September 1, 2023

KAREN VAN CAULIL
4401 VINELAND RD
STE A10
ORLANDO, FL 32811

Dear Ms. KAREN VAN CAULIL,

Thank you for your request regarding:

- **Pancreatic Cancer and Wegovy**
- **Pancreatitis and Wegovy**
- **Gastroparesis and Wegovy**

This information is supplied to you as a professional service in response to your specific request. This letter is meant to supplement information you have gathered from other sources and is not intended to promote or advocate the use of Novo Nordisk products in any manner other than described in the Prescribing Information.

Please note, if you are receiving this response by fax, it may contain icons and/or hyperlinks for additional information. This response is available via email upon request.

Prescribing Information for Wegovy® (semaglutide) injection can be accessed via the following link:
Wegovy® Prescribing Information

For prescribing information for other Novo Nordisk products mentioned in this response, please visit:
https://www.scientific-exchange.com

Please find the requested information enclosed.

In order to provide you with a timely response, Novo Nordisk may send you multiple responses as they become available. If you have additional questions, please contact Novo Nordisk Medical Information by calling (800) 727-6500 or visiting https://www.scientific-exchange.com.

Sincerely,
Khaled Abdelrahman, PharmD

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Thank you for your request for information regarding a Novo Nordisk product(s). Please find the information enclosed.

- **Wegovy® is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated 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 (e.g., hypertension, type 2 diabetes, or dyslipidemia).**
  - **Pediatric patients aged 12 years and older with an initial BMI at the 95th percentile or greater for age and sex (obesity).**
- **Prescribing Information Boxed 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)].
- **Some information contained in this letter or enclosed publication(s) may not be consistent with the approved indications and usage for the product. Novo Nordisk does not recommend the use of its products in any manner other than as described in the prescribing information.**
- **Please refer to the prescribing information for important safety information by clicking here: Wegovy® Prescribing Information**
- **The most common adverse reactions, reported in greater than or equal to 5% of adults or pediatric patients aged 12 years and older treated with Wegovy® are: nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia in patients with type 2 diabetes, flatulence, gastroenteritis, and gastroesophageal reflux disease, and nasopharyngitis.**
- **If you believe that your patient has experienced an adverse event while using Novo Nordisk products, please call (800) 727-6500 to report this event.**
- **Some of the references used in this response may refer to other Novo Nordisk Inc. product(s), please access the respective Prescribing Information at https://www.scientific-exchange.com/product-information/novonordisk.html.**
- **Please note that the Novo Nordisk product discussed within this response has the same active molecule as other Novo Nordisk products, which are approved under different brand names, for different indications, dosages and/or formulations. If you would like information on these or other Novo Nordisk products and the safety information about which you are inquiring,**

please do not hesitate to contact us by calling 1-800-727-6500 or visiting https://www.scientific-exchange.com/.

- **If you were unable to find information to address your specific question, please visit us at https://www.scientific-exchange.com/.**

Pancreatic Cancer and Wegovy® (semaglutide) injection

STEP Phase 3 Clinical Development Program

The STEP Phase 3 clinical development program evaluates the safety and efficacy of Wegovy® for weight management in patients with obesity or overweight with at least 1 weight-related comorbidity.[1-7] The STEP Phase 3a program includes STEP 1-4 and TEENS, and the STEP Phase 3b program includes STEP 5 and 8 (**Appendix A**).[1-8]

For all Phase 3 studies of Wegovy®, **patients were not eligible for inclusion if**

- they had a history of malignant neoplasm within 5 years prior to screening[10-13]
- a personal or first-degree relative history of multiple endocrine neoplasia syndrome type 2 or medullary thyroid carcinoma[10-13]

Note, in the adult Phase 3 trials (STEP 1-5 and 8), patients with basal cell and squamous cell skin cancer and any in situ carcinomas were eligible for inclusion.[10-12]

Pancreatic Cancer Events

No pancreatic cancer events were reported during the run-in or in-trial periods of STEP 1-5, 8 and TEENS.[10,11,14]

Pancreatic Cancer and Incretin-Based Therapies

Obesity has been associated with an increased risk of developing pancreatic cancer and other malignancies.[15,16] Conditions frequently comorbid with obesity, including type 2 diabetes, are believed to also increase the risk for pancreatic cancer, and it has been suggested that diabetes may play a role in the causal link between obesity and pancreatic cancer.[16]

A possible association between incretin-based therapies and the development of pancreatic neoplasms has been proposed.[17]

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) independently undertook comprehensive reviews of the pancreatic safety of incretin-based drugs.[18,19] Although they have not reached a final conclusion at this time, both agencies agree that claims in scientific literature and in the media concerning a causal relationship between incretin-based drugs and pancreatic safety concerns are **not** supported by available data. Both agencies continue to monitor the pancreatic safety signal.

There is currently no evidence from nonclinical studies, clinical trials, or postmarketing data demonstrating that semaglutide or other glucagon-like peptide-1 receptor agonists (GLP-1 RAs) increase the risk of pancreatic cancer.[10,18,20] Nonetheless, assessment of pancreatic neoplasms was included as a safety focus area in clinical trials for Wegovy®.

STEP Clinical Development Program

The STEP Phase 3 clinical development program evaluates the safety and efficacy of Wegovy® for weight management in patients with obesity or overweight with at least 1 weight-related comorbidity.[1-7] The STEP Phase 3a program includes STEP 1-4 and TEENS, and the STEP Phase 3b program includes STEP 5 and 8 (**Appendix A**).[1-8]

- STEP 1-4, 8 and TEENS consisted of a 68-week on-treatment period followed by a 7-week off-treatment follow-up period.[1-4,6,7] In STEP 4, all enrolled patients received Wegovy® during a 20-week run-in period, and patients who were able to achieve and maintain a target dose of Wegovy® 2.4 mg during the run-in period were randomized at Week 20 to either continue Wegovy® or to switch to placebo for a 48-week period. STEP 5 consisted of a 104-week on-treatment period followed by a 7-week off-treatment follow-up period.[9]
- For all Phase 3 trials of Wegovy®, patients were not eligible for inclusion if they had a history of malignant neoplasm within 5 years prior to screening or personal or first-degree relative history of multiple endocrine neoplasia syndrome type 2 (MEN 2) or medullary thyroid carcinoma (MTC).[10-13]
    - Note, in the adult Phase 3 trials (STEP 1-5 and 8), patients with basal cell and squamous cell skin cancer and any in situ carcinomas were eligible for inclusion.[10-12]

Pancreatic Cancer
No pancreatic cancer events were reported during the run-in or in-trial periods of STEP 1-5, 8 and TEENS.[10,11,14]

Postmarketing Experience

Wegovy® was approved by the Food and Drug Administration (FDA) on June 4, 2021. In the postmarketing (spontaneous) surveillance reports received by Novo Nordisk in 2022 for Wegovy®, pancreatic cancer was not a reported event. Because these adverse events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. Additionally, since postmarketing safety reports often lack important clinical information, it is difficult to determine a cause-effect relationship between Wegovy® and pancreatic cancer.

Background Information on Pancreatic Cancer and Incretin-Based Therapies

Obesity has been associated with an increased risk of developing pancreatic cancer and other malignancies.[15,16] Conditions frequently comorbid with obesity, including type 2 diabetes (T2D), are believed to also increase the risk for pancreatic cancer, and it has been suggested that T2D may play a role in the causal link between obesity and pancreatic cancer.[16] A possible association between incretin-based therapies and the development of pancreatic neoplasms has been proposed.[17]

The FDA and the European Medicines Agency (EMA) independently undertook comprehensive reviews of the pancreatic safety of incretin-based drugs.[18,19] Although they have not reached a final conclusion at this time, both agencies agree that claims in scientific literature and in the media concerning a causal

relationship between incretin-based drugs and pancreatic safety concerns are **not** supported by available data. Both agencies continue to monitor the pancreatic safety signal.

There is currently no evidence from nonclinical studies, clinical trials or postmarketing data demonstrating that semaglutide or other glucagon-like peptide-1 (GLP-1) receptor agonists increase the risk of pancreatic cancer.[10,18,20] Nonetheless, assessment of pancreatic neoplasms was included as a safety focus area in clinical trials for Wegovy®.

Appendix A

Overview of the STEP Phase 3 Clinical Development Program of Wegovy®[1-8]

The **S**emaglutide **T**reatment **E**ffect in **P**eople with Obesity (STEP) Phase 3 clinical development program evaluates the safety and efficacy of Wegovy®, administered subcutaneously once weekly for weight management in patients with obesity or overweight with at least one weight-related comorbidity.[1-7] The global STEP Phase 3a program includes five randomized, double-blind, parallel-group, multicenter clinical trials (STEP 1-4 and STEP TEENS), while the Phase 3b program includes STEP 5 (long-term weight management) and STEP 8 (versus Saxenda® [liraglutide] injection).[1-8] The studies are briefly described below.

Table A.1. STEP Phase 3 Clinical Development Program[1-8]

	Phase 3a Studies					Phase 3b Studies	
	STEP 1	**STEP 2**	**STEP 3**	**STEP 4**	**STEP TEENS[i]**	**STEP 5**	**STEP 8**
Randomized Patients (N)	1961	1210	611	803[a]	201	304	338
Patient Population	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but without diabetes	Adults with BMI ≥27 kg/m² and T2D (A1C 7%-10%) diagnosed ≥180 days before screening	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but without diabetes	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but without diabetes	Adolescents (age 12 to <18 years) with a BMI ≥95th percentile or ≥85th percentile (based on sex and age specific growth charts) with ≥1 weight-related comorbidity[b]	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but without diabetes	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but without diabetes
Duration (weeks)[c]	68	68	68	68	68	104	68
Randomization	2:1	1:1:1	2:1	2:1	2:1	1:1	3:1:3:1[g]
Comparator	Placebo	Placebo, Ozempic®[d] 1 mg	Placebo	Placebo	Placebo	Placebo	Saxenda®[h], Placebo
Background Treatment	Diet and exercise[f]	Diet and exercise[f] and 0-3 OADs[e]	IBT[f]	Diet and exercise[f]	Nutrition and physical activity counseling[f]	Diet and exercise[f]	Diet and exercise[f]

a. All enrolled patients (n=902) received Wegovy® during the trial's 20-week run-in period (including 16 weeks of dose escalation). Patients who were able to achieve and maintain a target dose of Wegovy® 2.4 mg during the run-in period (n=803) were randomized to either continue Wegovy® or switch to placebo.
b. Weight-related comorbidities: hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. In STEP TEENS, comorbidities included hypertension, dyslipidemia, obstructive sleep apnea or T2D.[13]
c. Each study had a 7-week off-treatment follow-up period.
d. Ozempic® (semaglutide) injection 1 mg
e. Treatment with up to 3 of the following OADs for at least 90 days prior to screening were allowed: MET, SU, SGLT2i, or TZD.
f. In STEP 1, 2, 4, 5 and 8, diet and exercise consisted of a 500 kcal/day deficit and at least 150 min/week of physical activity. In STEP TEENS, patients received individualized counseling with the goal of achieving weight loss and to encourage a goal of 60 min/day of moderate-to-high intensity physical activity. In STEP 3, IBT consisted of a low-calorie diet (1000-1200 kcal/day) in the form of meal replacements for the first 8 weeks after randomization. Patients then transitioned to a hypocaloric diet (1200-1800 kcal/day, depending on body weight) for the remainder of the 68 weeks. Prescribed physical activity began at 100 min per week (spread across 4-5 days) and was increased by 25 min every 4 weeks to reach 200 min per week. Patients received 30 individual IBT visits with a registered dietitian, who provided counseling related to diet, physical activity and behavior.
g. Patients were randomized 3:1:3:1 to Wegovy® (N=126) or matching placebo, or Saxenda® (N=127) or matching placebo (pooled placebo [N=85]).
h. Saxenda® (liraglutide) injection 3 mg
i. In STEP TEENS, after screening, a 12-week lifestyle intervention run-in period preceded randomization per regulatory guidelines. At randomization, Wegovy® was initiated at 0.25 mg and escalated to 2.4 mg (or maximum tolerated dose) over 16 weeks.
Abbreviations: A1C: glycosylated hemoglobin; BMI: body mass index; IBT: intensive behavioral therapy; MET: metformin; min: minutes; OAD: oral antidiabetic drugs; SGLT2i: sodium-glucose cotransporter-2 inhibitor; SU: sulfonylurea; T2D: type 2 diabetes; TZD: thiazolidinedione.

The STEP Phase 3a clinical development program also includes STEP 6 (East Asian trial), STEP 7 (multi-regional clinical trial including ≥1 East Asian country), STEP HFpEF (heart failure with preserved ejection fraction) and STEP HFpEF-DM (heart failure with preserved ejection fraction and T2D). The STEP Phase 3b program also includes STEP 9 (knee osteoarthritis), STEP 10 (prediabetes), STEP 11 (weight management in Asian patients with BMI ≥25 kg/m²) and SELECT (cardiovascular outcomes trial). For more information, please visit clinicaltrials.gov.

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Pancreatitis with Wegovy® (semaglutide) injection

Prescribing Information

Wegovy® **has not been studied in patients with a history of pancreatitis.**[1]

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 initiated. If acute pancreatitis is confirmed, Wegovy® should not be restarted.[1]

Predisposing Etiological Factors

Several well-established, predisposing etiological factors exist for pancreatitis, such as history of alcohol abuse, biliary tract disease or gallstones, hypertriglyceridemia, abdominal surgery, family history of pancreatitis, recent abdominal trauma, and recent, rapid weight loss.[15, 16]

Pancreatitis in the STEP Phase 3 Trials

The STEP Phase 3 clinical development program evaluates the safety and efficacy of Wegovy®, administered subcutaneously once weekly for weight management in patients with obesity or overweight with at least one weight-related comorbidity (**Appendix A**).[2-9] The Phase 3a program includes STEP 1-4 and STEP TEENS, while the Phase 3b program includes STEP 5 and 8.

Adverse Events (AEs) and Serious Adverse Events (SAEs) of Pancreatitis

In the adult Phase 3a pool (n=2650 for Wegovy®; n=1529 for placebo), which included patients from the randomized periods of STEP 1-4 (omitting the 20-week run-in period in STEP 4):[a]

Pancreatitis was reported as an AE in **3 (0.1%) Wegovy®-treated patients** vs **1 (<0.1%) placebo-treated patient.**[10]

Pancreatitis was reported as a SAE in **2 (<0.1%) Wegovy®-treated patients** vs **1 (<0.1%) placebo-treated patient (Table 1).**[10]

No AEs of acute pancreatitis were reported with Wegovy® or placebo-treated patients in STEP 5, 8 or STEP TEENS.[6,8]

[a]. A serious adverse event (SAE) is defined as an adverse event (AE) that fulfils at least one of the following: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, is a congenital anomaly/birth defect or is an important medical event.

Event Adjudication Committee (EAC)-Confirmed Events

Reported cases of acute pancreatitis were evaluated by an independent, blinded, external event adjudication committee (EAC) in STEP 1-4 and 5. In the adult Phase 3a pool, there were **5 EAC-confirmed events in 4 patients with Wegovy® and 1 EAC confirmed event with placebo** (Table 2).[10]
See **Appendix B** for details of the cases.

No events were submitted for adjudication in STEP 5.[11]

Amylase and Lipase

In the adult Phase 3a pool derived from STEP 1-3, patients exposed to Wegovy® had a **mean increase in amylase and lipase levels of 16% and 39%, respectively, from baseline to Week 68.** These changes were not observed in placebo-treated patients (Table 3).[10]

In STEP 4, during the run-in period (Week 0 to Week 20), **lipase and amylase increased**, although the increase in amylase in patients randomized to placebo at Week 20 was lower than in the patients randomized to Wegovy®.[12]

Elevations in mean serum lipase and amylase with Wegovy® **were not predictive of the later development of pancreatitis** (in the absence of other signs or symptoms of pancreatitis).[10]

In **STEP TEENS, geometric mean values of lipase and amylase remained within the normal reference range** throughout the on-treatment period.[13]

In **STEP 5, the geometric mean values of amylase and lipase remained within the normal reference range** throughout the on-treatment period.[11]

In **STEP 8, mean levels of lipase had increased by 45% and amylase by 12% in the Wegovy® group at Week 68;** lower increases were observed for Saxenda®, whereas mean levels were stable in the placebo arm.[14]

Medical Information Response

Pancreatitis and Wegovy® (semaglutide) injection

Summary

- Wegovy® has not been studied in patients with a history of pancreatitis.[1]
- 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.[1]

Reports of Pancreatitis in the STEP Clinical Trial Program

- The **S**emaglutide **T**reatment **E**ffect in **P**eople with Obesity (STEP) Phase 3 clinical development program evaluates the safety and efficacy of Wegovy® for weight management in patients with obesity or overweight with at least one weight-related comorbidity (**Appendix A**).[2-9] The global STEP Phase 3a program includes STEP 1-4 and STEP TEENS, while the Phase 3b program includes STEP 5 and 8.
- In the adult Phase 3a pool (n=2650 for Wegovy®; n=1529 for placebo), which included patients from the randomized periods of STEP 1-4 (omitting the 20-week run-in period in STEP 4), pancreatitis was reported as an adverse event (AE) in 3 (0.1%) Wegovy®-treated patients vs 1 (<0.1%) placebo-treated patient (**Table 1**).[10] No AEs of acute pancreatitis were reported in Wegovy® or placebo-treated patients in STEP 5, 8 or STEP TEENS.[6-8]
- Reported cases of acute pancreatitis were evaluated by an independent, blinded, external event adjudication committee (EAC) in STEP 1-4 and 5. In the adult Phase 3a pool, there were 5 EAC-confirmed events in 4 patients with Wegovy® and 1 EAC-confirmed event with placebo (**Table 2**).[10] See **Appendix B** for details of the cases. No events were submitted for adjudication in STEP 5.[11]

Amylase and Lipase

- In the adult Phase 3a pool derived from STEP 1-3, patients exposed to Wegovy® had a mean increase in amylase and lipase levels of 16% and 39%, respectively, from baseline to Week 68. These changes were not observed in placebo-treated patients (**Table 3**).[10]
- In STEP 4, during the run-in period (Week 0 to Week 20), lipase and amylase increased, although the increase in amylase in patients randomized to placebo at Week 20 was lower than in the patients randomized to Wegovy®.[12]
    - Elevations in mean serum lipase and amylase with Wegovy® were not predictive of the later development of pancreatitis (in the absence of other signs or symptoms of pancreatitis).[10]
- In STEP TEENS, the geometric mean values of lipase and amylase remained within the normal reference range throughout the on-treatment period.[13]
- In STEP 5, the geometric mean values of amylase and lipase remained within the normal reference range throughout the on-treatment period.[11] In STEP 8, mean levels of lipase had increased by 45% and amylase by 12% in the Wegovy® group at Week 68; lower increases were observed for Saxenda® (liraglutide) injection, whereas mean levels were stable in the placebo arm.[14]

- In the postmarketing (spontaneous) surveillance reports received by Novo Nordisk for Wegovy®, pancreatitis was reported. Because these adverse events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency.

Prescribing Information

Section 1: Indications and Usage, Limitations of Use[1]

Wegovy® has not been studied in patients with a history of pancreatitis.

Section 5.2: Warnings and Precautions, Acute Pancreatitis[1]

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with glucagon-like peptide-1 receptor agonists (GLP-1 RAs), including semaglutide. Acute pancreatitis was observed in patients treated with Wegovy® in clinical trials. 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.

Wegovy® has not been studied 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®.

Section 6.1: Adverse Reactions. Clinical Trial Experience[1]

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.

Wegovy® was evaluated for safety in 3 randomized, double-blind, placebo-controlled trials (STEP 1-3) that included 2116 patients with overweight or obesity treated with Wegovy® for up to 68 weeks and a 7 week off-drug follow-up period. Baseline characteristics included a mean age of 48 years, 71% women, 72% White, 42% with hypertension, 19% with type 2 diabetes (T2D), 43% with dyslipidemia, 28% with a BMI greater than 40 kg/m^2, and 4% with cardiovascular disease.

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. 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 237.0 lbs and mean BMI was 37 kg/m^2.

Acute Pancreatitis

In Wegovy® clinical trials in adults (STEP 1-3), acute pancreatitis was confirmed by adjudication in 4 Wegovy®-treated patients (0.2 cases per 100 patient years) vs 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 (STEP 4).

Laboratory Abnormalities
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.

Pancreatitis Background

Risk Factors for Pancreatitis
Several well-established, predisposing etiological factors exist for pancreatitis, such as history of alcohol abuse, biliary tract disease or gallstones, hypertriglyceridemia, abdominal surgery, family history of pancreatitis, recent abdominal trauma, and recent, rapid weight loss.[15,16] Many of the risk factors for acute pancreatitis are also commonly associated with T2D and obesity.[16] Obesity also increases the risk for severe acute pancreatitis 2.9 fold and the risk for mortality from acute pancreatitis by 2.1 fold.[17]

Incretin-Based Treatments and Pancreatitis
The use of incretin-based drugs has been associated with the risk of developing acute pancreatitis. Following post-marketing reports of pancreatitis with GLP-1 RAs and dipeptidyl peptidase-4 (DPP-4) inhibitors, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) independently investigated non-clinical and clinical data to evaluate the pancreatic safety of incretin-based drugs in patients with type 2 diabetes.[18] They concluded that although data do not support a causal association between incretin-based drugs and pancreatitis, both FDA and EMA continue to regard pancreatitis as a risk with these therapies, until more data have been collected.[18] All GLP-1 RAs and DPP-4 inhibitors currently carry label warnings concerning pancreatitis.[19]

Meta-analyses based on the cardiovascular outcomes trials (CVOTs) for GLP-1 RAs and DPP-4 inhibitors have been conducted to assess the risk for acute pancreatitis and are cited for reference.[20,21]

Pancreatitis in the STEP Trials

The **S**emaglutide **T**reatment **E**ffect in **P**eople with Obesity (STEP) Phase 3 clinical development program evaluates the safety and efficacy of Wegovy® for weight management in patients with obesity or overweight with at least one weight-related comorbidity (**Appendix A**).[2-9] The global STEP Phase 3a program includes STEP 1-4 and STEP TEENS, while the Phase 3b program includes STEP 5 and STEP 8.

Adult patients with acute pancreatitis within 180 days prior to screening or with a history or presence of chronic pancreatitis were excluded from the STEP trials.[2,11,22-25]

- Adult patients with a history of acute pancreatitis greater than 180 days before screening may have been randomized into the trials. At this time, no subgroup analyses evaluating the safety and efficacy of Wegovy® in this subpopulation have been conducted.

Pediatric patients with a history or presence of pancreatitis (acute or chronic) were excluded from the STEP TEENS trial.[26]

Pancreatitis AEs
All investigator-reported AEs and serious AEs (SAEs) of pancreatitis are summarized in **Table 1** for STEP 1-4, 5 and 8. Few events of pancreatitis were reported, with similar incidences between the Wegovy® and

placebo groups in the Phase 3a pool (STEP 1-4).[10] No AEs of acute pancreatitis were reported with Wegovy® in STEP 5 or STEP 8.[6,7]

In the STEP trials, a diagnosis of acute pancreatitis required 2 of the following 3 criteria[10,11,13,14]:

- Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
- Serum lipase activity (and/or amylase activity) at least 3x greater than the upper limit of normal (ULN)
- Characteristic findings of acute pancreatitis on imaging

Table 1. Investigator-Reported Pancreatitis AEs in STEP 1-4, STEP TEENS, STEP 5 and 8[6-8,10]

Phase 3a Pool (STEP 1-4)[a]	**Wegovy®**	**-**	**Placebo**
Total number of patients	N=2650	-	N=1529
AEs, n (adj. %)[b]	3 (0.1)	-	1 (<0.1)
SAEs, n (adj. %)[b]	2 (<0.1)	-	1 (<0.1)
STEP TEENS[c]	**Wegovy®**	**-**	**Placebo**
Total number of patients	N=133	-	N=67
AEs, n (%)	0	-	0
STEP 5[c]	**Wegovy®**	**-**	**Placebo**
Total number of patients	N=152	-	N=152
AEs, n (%)	0	-	0
STEP 8[c]	**Wegovy®**	**Saxenda®[d]**	**Placebo**
Total number of patients	N=126	N=127	N=85
AEs, n (%)	0	1 (0.8)	0

a. The Phase 3a pool included patients from the randomized periods of STEP 1-4 (omitting the 20-week run-in period in STEP 4).
b. The % is adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials.
c. Patients from the randomized periods are included.
d. Saxenda® (liraglutide) injection
Abbreviations: adj.: adjusted; AEs: adverse events; SAEs: serious adverse events; n: number of patients experiencing at least one event; N: number of patients.

EAC-Confirmed Acute Pancreatitis

Event adjudication was performed for the events of acute pancreatitis, evaluated by an independent external EAC according to the predefined criteria and guidelines in STEP 1-4 and 5. Events for adjudication were identified by one of three paths:[11,12,27-29]

- Investigator: direct reporting of event relevant for adjudication
- Preferred Term (PT) search: screening among all investigator reported AEs for any that met the pre-defined criteria that were not identified for adjudication by the investigator
- EAC: review of source documentation for another event for adjudication leading to identification of a new event in scope for adjudication that was not initially reported by the investigator

Across the Phase 3a STEP trials in adult patients (STEP 1-4), the few EAC-confirmed events of acute pancreatitis suggest that Wegovy® does not increase the risk of acute pancreatitis compared with placebo (**Table 2**).[10] See **Appendix B** for details of the cases. No events of acute pancreatitis were submitted for adjudication in STEP 5.[11]

Table 2. EAC-Confirmed Acute Pancreatitis in the On-Treatment Period of STEP 1-4[10]

	Wegovy®	Placebo
Phase 3a Pool (STEP 1-4)[a]	**n=2650**	**n=1529**
EAC-confirmed acute pancreatitis, n (%)[b]	4 (0.2)	1 (<0.1)
Moderately severe	1 (<0.1)	0
Mild	3 (0.1)	1 (<0.1)
STEP 4 Run-in Period	**n=902**	-
EAC-confirmed acute pancreatitis, n (%)	1 (<0.1)	-
Moderately severe	1 (<0.1)	-

a. The Phase 3a pool included patients from the randomized periods of STEP 1-4 (omitting the 20-week run-in period in STEP 4).
b. There were 5 EAC-confirmed events in 4 patients.
Abbreviations: EAC: Event Adjudication Committee; n: number of patients.

Pancreatic Enzyme Elevations in the STEP Trials

Similar to that described with other GLP-1 RA therapies, mean serum amylase and lipase activities increased with Wegovy® treatment.[10] For the Phase 3a Pool derived from STEP 1-3, the increase in lipase levels occurred during the initial 20 weeks of the clinical trials and then decreased slightly by Week 68 with Wegovy®. Amylase levels gradually increased during the trial with Wegovy®.[10] Please see **Table 3** for more information.

In the adult Phase 3a Pool derived from STEP 1-3, at Week 68, patients exposed to Wegovy® had a mean increase from baseline in amylase and lipase levels of 16% and 39%, respectively. These changes were not observed in placebo-treated patients.[10] The proportion of patients with elevated lipase levels >3x ULN at any time post-baseline was higher with Wegovy® compared with placebo in the Phase 3a trials (1.2% vs 0.8%). One Wegovy®-treated patients in STEP 3 had amylase >3x ULN at any time post-baselne.[10]

In STEP 4, during the run-in period (Week 0 to Week 20), lipase increased and amylase appeared to increase slightly although the increase in amylase in patients randomized to placebo at Week 20 was lower than in the patients randomized to Wegovy® at Week 20 (**Table 3**).[12] During the randomized period (Week 20-Week 68), lipase appeared to remain stable in the Wegovy® arm, while in the placebo arm, lipase levels decreased to approximately the level at Week 0. During this time, amylase appeared to slightly increase in the Wegovy® arm, while remaining stable in the placebo arm.[12]

In STEP TEENS, although there were greater increases from baseline in lipase and amylase levels observed in Wegovy®-treated patients vs placebo treated patients, the geometric mean values of lipase and amylase remained within the normal reference range throughout the on-treatment period (**Table 3**).[13]

In STEP 5, although there were increases from baseline in amylase and lipase in the Wegovy® arm compared to the placebo arm, the geometric mean values of amylase and lipase remained within the normal reference range throughout the on-treatment period (**Table 3**).[11] In STEP 8, at Week 68, mean levels of lipase had increased by 45% and amylase by 12% in the Wegovy® group; lower increases were observed for Saxenda®, whereas mean levels were stable in the placebo group.[14]

Elevations in mean serum lipase and amylase with Wegovy® were not predictive of the later development of pancreatitis (in the absence of other signs or symptoms of pancreatitis).[10]

Monitoring

Currently no guidelines recommend routine monitoring of serum amylase and lipase levels to diagnose asymptomatic pancreatitis in patients taking GLP-1 RAs. However, regulatory authorities have requested pharmaceutical companies routinely monitor pancreatic enzymes (amylase and lipase) in clinical trials as potential biomarkers for pancreatitis.

A significant limitation of serum amylase is its low specificity.[30] Besides acute pancreatitis, other conditions, including diabetic ketoacidosis and pregnancy, can increase serum amylase levels with or without abdominal pain. The conditions associated with elevation of amylase levels include malignancy of the breast, colon, lung and ovary, liver and renal failure, as well as chronic alcoholism.[31] Drug-induced increases in amylase have been associated with sulfonamides, tetracycline, estrogens, furosemide, salicylate, and calcium.[30]

Although the specificity of lipase levels may be slightly better than amylase, elevations in serum lipase are not specific to acute pancreatitis. Similar to amylase, changes in lipase levels may occur without abdominal pain including malignancy of the duodenum, esophagus, liver, tongue and stomach, as well as esophagitis, liver failure, and renal failure.[31] The decision to discontinue Wegovy® based on elevated amylase or lipase levels alone is at the discretion of the prescriber.

Table 3. Amylase and Lipase in the STEP Trials – On-Treatment[a,10-14]

Phase 3a Pool Derived from STEP 1-3[b]	**Wegovy®**	**-**	**Placebo**
Total number of patients	N=2116	-	N=1261
Amylase			
Baseline, U/L Geometric mean (CV)	49 (38.1)	-	49 (39.5)
Ratio to baseline (CV) at Week 68	1.16 (22.9)	-	1.04 (22.3)
Lipase			
Baseline, U/L Geometric mean (CV)	26 (57.6)	-	28 (62.9)
Ratio to baseline (CV) at Week 68	1.39 (51.5)	-	0.97 (43.0)

a. Observed data from on-treatment period. A timepoint is considered on-treatment if any dose of trial product has been administered within the prior 14 days.

b. This Phase 3a Pool is derived from patients randomized to Wegovy® or placebo during the controlled periods of STEP 1-3.

c. All enrolled patients (n=902) received Wegovy® during the trial's 20-week run-in period (including 16 weeks of dose escalation). Patients who were able to achieve and maintain a target dose of Wegovy® 2.4 mg during the run-in period (n=803) were randomized to either continue Wegovy® or switch to placebo.

Abbreviations: CV: coefficient of variation in percent; N: number of patients.

Table 3. Amylase and Lipase in the STEP Trials – On-Treatment Continued[a,10-14]

STEP 4[c]	**Wegovy®**	**-**	**Placebo**
Amylase			
Baseline, U/L Geometric mean (CV)	49 (37.7) (N=803)	-	-
Week 20, U/L Geometric mean (CV)	51 (39.0) (N=535)	-	51 (38.9) (N=268)
Ratio Week 20 vs Week 0 (CV)	1.06 (18.7)	-	1.02 (26.2)
Ratio Week 68 vs Week 20 (CV)	1.06 (19.9)	-	1.00 (24.9)
Lipase			
Baseline, U/L Geometric mean (CV)	26 (54.1) (N=803)	-	-
Week 20, U/L Geometric mean (CV)	37 (55.8) (N=535)	-	36 (56.7) (N=268)
Ratio Week 20 vs Week 0 (CV)	1.44 (40.2)	-	1.39 (53.5)
Ratio Week 68 vs Week 20 (CV)	0.94 (37.8)	-	0.68 (51.7)
STEP TEENS	**Wegovy®**	**-**	**Placebo**
Total number of patients	N=133	-	N=67
Amylase			
Baseline, U/L Geometric mean (CV)	46 (35.9)	-	44 (38.5)
Ratio to baseline (CV) at Week 68	1.15 (17.4)	-	1.04 (18.2)
Lipase			
Baseline, U/L Geometric mean (CV)	18 (43.2)	-	18 (52.7)
Ratio to baseline (CV) at Week 68	1.39 (37.3)	-	1.12 (37.0)
STEP 5	**Wegovy®**	**-**	**Placebo**
Total number of patients	N=152	-	N=152
Amylase			
Baseline, U/L Geometric mean (CV)	50 (39.7)	-	52 (33.9)
Ratio to baseline (CV) at Week 104	1.13 (20.7)	-	1.02 (15.1)
Lipase			
Baseline, U/L Geometric mean (CV)	22 (54.4)	-	23 (51.3)
Ratio to baseline (CV) at Week 104	1.47 (52.3)	-	1.00 (34.4)
STEP 8	**Wegovy®**	**Saxenda®**	**Placebo**
Total number of patients	N=126	N=127	N=85
Amylase			
Baseline, U/L Geometric mean (CV)	54 (36.9)	53 (43.3)	50 (42.0)
Ratio to baseline (CV) at Week 68	1.12 (24.4)	1.09 (27.4)	1.02 (15.9)
Lipase			
Baseline, U/L Geometric mean (CV)	26 (56.6)	26 (59.4)	25 (50.8)
Ratio to baseline (CV) at Week 68	1.45 (47.6)	1.26 (58.5)	0.92 (39.7)

a. Observed data from on-treatment period. A timepoint is considered on-treatment if any dose of trial product has been administered within the prior 14 days.

b. This Phase 3a Pool is derived from patients randomized to Wegovy® or placebo during the controlled periods of STEP 1-3.

c. All enrolled patients (n=902) received Wegovy® during the trial's 20-week run-in period (including 16 weeks of dose escalation). Patients who were able to achieve and maintain a target dose of Wegovy® 2.4 mg during the run-in period (n=803) were randomized to either continue Wegovy® or switch to placebo.

Abbreviations: CV: coefficient of variation in percent; N: number of patients.

Appendix A

Overview of the STEP Phase 3 Clinical Development Program of Wegovy®[2-9]

The **S**emaglutide **T**reatment **E**ffect in **P**eople with Obesity (STEP) Phase 3 clinical development program evaluates the safety and efficacy of Wegovy®, administered subcutaneously once weekly for weight management in patients with obesity or overweight with at least one weight-related comorbidity.[2-8] The global STEP Phase 3a program includes five randomized, double-blind, parallel-group, multicenter clinical trials (STEP 1-4 and STEP TEENS), while the Phase 3b program includes STEP 5 (long-term weight management) and STEP 8 (versus Saxenda® [liraglutide] injection).[2-9] The studies are briefly described below.

Table A.1. STEP Phase 3 Clinical Development Program[2-9]

	Phase 3a Studies					Phase 3b Studies	
	STEP 1	**STEP 2**	**STEP 3**	**STEP 4**	**STEP TEENS[i]**	**STEP 5**	**STEP 8**
Randomized Patients (N)	1961	1210	611	803[a]	201	304	338
Patient Population	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but without diabetes	Adults with BMI ≥27 kg/m² and T2D (A1C 7%-10%) diagnosed ≥180 days before screening	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but without diabetes	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but without diabetes	Adolescents (age 12 to <18 years) with a BMI ≥95th percentile or ≥85th percentile (based on sex and age specific growth charts) with ≥1 weight-related comorbidity[b]	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but without diabetes	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but without diabetes
Duration (weeks)[c]	68	68	68	68	68	104	68
Randomization	2:1	1:1:1	2:1	2:1	2:1	1:1	3:1:3:1[g]
Comparator	Placebo	Placebo, Ozempic®[d] 1 mg	Placebo	Placebo	Placebo	Placebo	Saxenda®[h], Placebo
Background Treatment	Diet and exercise[f]	Diet and exercise[f] and 0-3 OADs[e]	IBT[f]	Diet and exercise[f]	Nutrition and physical activity counseling[f]	Diet and exercise[f]	Diet and exercise[f]

a. All enrolled patients (n=902) received Wegovy® during the trial's 20-week run-in period (including 16 weeks of dose escalation). Patients who were able to achieve and maintain a target dose of Wegovy® 2.4 mg during the run-in period (n=803) were randomized to either continue Wegovy® or switch to placebo.
b. Weight-related comorbidities: hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. In STEP TEENS, comorbidities included hypertension, dyslipidemia, obstructive sleep apnea or T2D.[26]
c. Each study had a 7-week off-treatment follow-up period.
d. Ozempic® (semaglutide) injection 1 mg
e. Treatment with up to 3 of the following OADs for at least 90 days prior to screening were allowed: MET, SU, SGLT2i, or TZD.
f. In STEP 1, 2, 4, 5 and 8, diet and exercise consisted of a 500 kcal/day deficit and at least 150 min/week of physical activity. In STEP TEENS, patients received individualized counseling with the goal of achieving weight loss and to encourage a goal of 60 min/day of moderate-to-high intensity physical activity. In STEP 3, IBT consisted of a low-calorie diet (1000-1200 kcal/day) in the form of meal replacements for the first 8 weeks after randomization. Patients then transitioned to a hypocaloric diet (1200-1800 kcal/day, depending on body weight) for the remainder of the 68 weeks. Prescribed physical activity began at 100 min per week (spread across 4-5 days) and was increased by 25 min every 4 weeks to reach 200 min per week. Patients received 30 individual IBT visits with a registered dietitian, who provided counseling related to diet, physical activity and behavior.
g. Patients were randomized 3:1:3:1 to Wegovy® (N=126) or matching placebo, or Saxenda® (N=127) or matching placebo (pooled placebo [N=85]).
h. Saxenda® (liraglutide) injection 3 mg
i. In STEP TEENS, after screening, a 12-week lifestyle intervention run-in period preceded randomization per regulatory guidelines. At randomization, Wegovy® was initiated at 0.25 mg and escalated to 2.4 mg (or maximum tolerated dose) over 16 weeks.
Abbreviations: A1C: glycosylated hemoglobin; BMI: body mass index; IBT: intensive behavioral therapy; MET: metformin; min: minutes; OAD: oral antidiabetic drugs; SGLT2i: sodium-glucose cotransporter-2 inhibitor; SU: sulfonylurea; T2D: type 2 diabetes; TZD: thiazolidinedione.

The STEP Phase 3a clinical development program also includes STEP 6 (East Asian trial), STEP 7 (multi-regional clinical trial including ≥1 East Asian country), STEP HFpEF (heart failure with preserved ejection fraction) and STEP HFpEF-DM (heart failure with preserved ejection fraction and T2D). The STEP Phase 3b program also includes STEP 9 (knee osteoarthritis), STEP 10 (prediabetes), STEP 11 (weight management in Asian patients with BMI ≥25 kg/m²) and SELECT (cardiovascular outcomes trial). For more information, please visit clinicaltrials.gov.

Appendix B

Table B.1. Details of EAC-Confirmed Acute Pancreatitis in Phase 3a Clinical Trials (STEP 1-4)[10,12]

Trial	Treatment	Latency (days)	Seriousness	Severity	Action	Outcome	Was treatment a likely cause?	Amylase level	Lipase level	Additional details
STEP 1	Wegovy®	260	Serious	Severe	Permanent discontinuation	Recovered	Probable	N/A	Elevated	• Imaging results consistent with gallstones and not acute pancreatitis • Subject later diagnosed with cholecystitis and had a cholecystectomy
	Wegovy®	232	Serious	Moderate	Permanent discontinuation	Recovered	Possible	Elevated	Elevated	• No findings on imaging • Medical history of acute pancreatitis and alcohol consumption
	Wegovy®	508	Serious	Mild	Not applicable[a]	Recovered	Unlikely	Elevated	Elevated	• Imaging results consistent with gallstones and not acute pancreatitis • Subject had rapid weight loss
STEP 2	Wegovy®	87	Non-serious	Moderate	Permanent discontinuation	Recovered with sequelae	Probable	Elevated	Elevated	• Imaging results not available at time of investigator-reported events • Imaging results available at day 140 due to an SAE of chronic pancreatitis • Additional non-serious pancreatic event was reported by the investigator at day 225 (after the on-treatment period) as pancreatic necrosis but was not confirmed by EAC because the imaging showed chronic pancreatitis • No confounding factors reported
	Wegovy®	84	Non-serious	Mild	Not applicable	Not recovered	Probable	Elevated	Elevated	
	Placebo	253	Serious	Moderate	Dose not changed	Recovered	Unlikely	Elevated	Elevated	• Event was co-reported with acute cholecystitis, cholelithiasis, and liver cirrhosis
STEP 4	Wegovy®	N/A	Non-serious	Moderate	Permanent discontinuation	Recovered	Probable	N/A	Elevated	• Event occurred during run-in period • Event was confirmed by EAC based on symptoms and elevated lipase • Event resolved after 25 days

a. The event onset occurred during the 7-week follow-up period, after the last dose of trial product.
Abbreviations: EAC: event adjudication committee; SAE: serious adverse events; N/A: not available.

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Medical Information Response

Gastroparesis and Wegovy® (semaglutide) injection

Summary

- Gastroparesis events (including impaired gastric emptying and gastrointestinal [GI] motility disorder) were not frequently reported adverse events in the STEP clinical trials; and therefore, are not listed as commonly reported adverse events in the Wegovy® Prescribing Information.[1-5]
- The most common adverse reactions, reported in ≥5% of adults or pediatric patients aged 12 years and older treated with Wegovy®, include those that are GI in nature: nausea, diarrhea, vomiting, constipation, abdominal pain, dyspepsia, abdominal distension, eructation, flatulence, gastroenteritis, and gastroesophageal reflux disease.[1]
    - It is important to note that the Prescribing Information presents adverse reactions derived from a STEP Phase 3a pool, which consists of STEP 1-3 and STEP TEENS, but not STEP 4, in which dose escalation occurred prior to randomization (**Appendix A**).[1]
- There is no contraindication precluding the use of Wegovy® in patients with gastroparesis.[1]
- Wegovy® has not been specifically studied in patients with pre-existing gastroparesis. However, Wegovy® causes a delay of gastric emptying.[1] Decisions about the prescribing of Novo Nordisk products should be made based on the clinical judgment of the treating healthcare provider and an assessment of the benefits versus risks of therapy in the specific patient.
- A medical history of gastroparesis was not a specific exclusion criterion in the Wegovy® STEP clinical trial program (**Appendix A**); therefore, patients could have enrolled into the studies if they had a history of gastroparesis.[6-12]
    - At this time, no subgroup analyses have been performed to specifically assess the safety and efficacy of Wegovy® in patients with pre-existing gastroparesis.
- Across the STEP trials (including the run-in period of STEP 4), six Wegovy®-treated patients reported gastroparesis/impaired gastric emptying, and seven Wegovy®-treated patients reported GI motility disorder.[2-5,13]
- At this time, Novo Nordisk has not conducted analyses to specifically evaluate the duration or reversibility of gastroparesis, either in patients on Wegovy® or after discontinuation of treatment.
- In a study by Friedrichsen et al., paracetamol area under the concentration-time curve (AUC) from 0 to 5 hours after a standardized meal ($AUC_{0\text{-}5h,para}$), was 8% higher with Wegovy® compared with placebo.[14]
- In a study by Jensterle et al., patients without diabetes receiving semaglutide had significant gastric retention 4 hours post-consumption of a solid meal compared to placebo.[15]

Gastroparesis

Gastroparesis is a motility disorder defined by objective documentation of delayed gastric emptying of solid food with no mechanical obstruction.[16] Certain causes of gastroparesis include but are not limited to: hypothyroidism, certain autoimmune diseases, certain nervous system disorders, viral stomach infections and injury to the vagus nerve during operation of the esophagus, stomach or small intestine.[17] Please note, certain medications may also delay gastric emptying (e.g. select narcotics, antidepressants,

anticholinergics, pramlintide, glucagon-like peptide-1 receptor agonists [GLP1-RAs]).[17,18] Gastroparesis is a known chronic complication of diabetes and is more prevalent in patients with type 1 diabetes (T1D).[19,20] A study evaluating the 10-year cumulative incidence of gastroparesis estimated 5.2% in patients with T1D, 1.0% in patients with type 2 diabetes, and 0.2% in patients without diabetes, respectively.[19]

STEP Phase 3 Clinical Development Program

The **S**emaglutide **T**reatment **E**ffect in **P**eople with Obesity (STEP) Phase 3 clinical development program evaluates the safety and efficacy of Wegovy® for weight management in patients with obesity or overweight with at least one weight-related comorbidity (**Appendix A**).[21-27]

Use of Wegovy® in Patients with Gastroparesis

In the STEP clinical trials, impaired gastric emptying and/or GI motility disorder were identified at screening. Across the STEP trials, two patients randomized to Wegovy® and two patients randomized to placebo had a medical history or concomitant illness of impaired gastric emptying or GI motility disorder at screening.[3-5,13,28-30]

The safety and efficacy of Wegovy® was not specifically evaluated in patients with gastroparesis at baseline. The use of Wegovy® in patients with pre-existing gastroparesis should be based on your clinical judgement and an assessment of the benefits versus risks of the therapy in the specific patient.

Risk of Gastroparesis with Wegovy®

During the clinical development program of Wegovy®, gastroparesis was not a commonly reported adverse event, and therefore, is not listed as one of the most common side effects of Wegovy® in the Prescribing Information.[1]

Please see **Table 1** for reports of 'impaired gastric emptying' and 'GI motility disorder' from the randomized periods of the STEP Phase 3 trials. Additionally, during the run-in period of STEP 4 (Week 0 to Week 20), in which all patients were taking Wegovy®, three patients reported impaired gastric emptying and three patients reported GI motility disorder.[13]

In most cases across the randomized periods of the STEP trials, the adverse event reports of impaired gastric emptying and GI motility disorder were noted as 'recovered'.[3-5,13,28-30] One patient with a report of impaired gastric emptying and one patient with a report of GI motility disorder, both randomized to Wegovy®, were noted as 'not recovered'.

At this time, Novo Nordisk has not conducted analyses to specifically evaluate the duration or reversibility of gastroparesis, either in patients on Wegovy® or after discontinuation of treatment.

Table 1. 'Impaired Gastric Emptying' and 'GI Motility Disorder' in the STEP Phase 3 Trials[2-5a]

	Wegovy®	Placebo
Phase 3a Pool[b-f]	N=2650	N=1529
Impaired gastric emptying, n (Adj. %)	2 (<0.1)	1 (<0.1)
GI motility disorder, n (Adj. %)	4 (0.2)	0
Phase 3b[d,e]		
STEP 5	N=152	N=152
Impaired gastric emptying, n (%)	1 (0.7)	0
GI motility disorder, n (%)	NR	NR

a. **There were no reports of gastroparesis/impaired gastric emptying or GI motility disorder in STEP 8 and STEP TEENS.[4,5]**
b. Phase 3a pool: STEP 1-4 data from patients randomized to Wegovy® or placebo during the controlled periods of the trials. The 20-week run-in period of STEP 4 and Ozempic® (semaglutide) injection 1 mg treatment arm of STEP 2 are omitted.
c. In STEP 1, two patients taking Wegovy® reported gastroparesis/impaired gastric emptying which led to permanent discontinuation of the trial product.[28]
d. Adverse events with onset prior to randomization are not included.
e. Data from on-treatment period. Patients are considered on-treatment if any dose of trial product has been administered within the prior 49 days.
f. The % is adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials.
Abbreviations: GI: gastrointestinal; N: number of patients; n: number of patients experiencing at least one event; Adj.: adjusted; %: percentage of patients experiencing at least one event; NR: not reported.

In the STEP clinical trial program, a dose-response evaluation was not specifically conducted for impaired gastric emptying or GI motility disorder with Wegovy®; however, a dose-response effect in the reporting of GI adverse events is well-known with GLP1-RAs.[2] Other studies have shown that GLP1-RAs cause a dose-dependent delay in gastric emptying.[31,32]

Time Delay in Gastric Emptying

Friedrichsen et al.
A single-center, double-blind, parallel group, phase 1 study (n=72) in Germany evaluated the effects of Wegovy® 2.4 mg compared to placebo on gastric emptying, appetite and energy intake in adults with obesity (BMI 30-45 kg/m^2) for 20 weeks.[14]

- Gastric emptying was assessed by paracetamol (acetaminophen) absorption (indirect marker for gastric emptying; delayed gastric emptying would be anticipated to slow paracetamol absorption).[14] The primary endpoint, $AUC_{0\text{-}5h,para}$, was 8% higher with Wegovy® compared with placebo. In a post-hoc analysis, the difference was not statistically significant between the treatment groups when adjusted for body weight at Week 20 (ETD 1.05, *P*=.1218).
- Gastric emptying was also assessed with the secondary endpoints of AUC from 0 to 1 hour after a standardized meal ($AUC_{0\text{-}1h,para}$), maximum observed paracetamol concentration ($C_{max,para}$) and time to maximum observed paracetamol concentration ($T_{max,para}$).[14] There were no differences between the treatment groups for these secondary endpoints.

Jensterle et al.
A single center, randomized, single-blind, placebo-controlled trial evaluated the effect of semaglutide on gastric emptying using technetium scintigraphy in 20 women with obesity and polycystic ovarian syndrome compared to placebo.[15] Patients with serious chronic illness (i.e. diabetes) were excluded from the study. Patients were randomized 1:1 to receive either semaglutide subcutaneous injection (semaglutide 0.25 mg for 2 weeks, semaglutide 0.5 mg for 2 weeks, and semaglutide 1 mg for 8 weeks) or

placebo for 12 weeks.

Gastric emptying was evaluated by scintigraphy (sequential static imaging and dynamic processing) at baseline and at week 13 after consumption of a standardized solid meal labeled with a ^{99m}Tc-radiopharmaceutical.[15] Patients receiving semaglutide retained 37% of the meal 4 hours post-consumption while gastric retention was not seen in the placebo group (P=.002). In patients receiving semaglutide, the time taken to empty the meal from the stomach compared to placebo was significantly longer (171 minutes versus 118 minutes; P<.001).

Appendix A

Overview of the STEP Phase 3 Clinical Development Program of Wegovy®[21-27,33,34]

The **S**emaglutide **T**reatment **E**ffect in **P**eople with Obesity (STEP) Phase 3 clinical development program evaluates the safety and efficacy of Wegovy®, administered subcutaneously once weekly for weight management in patients with obesity or overweight with at least one weight-related comorbidity.[21-27,34] The STEP Phase 3a program includes six randomized, double-blind, parallel-group, multicenter clinical trials (STEP 1-4, 6 and STEP TEENS), while the Phase 3b program includes STEP 5 (long-term weight management) and STEP 8 (versus Saxenda® [liraglutide] injection).[21-27,33,34] The studies are briefly described below.

Table A.1. STEP Phase 3 Clinical Development Program[21-27,33,34]

	Phase 3a Studies						Phase 3b Studies	
	STEP 1	**STEP 2**	**STEP 3**	**STEP 4**	**STEP 6**	**STEP TEENS**	**STEP 5**	**STEP 8**
Randomized Patients (N)	1961	1210	611	803[a]	401	201	304	338
Patient Population	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but w/o diabetes	Adults with BMI ≥27 kg/m² and T2D (A1C 7%-10%) diagnosed ≥180 days before screening	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but w/o diabetes	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but w/o diabetes	East Asian adults[c] with BMI of ≥35 kg/m² and ≥1 weight-related comorbidity[d], or ≥27 kg/m² and ≥2 weight-related comorbidities[d]	Adolescents (age 12 to <18 years) with a BMI ≥95th percentile or ≥85th percentile (based on sex and age) with ≥1 weight-related comorbidity[b]	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but w/o diabetes	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but w/o diabetes
Duration (weeks)	68	68	68	68	68	68	104	68
Randomization	2:1	1:1:1	2:1	2:1	4:1:2:1[g]	2:1	1:1	3:1:3:1[h]
Comparator	Placebo	Placebo, Ozempic® 1 mg[e]	Placebo	Placebo	Wegovy® 1.7 mg, Placebo	Placebo	Placebo	Saxenda®[i], Placebo
Background Treatment	Diet and exercise[f]	Diet and exercise[f] and 0-3 OADs (MET, SU, SGLT2i, or TZD)	IBT[f]	Diet and exercise[f]	Diet and exercise[f]	Nutrition and physical activity counseling[f]	Diet and exercise[f]	Diet and exercise[f]

a. All enrolled patients (n=902) received Wegovy® during the trial's 20-week run-in period (including 16 weeks of dose escalation). Patients who were able to achieve and maintain a target dose of Wegovy® 2.4 mg during the run-in period (n=803) were randomized to either continue Wegovy® or switch to placebo.
b. Weight-related comorbidities: hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. In STEP TEENS, comorbidities included hypertension, dyslipidemia, obstructive sleep apnea or T2D.[12]
c. STEP 6 was conducted in South Korea and Japan. The adult age is ≥18 years old in South Korea, and ≥20 years old in Japan. Adults were included if they had ≥1 self-reported unsuccessful diet attempt to lose weight.
d. Weight-related comorbidities according to JASSO guidelines. At least 1 comorbid condition had to include hypertension or dyslipidemia, or, in Japan only, T2D.
e. Ozempic® (semaglutide) injection 1 mg.
f. In STEP 1, 2, 4-6 and 8, diet and exercise consisted of a 500 kcal/day deficit and at least 150 min/week of physical activity. In STEP TEENS, patients received individualized counseling on achieving weight loss and to encourage 60 min/day of moderate-to-high intensity physical activity. In STEP 3, IBT consisted of a low-calorie diet (1000-1200 kcal/day) with meal replacements for the first 8 weeks after randomization. Patients then transitioned to a hypocaloric diet (1200-1800 kcal/day, depending on body weight) for the remainder of the 68 weeks. Prescribed physical activity began at 100 min/week (over 4-5 days) and was increased by 25 min every 4 weeks to reach 200 min/week. Patients received 30 individual IBT visits with a registered dietitian, who provided counseling related to diet, physical activity and behavior.
g. Patients were randomized 4:1:2:1 to Wegovy® 2.4 mg (N=199) or matching placebo, or Wegovy® 1.7 mg (N=101) or matching placebo (pooled placebo [N=101]).
h. Patients were randomized 3:1:3:1 to Wegovy® (N=126) or matching placebo, or Saxenda® (N=127) or matching placebo (pooled placebo [N=85]).
i. Saxenda® (liraglutide) injection 3 mg.
Abbreviations: A1C: glycosylated hemoglobin; BMI: body mass index; IBT: intensive behavioral therapy; JASSO: Japanese Society for the Study of Obesity; MET: metformin; min: minutes; OAD: oral antidiabetic drugs; SGLT2i: sodium-glucose cotransporter-2 inhibitor; SU: sulfonylurea; T2D: type 2 diabetes; TZD: thiazolidinedione; w/o: without.

The STEP Phase 3a program also includes STEP 7 (multi-regional clinical trial including ≥1 East Asian country), STEP HFpEF (heart failure with preserved ejection fraction) and STEP HFpEF-DM (heart failure with preserved ejection fraction and T2D). The STEP Phase 3b program also includes STEP 9 (knee osteoarthritis), STEP 10 (prediabetes), STEP 11 (weight management in Asian patients with BMI ≥25 kg/m²) and SELECT (cardiovascular outcomes trial). For more information, please visit clinicaltrials.gov.

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September 5, 2023

KAREN VAN CAULIL
4401 VINELAND RD
STE A10
ORLANDO, FL 32811

Dear Ms. KAREN VAN CAULIL,

Thank you for your request regarding:

- **Long-Term Safety Data with Wegovy**

This information is supplied to you as a professional service in response to your specific request. This letter is meant to supplement information you have gathered from other sources and is not intended to promote or advocate the use of Novo Nordisk products in any manner other than described in the Prescribing Information.

Please note, if you are receiving this response by fax, it may contain icons and/or hyperlinks for additional information. This response is available via email upon request.

Prescribing Information for Wegovy® (semaglutide) injection can be accessed via the following link:
Wegovy® Prescribing Information

For prescribing information for other Novo Nordisk products mentioned in this response, please visit:
https://www.scientific-exchange.com

Please find the requested information enclosed.

In order to provide you with a timely response, Novo Nordisk may send you multiple responses as they become available. If you have additional questions, please contact Novo Nordisk Medical Information by calling (800) 727-6500 or visiting https://www.scientific-exchange.com.

Sincerely,
Khaled Abdelrahman, PharmD

For copyright purposes the PDF(s) provided is (are) for your personal use only; storage and further distribution is not permitted.

Thank you for your request for information regarding a Novo Nordisk product(s). Please find the information enclosed.

- **Wegovy® is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated 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 (e.g., hypertension, type 2 diabetes, or dyslipidemia).**
  - **Pediatric patients aged 12 years and older with an initial BMI at the 95th percentile or greater for age and sex (obesity).**
- **<u>Prescribing Information Boxed Warning: Risk of Thyroid C-Cell Tumors</u>**
  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)].
- **Some information contained in this letter or enclosed publication(s) may not be consistent with the approved indications and usage for the product. Novo Nordisk does not recommend the use of its products in any manner other than as described in the prescribing information.**
- **Please refer to the prescribing information for important safety information by clicking here: Wegovy® Prescribing Information**
- **The most common adverse reactions, reported in greater than or equal to 5% of adults or pediatric patients aged 12 years and older treated with Wegovy® are: nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia in patients with type 2 diabetes, flatulence, gastroenteritis, and gastroesophageal reflux disease, and nasopharyngitis.**
- **If you believe that your patient has experienced an adverse event while using Novo Nordisk products, please call (800) 727-6500 to report this event.**
- **Some of the references used in this response may refer to other Novo Nordisk Inc. product(s), please access the respective Prescribing Information at https://www.scientific-exchange.com/product-information/novonordisk.html.**
- **Please note that the Novo Nordisk product discussed within this response has the same active molecule as other Novo Nordisk products, which are approved under different brand names, for different indications, dosages and/or formulations. If you would like information on these or other Novo Nordisk products and the safety information about which you are inquiring,**

please do not hesitate to contact us by calling 1-800-727-6500 or visiting https://www.scientific-exchange.com/.

- **If you were unable to find information to address your specific question, please visit us at https://www.scientific-exchange.com/.**

Medical Information Response

Long-Term Safety Data with Wegovy® (semaglutide) injection

Summary

- Wegovy® is indicated as an adjunct to a reduced calorie diet and increased physical activity for **chronic weight management** in adults 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 (e.g., hypertension, type 2 diabetes mellitus [T2D], or dyslipidemia) and pediatric patients aged 12 years and older with an initial BMI at the 95th percentile or greater standardized for age and sex (obesity).[1]
- The Phase 3 clinical development program, STEP (**S**emaglutide **T**reatment **E**ffect in **P**eople with obesity), evaluated the safety and efficacy of Wegovy® once-weekly as an adjunct to lifestyle intervention for weight management in adult patients with overweight or obesity, with and without T2D.[2-8] The Phase 3a program includes STEP 1-4, while the Phase 3b program includes STEP 5 and STEP 8.
    - The main phases of STEP 1-4 and 8 were each 75 weeks in duration (68-week on-treatment period + 7-week follow up period).[2-5,8] Due to their shorter duration, the main phases of STEP 1-4 and 8 are excluded from this response. For additional details on the study design of these STEP trials, please see **Appendix A.**
    - Currently, the longest completed weight management trial evaluating Wegovy® is the Phase 3b STEP 5 clinical trial with a 104 week on-treatment period + 7 week off-treatment follow up period.[6,8]
- **STEP 5**
    - In STEP 5, 96.1% of Wegovy®-treated patients vs 89.5% of patients treated with placebo reported adverse events (AEs).[6] Gastrointestinal (GI) related AEs occurred in 82.2% of Wegovy®-treated patients in comparison to 53.9% of patients treated with placebo (**Table 1**).
- Novo Nordisk is unable to provide patient-specific treatment or monitoring recommendations. It is up to the prescribing health care professional's clinical judgement to prescribe Wegovy® for a longer or shorter period of time based on an assessment of the benefits versus risks of the therapy in the specific patient and whether the patient is reaching their treatment goals.

Long-Term Use

STEP 5 was a 104-week randomized, double-blind, placebo-controlled, international Phase 3b trial that evaluated the safety and efficacy of Wegovy® at a dose of 2.4 mg administered once weekly for long-term weight management in adults with obesity (body mass index [BMI] ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with at least 1 weight-related comorbidity and without T2D.[6] Of the trials in the STEP program, STEP 5 has the longest duration.

Patients were randomly assigned (1:1) to receive once weekly Wegovy® or placebo, both as an adjunct to a reduced-calorie diet and increased physical activity.[6] The co-primary endpoints were change in body weight (%) from Week 0 to Week 104 and proportion of patients achieving ≥5% body weight by Week 104.

The following were confirmatory secondary endpoints in STEP 5: proportion of patients achieving ≥10% and ≥15% weight loss and changes in waist circumference and systolic blood pressure (SBP) from baseline to Week 104.[6]

Baseline body weight for the 304 patients randomized into the study was 106.0 kg (233.7 lb).[6] Additional baseline characteristics included the following: 77.6% female; 93.1% white; mean age 47.3 years; mean BMI 38.5 kg/m^2.

In total, 96.1% of Wegovy®-treated patients vs 89.5% of patients treated with placebo reported AEs.[6] AEs that led to permanent trial product discontinuation occurred in 5.9% and 4.6% of patients treated with Wegovy® and placebo, respectively. Please see **Table 1** for reports of adverse events in STEP 5.

Table 1: Adverse Events within Safety Focus Areas in STEP 5 – On-Treatment[a,6]

	Wegovy® (N=152)	Placebo (N=152)
GI disorders, n (%)	125 (82.2)	82 (53.9)
Gallbladder-related disorders, n (%)	4 (2.6)	2 (1.3)
Hepatic disorders, n (%)	3 (2.0)	3 (2.0)
Acute pancreatitis, n (%)	0	0
Cardiovascular disorders[b], n (%)	17 (11.2)	32 (21.1)
Allergic reactions, n (%)	23 (15.1)	8 (5.3)
Injection site reactions, n (%)	10 (6.6)	15 (9.9)
Malignant neoplasms[b], n (%)	2 (1.3)	4 (2.6)
Psychiatric disorders, n (%)	26 (17.1)	25 (16.4)
Acute renal failure, n (%)	0	0
Hypoglycemia, n (%)	4 (2.6)	0
Rare events[c], n (%)	0	1 (0.7)
Overdose, n (%)	0	1 (0.7)

a. Observed proportions assessed during the on-treatment period (time from first to last trial product administration plus 7 weeks of follow-up and excluding any period of temporary treatment interruption defined as >7 consecutive missed doses), unless otherwise noted.
b. Events occurred during the in-trial period (uninterrupted time from randomization to last contact with trial site, regardless of rescue intervention or adherence to trial product).
c. One serious adverse event of Arnold-Chiari malformation was identified in a patient in the placebo arm. The event was serious, judged to be unlikely related to trial product and not recovered (chronic condition).[9]
Abbreviations: GI: gastrointestinal; N: total number of patients; n: number of patients with at least 1 event.

Appendix A

Overview of the STEP Phase 3 Clinical Development Program of Wegovy®[2-8,10,11]

The **S**emaglutide **T**reatment **E**ffect in **P**eople with Obesity (STEP) Phase 3 clinical development program evaluates the safety and efficacy of Wegovy®, administered subcutaneously once weekly for weight management in patients with obesity or overweight with at least one weight-related comorbidity.[2-7,10,11] The STEP Phase 3a program includes six randomized, double-blind, parallel-group, multicenter clinical trials (STEP 1-4, 6 and STEP TEENS), while the Phase 3b program includes STEP 5 (long-term weight management) and STEP 8 (versus Saxenda® [liraglutide] injection).[2-8,10,11] The studies are briefly described below.

Table A.1. STEP Phase 3 Clinical Development Program[2-8,10,11]

	Phase 3a Studies						Phase 3b Studies	
	STEP 1	**STEP 2**	**STEP 3**	**STEP 4**	**STEP 6**	**STEP TEENS**	**STEP 5**	**STEP 8**
Randomized Patients (N)	1961	1210	611	803[a]	401	201	304	338
Patient Population	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but w/o diabetes	Adults with BMI ≥27 kg/m² and T2D (A1C 7%-10%) diagnosed ≥180 days before screening	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but w/o diabetes	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but w/o diabetes	East Asian adults[c] with BMI of ≥35 kg/m² and ≥1 weight-related comorbidity[d], or ≥27 kg/m² and ≥2 weight-related comorbidities[d]	Adolescents (age 12 to <18 years) with a BMI ≥95th percentile or ≥85th percentile (based on sex and age) with ≥1 weight-related comorbidity[b]	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but w/o diabetes	Adults with BMI ≥30 kg/m², or ≥27 kg/m² and ≥1 weight-related comorbidity[b] but w/o diabetes
Duration (weeks)	68	68	68	68	68	68	104	68
Randomization	2:1	1:1:1	2:1	2:1	4:1:2:1[g]	2:1	1:1	3:1:3:1[h]
Comparator	Placebo	Placebo, Ozempic® 1 mg[e]	Placebo	Placebo	Wegovy® 1.7 mg, Placebo	Placebo	Placebo	Saxenda®[i], Placebo
Background Treatment	Diet and exercise[f]	Diet and exercise[f] and 0-3 OADs (MET, SU, SGLT2i, or TZD)	IBT[f]	Diet and exercise[f]	Diet and exercise[f]	Nutrition and physical activity counseling[f]	Diet and exercise[f]	Diet and exercise[f]

a. All enrolled patients (n=902) received Wegovy® during the trial's 20-week run-in period (including 16 weeks of dose escalation). Patients who were able to achieve and maintain a target dose of Wegovy® 2.4 mg during the run-in period (n=803) were randomized to either continue Wegovy® or switch to placebo.
b. Weight-related comorbidities: hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. In STEP TEENS, comorbidities included hypertension, dyslipidemia, obstructive sleep apnea or T2D.[12]
c. STEP 6 was conducted in South Korea and Japan. The adult age is ≥18 years old in South Korea, and ≥20 years old in Japan. Adults were included if they had ≥1 self-reported unsuccessful diet attempt to lose weight.
d. Weight-related comorbidities according to JASSO guidelines. At least 1 comorbid condition had to include hypertension or dyslipidemia, or, in Japan only, T2D.
e. Ozempic® (semaglutide) injection 1 mg.
f. In STEP 1, 2, 4-6 and 8, diet and exercise consisted of a 500 kcal/day deficit and at least 150 min/week of physical activity. In STEP TEENS, patients received individualized counseling on achieving weight loss and to encourage 60 min/day of moderate-to-high intensity physical activity. In STEP 3, IBT consisted of a low-calorie diet (1000-1200 kcal/day) with meal replacements for the first 8 weeks after randomization. Patients then transitioned to a hypocaloric diet (1200-1800 kcal/day, depending on body weight) for the remainder of the 68 weeks. Prescribed physical activity began at 100 min/week (over 4-5 days) and was increased by 25 min every 4 weeks to reach 200 min/week. Patients received 30 individual IBT visits with a registered dietitian, who provided counseling related to diet, physical activity and behavior.
g. Patients were randomized 4:1:2:1 to Wegovy® 2.4 mg (N=199) or matching placebo, or Wegovy® 1.7 mg (N=101) or matching placebo (pooled placebo [N=101]).
h. Patients were randomized 3:1:3:1 to Wegovy® (N=126) or matching placebo, or Saxenda® (N=127) or matching placebo (pooled placebo [N=85]).
i. Saxenda® (liraglutide) injection 3 mg.
Abbreviations: A1C: glycosylated hemoglobin; BMI: body mass index; IBT: intensive behavioral therapy; JASSO: Japanese Society for the Study of Obesity; MET: metformin; min: minutes; OAD: oral antidiabetic drugs; SGLT2i: sodium-glucose cotransporter-2 inhibitor; SU: sulfonylurea; T2D: type 2 diabetes; TZD: thiazolidinedione; w/o: without.

The STEP Phase 3a program also includes STEP 7 (multi-regional clinical trial including ≥1 East Asian country), STEP HFpEF (heart failure with preserved ejection fraction) and STEP HFpEF-DM (heart failure with preserved ejection fraction and T2D). The STEP Phase 3b program also includes STEP 9 (knee osteoarthritis), STEP 10 (prediabetes), STEP 11 (weight management in Asian patients with BMI ≥25 kg/m²) and SELECT (cardiovascular outcomes trial). For more information, please visit clinicaltrials.gov.

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