adjudication committee (EAC) to ensure an independent, blinded, and uniform evaluation of event categories.

Primary endpoint
The primary endpoint was time from randomization to first occurrence of 3-point MACE, a 3-component composite endpoint consisting of CV death, non-fatal MI, or non-fatal stroke.

Secondary Endpoints
The confirmatory secondary endpoints are listed below:

1. Time from randomization to CV death
2. Time from randomization to first occurrence of a composite HF endpoint consisting of: HF hospitalization, urgent HF visit or CV death.
3. Time from randomization to all-cause death.

Other secondary endpoints include:

a. Time to first occurrence of fatal or non-fatal MI
b. Time to first occurrence of fatal or non-fatal stroke.

Once the superiority for the primary endpoint was confirmed, the superiority of the 3 confirmatory secondary endpoints were to be tested sequentially in the same order they appear. The other secondary endpoints (a and b above) are not included in the testing hierarchy and their superiority was not tested.

3.2.2 Statistical Methodologies

Primary Analyses

The analysis population was the intention-to-treat (ITT) population defined as all randomized patients.

All the time-to-event (TTE) endpoints were analyzed by using a Cox proportional hazards model with treatment group (semaglutide 2.4 mg, placebo) as fixed factor under the assumption of independent censoring. Non-CV death was treated as competing risk, not part of the independent censoring assumption. Cumulative incidence functions for TTE endpoints were estimated by the Aalen-Johansen estimator accounting for the competing risks. Fatal MI was defined as an EAC-confirmed MI occurring within (≤) 30 days of an EAC-confirmed CV death classified with cause of death being MI. All other MIs were defined as non-fatal. A similar definition is applied for fatal/non-fatal stroke. Deaths attributed to the category "undetermined cause of death" are presumed cardiovascular death.

The hazards ratio (HR) for comparing semaglutide 2.4 mg versus placebo and the 95% CI were calculated from the Cox proportional hazards model. Given superiority for the primary endpoint, the superiority of the 3 confirmatory secondary endpoints were to be tested under multiplicity control (one sided alpha of 0.025) via sequential testing hierarchy (in the same order the confirmatory secondary endpoints appear). 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.

Interim Analyses

One interim analysis was planned for the primary efficacy endpoint when approximately two thirds of the total planned number of primary endpoint events was accrued. The one-sided alpha spending function (based on O'Brien-Fleming boundaries generated using the Lan-DeMets alpha-spending function) was used to test superiority at a study-wise one-sided type I error rate of 2.5%. Results of the interim analysis were monitored by an independent DMC.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

The summary of the subject disposition in SELECT is given below in Table 2. A total of 21,089 subjects were screened for this trial, of which 3,480 (16.5% of all screened) were screening failures. A total of 17609 subjects were randomized (1:1) to treatment with semaglutide 2.4 mg (8,805 subjects) or placebo (8,804 subjects). Three subjects were randomized twice in the trial and 1 subject was randomized three times; thus, 5 subject identifiers were not included in the FAS (Table 1). 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).

Table 1: Subject Disposition - FAS

	Sema 2.4mg n (%)	Placebo n (%)	Total n (%)
Screened			21089
Screening failure			3480 (16.5)
All randomized	8805	8804	17609

Subjects removed due to Randomized more than once	2	3	5
FAS	8803 (100)	8801 (100)	17604 (100)
Trial completers	8544 (97.1)	8517 (96.8)	17061 (96.9)
Attended follow-up visit	8169 (92.8)	8059 (91.6)	16228 (92.2)
Deceased	375 (4.3)	458 (5.2)	833 (4.7)
Non-completers	259 (2.9)	284 (3.8)	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(<0.1)	6(<0.1)
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)
Permanently discontinued	2694(30.6)	2375(27.0)	5069(28.8)

n = Number of subjects in the group; Percentages are shown within parentheses.
Source: CSR page 83, Table 10-1 verified by the Statistics reviewer

In total, 96.9% of randomized subjects in the FAS completed the trial. A total of 543 randomized subjects (3.1%) did not complete the trial due to either withdrawal of consent or being lost to follow-up (LTFU). The percentage of non-completers was similar between treatment groups. We see that the proportion of subjects that permanently discontinued the trial product was similar with semaglutide 2.4 mg (30.6%) and placebo (27%). The disposition of these permanently discontinued subjects is shown in Table 2. Permanent discontinuation of trial product due to an adverse event was more frequent with semaglutide 2.4 mg, whereas discontinuation due to lack of effect was more frequent with placebo. A total of 82 subjects (39 in the semaglutide 2.4 mg group and 43 in the placebo group) had trial product permanently discontinued due to the COVID-19 pandemic.

Table 2: Reasons for permanent treatment discontinuation

	Sema 2.4mg N= 8803 n (%)	**Placebo N=8801 n (%)**	**Total N=17604 n (%)**
Total number of subjects discontinued treatment	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 (<0.1)	4 (<0.1)	7 (<0.1)
Simultaneous use of prohibited medication	5 (<0.1)	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)

Source: CSR page 83, Table 10-1 verified by the Statistics reviewer

Baseline demographics for the FAS population are shown in Table 3. 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. Approximately, 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%, hereof 20.7% recruited from sites in the United States).

Table 3: Demographics and Baseline Characteristics – FAS

	Sema 2.4mg N=8803 n (%)	**Placebo N=8801 n (%)**	**Total N=17604 n (%)**
Age			
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)			
< 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			
Female	2448 (27.8)	2424 (27.5)	4872 (27.7)
Male	6355 (72.2)	6377 (72.5)	12732 (72.3)
Region			
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			
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 (<0.1)	5 (<0.1)	8 (<0.1)
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			
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)

N = Total number of subjects randomized and dosed in the full analysis set; n = number of subjects in the group
Source: CSR page 86, Table 10-2 verified by the Statistics reviewer

3.2.4 Results and Conclusions

Table 4 below shows the analysis results of the primary endpoint. There is a statistically significant reduction in CV risk of semaglutide 2.4mg compared to placebo. When comparing semaglutide to placebo, the hazard ratio for time to first occurrence of 3-point MACE is 0.80 with a 95% CI of (0.72, 0.89). We see that nonfatal MI had the highest percent of event occurrence among the components of the primary endpoint.

Table 4: Primary analysis of the primary endpoint – Time to the First Occurrence of 3-point MACE – FAS

	Sema 2.4mg (N=8803) n (%)	**Placebo (N=8801) n (%)**	**HR (95% C.I.): Sema 2.4mg vs. Placebo**	**P-value**
Primary endpoint	569 (6.5)	701 (8.0)	0.80 (0.72, 0.89)	< 0.0001
Components Contribution to the Primary Endpoint				
CV Death	191 (2.2)	221 (2.5)		
Nonfatal MI	230 (2.6)	321 (3.6)		
Nonfatal Stroke	148 (1.7)	159 (1.8)		

N = Total number of subjects randomized and dosed in the full analysis set; n = number of EAC-confirmed events; P-value: one-sided p-value
Source: CSR (Page 117) and Statistical Reviewer's Analysis

The above table also displays the number of first occurrence of each of the individual components of the primary endpoint. A total of 1,270 first MACE with onset during the in-trial observation period were confirmed by the EAC. The proportion of subjects with first MACE was lower with semaglutide 2.4 mg (6.5%) than with placebo (8.0%). We see that nonfatal MI had the highest percent of event occurrence among the components of the primary endpoint.

Table 5 below characterizes the follow-up. The percentage of patients enrolled in the study who experienced a 3-point MACE event is 7.21%, while 88.1% of patients were followed through the end of the study (EOS) without experiencing an event. The percentage of patients whose times were censored for a non-CV death was 1.8%. About 2.93% of patients were lost-to-follow up before experiencing an event (i.e., censored before the EOS).

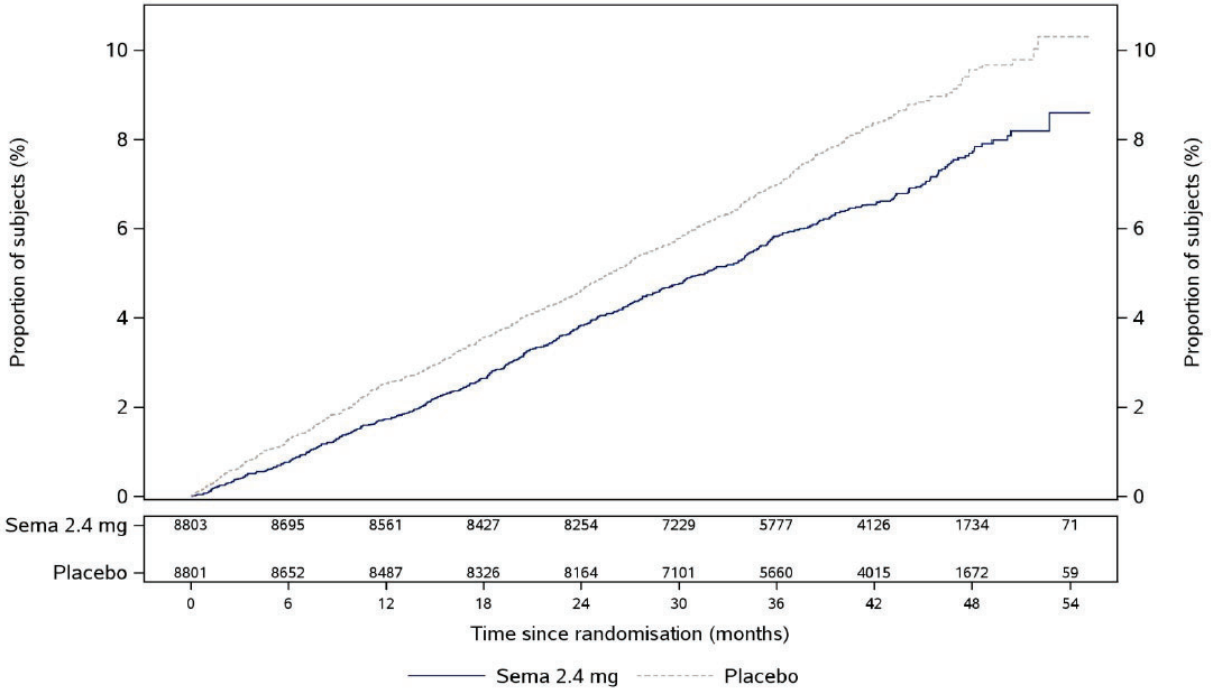
Table 5: Characterization of Follow-Up

Follow-up for 3-point MACE	Sema 2.4mg (N=8803) n (%)	Placebo (N=8801) n (%)	Total (N=17604) n (%)
3-point MACE Event	569 (6.46)	701 (7.97)	1270 (7.21)
Censored at EOS Without any 3-point MACE Event	7850 (89.2)	7652 (86.9)	15502 (88.1)
Censored for Non-CV Death	141 (1.60)	176 (2.0)	317 (1.80)
Censored Before EOS (Missing Follow-Up)	243 (2.76)	272 (3.09)	515 (2.93)

N = Total number of subjects randomized and dosed in the full analysis set; n = number of subjects in the group
Source: Response to FDA Information Request dated 11/09/2023 (Page 12) and Statistical Reviewer's Analysis

Figure 2 below displays the cumulative incidence plot based on Aalen-Johansen estimator for time to first occurrence of 3-point MACE by treatment groups.

Figure 2: Cumulative incidence plot of the Primary Endpoint – FAS



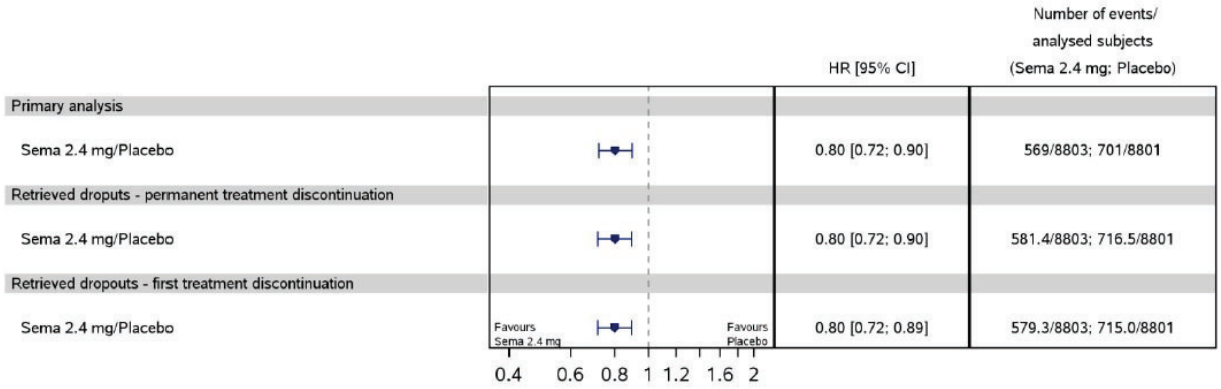
Source: CSR (Page 118) and Statistical Reviewer's Analysis

Sensitivity Analyses

Two protocol prespecified sensitivity analyses were performed using retrieved dropout by imputing event times for subjects who withdrew or were LTFU. If the imputed event time occurs after the subjects planned end-of-trial time the subject was censored at the planned end-of-trial time:

1. One analysis used an estimated annual event rate from subjects who discontinued treatment permanently but remained in the trial. Event times for subjects who were lost to follow up or withdrew consent were multiple imputed using hazard rates from retrieved dropouts in the same treatment arm. Retrieved dropouts were defined as subjects who permanently discontinued treatment but remained in trial. Hazard rates were estimated from observations after the on-treatment period using a piecewise exponential model with 3 time intervals (0-1, 1-2 and 2+ years from treatment discontinuation). The imputed data sets were analyzed using the same Cox regression model as for the primary analysis and results were combined using Rubin's rules.
2. The other analysis uses an estimated annual event rate for subjects who discontinued treatment at any point in the trial. The method of imputation was similar to 1 above.

Figure 3: Sensitivity analyses of the Primary Endpoint



Source: CSR (Page 119) and Statistical Reviewer's Analysis.

The results of both sensitivity analyses (Figure 3) were consistent with the result from the primary analysis.

The Applicant also performed sensitivity analyses evaluating the impact of COVID-19. The results indicated that COVID-19 had little impact on the study results.

Secondary endpoints

Table 6 below shows the results of the confirmatory secondary endpoints and other secondary endpoints. Superiority of semaglutide 2.4 mg over placebo was not confirmed for the confirmatory secondary endpoint time to CV death. Based on the prespecified testing order, superiority of semaglutide 2.4 mg versus placebo could not be considered statistically significant for the confirmatory secondary endpoints of time to first composite HF outcome and time to all-cause death, despite both achieved nominal statistical significance (at one sided $\alpha = 0.025$).

Table 6: Primary analysis of the Secondary Endpoints - FAS

	Sema 2.4mg (N=8803) n (%)	Placebo (N=8801) n (%)	HR (95% C.I.): Sema 2.4mg vs. Placebo	P-value
Time to first occurrence of				
CV Death[1, 2]	223 (2.5%)	262 (3.0%)	0.85 (0.71, 1.01)	One sided p-value 0.0327
Composite of HF hospitalization, urgent HF visit or CV death[1, 3]	300 (3.4%)	361 (4.1%)	0.82 (0.71, 0.96)	
HF hospitalization and urgent HF visit[4]	97 (1.1%)	122 (1.4%)	0.79 (0.60, 1.03)	
All cause death[1, 3]	375 (4.3%)	458 (5.2%)	0.81 (0.71, 0.93)	
Nonfatal Stroke[4]	154 (1.7%)	165 (1.9%)	0.93 (0.74, 1.15)	
Nonfatal MI[4]	234 (2.7%)	322 (3.7%)	0.72 (0.61, 0.85)	
Fatal or Non-fatal MI[4]	243 (2.8%)	334 (3.8%)	0.72 (0.61, 0.85)	
Fatal or Non-fatal Stroke[4]	160 (1.8%)	178 (2.0%)	0.89 (0.72, 1.11)	

Source: Statistical Reviewer's Analysis
N = Total number of subjects randomized and dosed in the full analysis set; n = number of subjects
[1] : Confirmatory secondary endpoint
[2]: Time to first occurrence of CV death was the first confirmatory secondary endpoint in the sequential testing hierarchy and it did not achieve significance at one sided $\alpha = 0.025$.
[3] : Not statistically significant based on the prespecified testing hierarchy.
[4] : Not included in the prespecified testing hierarchy for controlling type-I error.

Other secondary endpoints

Table 7 below shows the results of the supportive endpoints. These anthropometric and cardiometabolic endpoints were analyzed using an ANCOVA with treatment as fixed factor and baseline value as covariate and were not included in the pre-specified hierarchical testing strategy (and hence superiority was not tested).

Table 7: Mean Changes in Anthropometry and Cardiometabolic Parameters[1] at Week 104

	Placebo		Sema 2.4mg		
	Baseline	Change from Baseline (LSMean)	Baseline	Change from Baseline (LSMean)	Treatment Difference (Placebo – Sema 2.4mg)
Waist Circumference (cm)	111.4	-1.0	111.3	-7.6	-6.5

Systolic Blood Pressure (mmHg)	131	-0.5	131	-3.8	-3.3
Diastolic Blood Pressure (mmHg)	79	-0.5	79	-1.0	-0.6
Heart Rate	69	0.7	69	3.8	3.1
HbA1c (%)	5.8	0.0	5.8	-0.3	-0.3
	Baseline	**% Change from Baseline (LSMean)**	**Baseline**	**% Change from Baseline (LSMean)**	**Treatment difference (Placebo – Sema 2.4mg)**
Body Weight (kg)	96.8	-0.9	96.5	-9.4	-8.5
Total Cholesterol (mg/dL)[3]	156.0	-1.9	155.5	-4.6	-2.8
LDL Cholesterol (mg/dL)[3]	78.5	-3.1	78.5	-5.3	-2.2
HDL Cholesterol (mg/dL)[3]	44.2	0.6	44.1	4.9	4.2
Triglycerides (mg/dL)[3]	139.5	-3.2	138.6	-18.3	-15.6

Source: CSR verified by Statistics Reviewer.

[1] : Parameters listed in the table were not included in the pre-specified hierarchical testing and superiority was not tested.

[2] : Responses were analysed using an ANCOVA with treatment as fixed factor and baseline value as covariate. Missing data were multiply 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.

[3] : Baseline value is the geometric mean

LSMean: Least Square Mean.

Interim Analysis

The Data Monitoring Committee (DMC) review meeting held in July 2022 discussed the interim analysis results, when 68% (831 events) of the final adjudicated primary endpoint events (1225 events) had occurred and had been adjudicated. The 1-sided alpha levels and boundaries based on a Z-test for the interim analysis is provided in Table 8 below. Despite that interim analysis achieved statistically significant results for the primary endpoint, the DMC recommended the study to continue to observe more data for assessing the treatment effect on reducing the risk of CV and all-cause mortality.

Table 8: Interim analysis results

	Event counts			Treatment effect		Efficacy boundary		
Event type	*Total (information fraction[e])*	*SEM*	*PBO*	*Hazard Ratio[f]*	*95% Confidence Interval[f]*	*One-sided p-value[g]*	*P-value boundary[h]*	*Boundary crossed?*
Primary: MACE[a]	831 (0.678)	369	462	0.791	(0.690,0.907)	0.0004	0.00650	Yes
Confirmatory: CV death[b]	279 (0.678)	134	145	0.920	(0.727,1.163)	0.25	0.01857	No
Confirmatory: CV death + HF[c]	381 (0.678)	177	204	0.863	(0.705,1.054)	0.075	0.01857	No
Confirmatory: Death[d]	514 (0.678)	233	281	0.826	(0.693,0.981)	0.016	0.01857	Yes

Source: Page 168 of DMC Meeting Minutes.

a. The primary endpoint includes events adjudicated as CV death (see footnote b), non-fatal myocardial infarction, or non-fatal stroke.

b. This confirmatory endpoint includes deaths adjudicated as CV or undetermined.

c. This confirmatory endpoint includes events adjudicated as CV death (see footnote b) or HF, including HF hospitalization and urgent HF visits.

d. This confirmatory endpoint includes all deaths with an adjudicated cause and date; other deaths are censored at the date reported by the investigators.

e. The trial is fully enrolled with 17,605 subjects, and the information fraction for all endpoints is the number of primary events at the time of the interim analysis divided by the target number of 1,225.

f. The hazard ratio for comparing SEM versus PBO is estimated from a Cox proportional hazards model in the full analysis set population with treatment group as a fixed factor, censoring of competing events, and the exact method for handling ties. The confidence intervals are based on the profile likelihood method.

g. The one-sided p-value is from the score test of the Cox proportional hazards model with treatment group as a fixed factor.

h. Constructed using East according to Lan-DeMets group sequential design for the primary endpoint.

3.3 Evaluation of Safety

The evaluation of safety was primarily conducted by clinical team. It appears no major concerns on safety have been identified.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section summarizes results from the analysis of the primary endpoint within subgroup levels. The subgroup levels explored are:

- Chronic HF (Yes, No)
- eGFR level (mL/min/1.73m2) (<60, ≥60)
- Sex (Male, Female)
- Age (<55, 55 to 65, 65 to 75, ≥75)
- Race (White, Black or African America, Asian and Other)
- Ethnicity (Hispanic/Latino, Non-Hispanic/Latino)
- Region (North America, Europe and Asia)

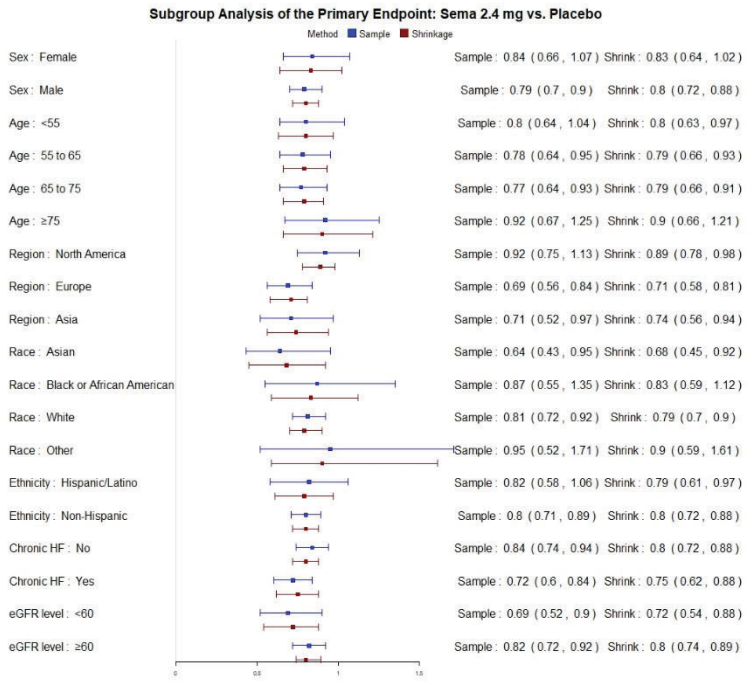
Figure 4 below displays the results of the subgroup analyses for risk category, eGFR level, sex, age, race, ethnicity and region based off the sponsors primary analysis. Additionally, Figure 4 provides shrinkage estimates of HR and its 95% credible interval based on Bayesian hierarchical model. Bayesian hierarchical modeling produces shrinkage estimates of the individual study treatment effects by removing the within study variability. Further, treatment effects are regarded as exchangeable, which allows them to be different but related. Therefore, shrinkage estimates tend to be more precise and provide narrower credible intervals. Below is the model used in the analysis for chronic HF, eGFR level, sex, race, age group, ethnicity and region:

$$Y_i = \log HR \sim N(\mu_i, \sigma_i^2), i = 1, 2, \ldots, 19.$$
$$\mu_i \sim N(\mu, \tau^2)$$
$$\mu \sim N(0, 16), \tau^{-2} \sim Gamma(0.001, 0.001)$$

Here Y_i denotes the observed subgroup $\log HR$ and we assume that before seeing data, the log hazard ratio is 0 based on one eighth of an event on each treatment arms. Thus,

$$Var\ (log\ HR) \approx \frac{1}{\frac{1}{8}} + \frac{1}{\frac{1}{8}} = 16.$$

Figure 4: Subgroup analysis of the Primary Endpoint



Source: Statistical Reviewer's Analysis.

The results of the predefined subpopulation analyses are overall consistent with the results from the primary analysis. In some of the subpopulations (e.g. Age ≥75, Race: Other, Race: Black or African American etc.) the number of subjects with events were low which produce wider confidence intervals based on the primary analysis.

5 SUMMARY AND CONCLUSION

5.1 Statistical Issues

There were no major statistical issues identified during the course of this review. Overall, the missing data was minimal (3.1%). Results from sensitivity analyses suggest that the methods for handling missing data have minimal impact on primary efficacy results.

5.2 Collective Evidence

The primary analysis showed statistically significant treatment effect in reduction of CV risk. Secondary endpoints are consistently in favor of semaglutide. Results from subgroup efficacy analyses were consistent with findings from the overall population.

5.3 Conclusions and Recommendations

The collective evidence from the submitted data demonstrated efficacy of semaglutide 2.4 mg in the study population. There was no major concern in the safety profile. We recommend approval for the proposed indication based on findings from the submitted results.

5.4 Labeling and Recommendations

Labeling review is still ongoing while this review is finalized. Based on the review of the submitted data, the following are proposed edits to the label in section 14.

- (b) (4)
-
-

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SATYAJIT GHOSH
02/15/2024 01:27:55 PM

FENG LI
02/15/2024 01:40:22 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215256Orig1s011

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 29, 2024
To:	Martin White M.S. Senior Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	WEGOVY (semaglutide)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 215256
Supplement Number:	S-011
Applicant:	Novo Nordisk Inc.

1 INTRODUCTION

On September 8, 2023, Novo Nordisk Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) Efficacy to the New Drug Application (NDA) 215256 S-011 for WEGOVY (semaglutide) injection, for subcutaneous use. This supplemental application proposes the addition of the following indication:

- (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) on September 15, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for WEGOVY (semaglutide) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft WEGOVY (semaglutide) MG received on September 8, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 26, 2024.
- Draft WEGOVY (semaglutide) Prescribing Information (PI) received on September 8, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 26, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KELLY D JACKSON
02/29/2024 12:19:08 PM

ANKUR S KALOLA
02/29/2024 12:29:30 PM

MARCIA B WILLIAMS
02/29/2024 12:54:05 PM

LASHAWN M GRIFFITHS
02/29/2024 01:30:01 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 28, 2024

To: Martin White, Regulatory Project Manager, Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Melinda Wilson, Associate Director for Labeling, DDLO

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for WEGOVY (semaglutide) injection, for subcutaneous use

NDA: 215256, S-11

Background:

In response to DDLO's consult request dated September 15, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for supplement 11 for Wegovy. This supplement provides for updates to the PI based on the results from the cardiovascular outcomes clinical trial, SELECT (EX9536-4388).

PI & Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on February 26, 2024, and are comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide, and comments will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

35 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANKUR S KALOLA
02/28/2024 12:54:28 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUGS
DIVISION OF CARDIOLOGY AND NEPHROLOGY

Date: 15 February 2024

Receipt: 21 September 2024

From: Jordan E Pomeroy, MD, PhD, Medical Officer
Division of Cardiology and Nephrology

Through: Fred Senatore, MD, PhD, FACC, Clinical Team Leader
Norman Stockbridge, MD, PhD, Division Director
Division of Cardiology and Nephrology (DCN)

To: Martin White, Senior Regulatory Project Manager
Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Sponsor: Novo Nordisk

Program: NDA 215256/S-011 – Wegovy (semaglutide)
Semaglutide is a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA) approved for chronic weight management as a subcutaneous (SC) injection (Wegovy, NDA 215256) and for the treatment of type 2 diabetes mellitus (T2DM) as a SC injection (Ozempic, NDA 209637) and as an oral tablet (Rybelsus, NDA 213182). Ozempic is also approved to reduce the risk of major adverse cardiovascular (CV) events (MACE) in patients with T2DM and established CV disease (CVD)

Subject: Review of the SELECT trial data (b) (4) (HF) endpoints

Documents: **[Synopsis]** \\CDSESUB1\EVSPROD\nda215256\0431\m5\53-clin-stud-rep\535-rep-effic-safety-stud\cardiovascular-risk-reduction\5351-stud-rep-contr\ex9536-4388\synopsis.pdf
[CSR Body] \\CDSESUB1\EVSPROD\nda215256\0431\m5\53-clin-stud-rep\535-rep-effic-safety-stud\cardiovascular-risk-reduction\5351-stud-rep-contr\ex9536-4388\study-report-body.pdf

Statement of Consult Request

The SELECT trial (EX9536-4388) was a dedicated cardiovascular outcome trial (CVOT) designed to demonstrate superiority of Wegovy versus placebo in subjects with established CVD and overweight or obesity, but without diabetes, in reducing the risk of major adverse cardiovascular event (MACE: CV death, nonfatal myocardial infarction (MI), or nonfatal stroke). SELECT has recently been submitted to

DDLO as an efficacy supplement (S-011) to include the results of this trial in the Wegovy prescribing information.

A total of 17604 subjects were randomized 1:1 to Wegovy or placebo. Top-line results suggested that Wegovy reduced the risk of MACE in the studied population with an estimated hazard ratio (HR) of 0.80 (95% CI 0.72, 0.90). Superiority of Wegovy vs placebo was not confirmed for the confirmatory secondary endpoint of time CV death [HR 0.85 (0.71, 1.01)]. The confirmatory secondary endpoint of time to first composite HF outcome endpoint (HF hospitalization, urgent HF visit, or CV death) was therefore not formally tested [HR 0.82 (0.71, 0.96)].

(b) (4)

1. DCN Summary and Assessment

We reviewed your DCN consult request (21 September 2023) along with the Applicant's study report synopsis and study report body for the completed SELECT (EX9536-4388) CVOT submitted under NDA 215256/S-011 (SN0431; 08 September 2023). In addition, we participated in DDLO internal review meetings for NDA 215256/S-011, inclusive of Filing (05 October 2023), Mid-Cycle (08 December 2023), and (b) (4). Notably, DDLO is likely to approve an indication for (b) (4) based on the positive result for the SELECT primary composite endpoint (HR 0.80 [95% CI: 0.72-0.90).

(b) (4)

2. SELECT: Published Topline Results

Table 2. Primary and Secondary Time-to-First-Event Efficacy End Points.*

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Hazard Ratio (95% CI)	P Value
	number of patients (percent)			
Primary cardiovascular composite end point†	569 (6.5)	701 (8.0)	0.80 (0.72 to 0.90)	<0.001
Confirmatory secondary end points‡				
Death from cardiovascular causes	223 (2.5)	262 (3.0)	0.85 (0.71 to 1.01)	0.07
Heart failure composite end point§	300 (3.4)	361 (4.1)	0.82 (0.71 to 0.96)	NA
Death from any cause	375 (4.3)	458 (5.2)	0.81 (0.71 to 0.93)	NA
Supportive secondary end points¶				
Cardiovascular expanded composite end point‖	873 (9.9)	1074 (12.2)	0.80 (0.73 to 0.87)	NA
Cardiovascular composite end point with death from any cause**	710 (8.1)	877 (10.0)	0.80 (0.72 to 0.88)	NA
Nonfatal myocardial infarction	234 (2.7)	322 (3.7)	0.72 (0.61 to 0.85)	NA
Nonfatal stroke	154 (1.7)	165 (1.9)	0.93 (0.74 to 1.15)	NA
Hospitalization or urgent medical visit for heart failure	97 (1.1)	122 (1.4)	0.79 (0.60 to 1.03)	NA
Coronary revascularization	473 (5.4)	608 (6.9)	0.77 (0.68 to 0.87)	NA
Unstable angina leading to hospitalization	109 (1.2)	124 (1.4)	0.87 (0.67 to 1.13)	NA
Glycated hemoglobin level ≥6.5%††	306 (3.5)	1059 (12.0)	0.27 (0.24 to 0.31)	NA
Nephropathy composite end point‡‡	155 (1.8)	198 (2.2)	0.78 (0.63 to 0.96)	NA
Glycated hemoglobin level ≥5.7% among patients with baseline glycated hemoglobin <5.7%§§	623 (21.3)	1501 (50.4)	0.33 (0.30 to 0.36)	NA

* Data are for the full analysis population during the in-trial observation period (from randomization to the final follow-up visit). All end points were analyzed with the use of a Cox proportional hazards model with treatment as a categorical fixed factor. Data from patients without events of interest were censored at the end of their in-trial period. NA denotes not applicable.

† The primary efficacy end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The hazard ratio, 95% confidence interval, and P value were adjusted for the group sequential design with the use of likelihood-ratio ordering, and the nominal two-sided significance level was 0.046.

‡ Confirmatory secondary end points were analyzed under multiplicity control through a stagewise hierarchical testing scheme in which all P values after the first nonsignificant P value are not reported. The P values (unadjusted) for the primary and confirmatory secondary end points were to be compared with the nominal significance level derived from the relevant alpha spending function for the end point; if the P value was below the nominal limit, superiority would be shown. The nominal two-sided significance level was 0.023 for death from cardiovascular causes.

§ The heart failure composite end point was the first occurrence of death from cardiovascular causes or hospitalization or an urgent medical visit for heart failure.

¶ Because supportive secondary end points were not corrected for multiplicity, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and therefore should not be used to infer definitive treatment effects for supportive secondary end points.

‖ The cardiovascular expanded end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina leading to hospitalization.

** The cardiovascular end point with death from any cause was a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke.

Source: Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S, Hovingh GK, Kahn SE, Kushner RF, Lingvay I, Oral TK, Michelsen MM, Plutzky J, Tornøe CW, Ryan DH; SELECT Trial Investigators. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023 Dec 14;389(24):2221-2232. doi: 10.1056/NEJMoa2307563. Epub 2023 Nov 11. PMID: 37952131.

(b) (4)


(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JORDAN E POMEROY
02/15/2024 04:21:24 PM

FORTUNATO F SENATORE
02/15/2024 04:36:38 PM

NORMAN L STOCKBRIDGE
02/15/2024 04:47:18 PM

Clinical Inspection Summary

Date	January 31, 2024
From	Ling Yang, M.D., Ph.D., FAAFP Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Julie Golden, M.D., Medical Officer Laura Higginbotham, M.D., Clinical Team Leader Martin White, Senior Regulatory Project Manager Division of Diabetes, Lipid Disorders and Obesity (DDLO)
NDA #	215256/S-011
Applicant	Novo Nordisk A/S
Drug	Wegovy® (semaglutide) Subcutaneous Injection
NME (Yes/No)	No
Review Priority	Priority
Proposed Indication(s)	(b) (4)
Consultation Request Date	October 06, 2023
Summary Goal Date	February 08, 2024
Action Goal Date	March 08, 2024
PDUFA Date	March 08, 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study EX9536-4388 entitled "SELECT-Semaglutide effects on cardiovascular outcomes in people with overweight or obesity" were submitted to support the supplemental New Drug Application (sNDA) for Wegovy® (semaglutide) subcutaneous (SC) injection on 09/08/2023 to fulfill post marketing requirement (PMR) 4081-6 and to evaluate the long-term effects of semaglutide. Three clinical investigators (CIs): Drs. Paul Poirier (Site #2216; Canada), Coen Van Der Zwaan (Site# 2847; Netherlands) and Jesse Doran (Site #3630; US) and the contract research organization (CRO) (b) (4) were inspected for the study.

Based on the overall inspection results of these three CIs, the CRO and the regulatory assessments, the data generated by these CI sites and the primary endpoint data adjudicated by the CRO are verifiable. Study EX9536-4388 appears to have been conducted adequately and the clinical data submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Wegovy® (semaglutide) SC injection (0.25 mg, 0.5 mg, 1 mg, and 2.4 mg in pre-filled, single-dose pens) was approved on 06/04/2021 under NDA 215256 as an adjunct to a reduced calorie diet and

increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m^2 or greater (obesity); or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition [e.g., hypertension, type 2 diabetes mellitus (T2DM), or dyslipidemia].

Novo Nordisk Inc. submitted an efficacy supplement S-011 to NDA 215256 Wegovy® SC injection on 09/08/2023 to fulfill PMR 4081-6 and to evaluate the long-term effects of semaglutide. Data from a Phase 3 study EX9536-4388 entitled "SELECT-Semaglutide effects on cardiovascular outcomes in people with overweight or obesity" were submitted to support the approval.

Study EX9536-4388

Study EX9536-4388 was a randomized, double-blind, parallel group, placebo-controlled study comparing once weekly SC semaglutide 2.4 mg with placebo in subjects with established cardiovascular (CV) disease and overweight or obesity and without T2DM.

The primary study objective was to demonstrate that added to standard of care in subjects with established CV disease and overweight or obesity, compared to placebo, once weekly semaglutide SC 2.4 mg lowers the incidence of MACE [CV death, nonfatal myocardial infarction (MI) or nonfatal stroke].

The primary efficacy endpoint was the time from randomization to first occurrence of a composite endpoint consisting of CV death, non-fatal MI, or non-fatal stroke.

Study Procedures

- Eligible subjects were randomized at a 1:1 ratio to receive blinded once-weekly SC treatment of semaglutide 2.4 mg, or placebo as an adjunct to a reduced-calorie diet and increased physical activity.
- Dose Escalation Period (16-week): Dosing was once weekly with dose escalation every 4th week until maintenance dose (2.4 mg) was reached. Dose escalations were: 0.24 mg, 0.5 mg, 1.0 mg, 1.7 mg, and 2.4 mg. If a subject could not tolerate the recommended escalated dose, the subject could stay at a lower dose level.
- Maintenance Period: Treatment continued on the once-weekly maintenance dose of 2.4 mg or placebo until the end of treatment.
- Follow-up Period (5-week): safety assessments 5 weeks after the end of treatment.
- An independent data monitoring committee (DMC) oversees the efficacy and subjects' safety; and could recommend stopping the trial early when the targeted number of primary endpoint events was reached.

The study screened 21,089 subjects, randomized 17,609 subjects (8,805 subjects in the semaglutide group; and 8,804 in the placebo group) at 804 study sites in 41 countries around the world with 202 sites in the US. The study was initiated on 10/24/2018 and was completed on 06/29/2023. A total of 17,061 subjects completed the study (8,544 subjects in the semaglutide group and 8,517 in the placebo group). The overall median time in-trial was 41.8 months (41.9 months for the semaglutide group and 41.7 months for the placebo group) and overall median on-

treatment time was 38.2 months (37.3 months for the semaglutide group and 38.6 months for the placebo group). The study data cutoff date was 07/18/2023.

III. RESULTS

1. **Paul Poirier, M.D.** (Site #2216)
   2725 Che Sainte-Foy
   Institut universitaire de cardiologie et de pneumologie de Quebec-Universite Laval
   QUEBEC, QC G1V 4G5
   Canada

This CI was inspected on 12/04-08/2023 as a data audit for Study EX9536-4388. The inspection was facilitated by an independent interpreter to provide French translation. This was the first FDA inspection of Dr. Poirier.

For the inspected study, the site (#2216) screened 98 subjects, enrolled 91 subjects, with all 91 subjects completed the study. Because subject ID was limited to 2 digits, this site also enrolled additional 15 subjects under a different site # as Site #2232. Thus, a total of 106 subjects were enrolled under this CI. The first subject consented on 02/19/2019 and the last subject's last visit was on 06/20/2023. Source records for all 91 enrolled subjects at Site # 2216 were reviewed. The inspection did not review records of subjects enrolled at Site #2232.

The inspection reviewed the study protocol and amendments, Informed Consent Forms (ICFs) and versions, documentation of eligibility criteria and enrollment logs, medical records [including visit data, laboratory tests, physical exam results, adverse events (AEs) and serious AEs (SAEs) reports], investigational product (IP) accountability records, paper Case Report Forms (CRFs) with electronic CRFs (eCRFs) entries and electronic data capture (EDC) system, protocol deviations and related regulatory documents [e.g., Institutional Review Board (IRB) approvals and communications, staff trainings, monitoring log, records retention, financial disclosures and delegation of authority].

The primary efficacy endpoint of the time from randomization to first occurrence of a CV death, non-fatal MI, or non-fatal stroke were centrally adjudicated. The inspection verified that the site documented and submitted accurate dates of these events to the sponsor's endpoint adjudication system with no discrepancies. There were no underreporting of AEs or SAEs.

In general, the inspection verified adequate source data for the inspected study subjects.

2. **Coen Van Der Zwaan, M.D., Ph.D.** (Site #2847)
   President Kennedylaan 1, Ziekenhuis Rivierenland
   Tiel, Gelderland, 4002 WP
   Netherlands

This CI was inspected on 12/11-15/2023 as a data audit for Study EX9536-4388. The inspection was facilitated by an independent interpreter to provide Dutch translation. This was the first FDA inspection of Dr. Zwaan.

The study site screened 79 subjects, enrolled 66 subjects, with all 66 subjects completed the study. The first subject consented on 03/20/2019 and the last subject's last visit was on 06/19/2023. Source records for all 66 enrolled subjects were reviewed.

The inspection reviewed the study protocol and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (including visit data, laboratory tests, AEs and SAEs reports), IP accountability records, paper CRFs with eCRFs entries and the audit trails, the EDC system, protocol deviations and related regulatory documents [e.g., central and local Ethics Committees (EC) approvals and communications, staff trainings, monitoring procedure and logs, records retention, financial disclosures and delegation of authority].

The primary efficacy endpoint of the time from randomization to first occurrence of a CV death, non-fatal MI, or non-fatal stroke were centrally adjudicated. The inspection verified that the site documented submitted accurate dates of these events to the Sponsor's endpoint adjudication system with no discrepancies. There were no underreporting of AEs or SAEs, except that one AE of cardiac arrhythmia was not reported.

There were two discussion items:

- One AE was not reported: Subject # (b) (6) 's (placebo group) AE of cardiac arrhythmia dated on (b) (6) was not reported in the eCRF and was not submitted to the FDA.
- Delayed reporting of SAEs: one was percutaneous coronary intervention for Subject (b) (6) (placebo group). The other one was "strange behavior with dissociative amnesia" for Subject (b) (6) (semaglutide 2.4 mg group)

Reviewer's Comment:
Subject # (b) (6) 's AE of cardiac arrhythmia should have been reported; and all SAEs should be reported to the sponsor within 24 hours after the CI became aware. However, these isolated events may not affect the efficacy or safety evaluation of the submission.

In general, the inspection verified adequate source data for the inspected study subjects, with no significant deficiencies reported.

3. Jesse A. Doran, M.D. (Site #3630)
3407 Wilkens Ave. Suite 300
Baltimore, MD 21229-5222

This CI was inspected on 01/08-11/2024 as a data audit for Study EX9536-4388. This was the first FDA inspection of Dr. Doran. Dr. Doran became the CI on 09/29/2022 when the original CI Dr. Kabir Yousuf left the site.

The study site screened 91 subjects, enrolled 77 subjects, with 74 subjects completed the study. One subject was transferred to another site and 2 subjects dead during the study. The first subject consented on 11/30/2018 and the last subject's last visit was on 06/14/2023. Source records for 26 of 77 (34%) enrolled subjects were reviewed.

The inspection reviewed the study protocol and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (including visit data, laboratory tests, AEs and SAEs reports), IP accountability records, paper CRFs with eCRFs entries, the EDC system, protocol deviations and related regulatory documents (e.g., IRB approvals and communications, staff trainings, monitoring procedure and logs, records retention, financial disclosures and delegation of authority).

The primary efficacy endpoint of the time from randomization to first occurrence of a CV death, non-fatal MI, or non-fatal stroke were centrally adjudicated. The inspection verified that the site documented and submitted accurate dates of these events to the Sponsor's endpoint adjudication system with no discrepancies. The primary efficacy endpoint data were confirmed during the CRO (who did the adjudication) inspection with no discrepancies. There were no underreporting of AEs or SAEs.

In general, the inspection verified adequate source data for the inspected study subjects, with no significant deficiencies reported.

4. (b) (4)

The CRO was inspected on 01/08-11/2024 as a data audit for Study EX9536-4388. This entity was inspected in 12/2021. (b) (4) .

The inspection reviewed the CRO's organizational charts, standard operating procedures (SOPs), adjudicator training, experience, and financial disclosures, contracts/subcontracts and charter, meeting minutes, email correspondence with the sponsor regarding the progress and action of activities per contracts/charter for this study.

The CRO's responsibilities for the inspected study included the Independent DMC and Independent Endpoint Adjudication (IDEA) for adjudication of primary endpoint events and death; central laboratory services to provide supplies and laboratory testing; training and lost to follow up (LTFU) services to the study sites.

The CRO's adjudication activities included establishing, training, and overseeing the event adjudication committee (EAC), preparing, and maintaining documents related to the adjudication process, setting up activities and managing the event adjudication database ((b) (4)) including reports, collecting, preparing event data dossier, and completing data transfers to the sponsor. The inspection reviewed the EAC's responsibilities to ensure that all events and deaths are adjudicated uniformly while blinded to treatment assignment. The EAC's charter, all 21 members/adjudicator's curriculum vitae and qualifications were reviewed together with detailed adjudication process.

In particular, the inspection reviewed adjudication data with AE records, discontinuation,

efficacy endpoints for sites #2216, 2847, 3031 and 3630, and compared the data with the submitted listings with no discrepancies identified.

The inspection also reviewed the CRO's central lab service, training records for study sites.

In general, the inspection verified adequate source data adjudicated by the CRO, with no deficiencies reported.

{See appended electronic signature page}

Ling Yang, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Director, Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.\NDA 215256/S-011
DDLO\Director\John Sharretts
DDLO\CDTL\Laura Higginbotham
DDLO\Reviewer\Julie Golden
DDLO\Project Manager\Martin White
OSI\Director\David Burrow
OSI\Deputy Director\Laurie Muldowney
OSI\DCCE\Division Director\Kassa Ayalew
OSI\DCCE\GCPAB\Branch Chief\Jenn Sellers
OSI\DCCE\GCPAB\Team Leader\Min Lu

OSI\DCCE\GCPAB\Reviewer\Ling Yang
OSI\DCCE\Program Analysts\Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LING YANG
01/31/2024 02:56:40 PM

MIN LU
01/31/2024 02:57:43 PM

JENN W SELLERS
01/31/2024 03:10:22 PM

LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 8, 2023
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 215256/S-011
Product Name, Dosage Form, and Strength:	Wegovy (semaglutide) injection, 0.25 mg/0.5 mL, 0.5 mg/0.5 mL, 1 mg/0.5 mL, 1.7 mg/0.75 mL, 2.4 mg/0.75 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novo Nordisk Inc.
FDA Received Date:	September 08, 2023
OSE RCM #:	2023-6602
DMEPA 1 Safety Evaluator:	Vraj Patel, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 REASON FOR REVIEW

Novo Nordisk Inc. submitted a Efficacy Supplement for Wegovy (semaglutide) injection to update the prescribing information and introduce a new indication (b) (4) Subsequently, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the proposed Wegovy prescribing information (PI) and medication guide for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed Wegovy prescribing information and medication guide did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Wegovy that Novo Nordisk Inc. submitted on September 08, 2023.

Table 2. Relevant Product Information for Wegovy	
Initial Approval Date	June 04, 2021
Active Ingredient	Semaglutide

Indication	• An adjunct to a reduced calorie meal plan and increased physical activity for chronic weight management in:
	  ○ adult patients with an initial body mass index (BMI) of
	  ▪ 30 kg/m2 or greater (obesity) or
	  ▪ 27 kg/m2 or greater (excess weight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).
	  ○ pediatric patients aged 12 years and older with an initial BMI at the 95th percentile or greater for age and sex (obesity)
	• (b) (4)

Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	0.25 mg/0.5 mL, 0.5 mg/0.5 mL, 1 mg/0.5 mL, 1.7 mg/0.75 mL, 2.4 mg/0.75 mL
Dose and Frequency	• Administer WEGOVY once weekly, on the same day each week, at any time of day, with or without meals. • Initiate at 0.25 mg once weekly for 4 weeks. In 4 week intervals, increase the dose until a dose of 2.4 mg is reached. • The maintenance dosage of WEGOVY in adults is 2.4 mg once weekly (recommended) or 1.7 mg once weekly. • The maintenance dosage of WEGOVY in pediatric patients aged 12 years and old is 2.4 mg weekly.
How Supplied	Pre-filled, disposable, single-dose pens

Table 2. Relevant Product Information for Wegovy	
Storage	Store the WEGOVY single-dose pen in the refrigerator from 2°C to 8°C (36°F to 46°F).

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 4, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "NDA 215256". Our search identified 5 previous reviews[a, b, c, d, e] and we considered our previous recommendations to see if they are applicable for this current review.

[a] Conrad, A. Label and Labeling Review for Wegovy (NDA 215256/S-07). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Jun 06. TTT ID No.: 2022-2408.

[b] Conrad, A. Label and Labeling Review for Wegovy (NDA 215256/S-05 and NDA 215256/S-06). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Nov 7. TTT ID No.: 2022-668 and 2022-1094.

[c] Conrad, A. Review of Revised Label and Labeling for Wegovy (NDA 215256/S-003). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Aug 22. RCM No.: 2022-478-1.

[d] Conrad, A. Review of Revised Label and Labeling for Wegovy (NDA 215256/S-003). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Jul 7. RCM No.: 2022-478.

[e] Flint, J. Human Factors Study Report and Label and Labeling Review for semaglutide (NDA 215256). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Mar 15. RCM No.: 2020-2568, 2020-2567.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error experiences with similar products, we reviewed the following Wegovy labels and labeling submitted by Novo Nordisk Inc.

- Medication Guide received on September 08, 2023, available from \\CDSESUB1\EVSPROD\nda215256\0431\m1\us\m1-14-1-3-proposed-wegovy-med-guide-select.pdf
- Prescribing Information (Image not shown) received on September 08, 2023, available from \\CDSESUB1\EVSPROD\nda215256\0431\m1\us\m1-14-1-2-annotated-draft-labeling-text.pdf

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VRAJ K PATEL
12/08/2023 03:51:14 PM

DAMON A BIRKEMEIER
12/08/2023 03:58:46 PM