# Division Director Summary Review for Regulatory Action

<table>
<thead>
<tr>
<th>Date</th>
<th>(electronic stamp)</th>
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<tbody>
<tr>
<td>From</td>
<td>John Sharretts, M.D.</td>
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<tr>
<td>Subject</td>
<td>Deputy Division Director Summary Review</td>
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<tr>
<td>NDA/BLA # and Supplement #</td>
<td>NDA 215256</td>
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<tr>
<td>Applicant</td>
<td>Novo Nordisk Inc.</td>
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<tr>
<td>Date of Submission</td>
<td>December 4, 2020</td>
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<tr>
<td>PDUFA Goal Date</td>
<td>June 4, 2021</td>
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<tr>
<td>Proprietary Name</td>
<td>Wegovy</td>
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<tr>
<td>Established or Proper Name</td>
<td>Semaglutide</td>
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<tr>
<td>Dosage Form(s)</td>
<td>Injection, for subcutaneous use</td>
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</table>
| Applicant Proposed Indication(s)/Population(s) | as 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 |
| Action or Recommended Action: | Approval |
| Approved/Recommended Indication(s)/Population(s) (if applicable) | 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/m² or greater (obesity) or  
- 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia) |
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<tr>
<th>Material Reviewed/Consulted</th>
<th>Names of discipline reviewers</th>
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<tr>
<td><strong>OND Action Package, including:</strong></td>
<td>Julie Golden, M.D.</td>
</tr>
<tr>
<td>Medical Officer Review</td>
<td>Kyunghee Song, Ph.D.</td>
</tr>
<tr>
<td>Statistical Review</td>
<td>Elena Braithwaite, Ph.D.</td>
</tr>
<tr>
<td>Pharmacology Toxicology Review</td>
<td>Muthukumar Ramaswamy, Ph.D.</td>
</tr>
<tr>
<td>OPQ Review – Lead</td>
<td>Daniel Jansen, Ph.D.</td>
</tr>
<tr>
<td>Drug Substance</td>
<td>Ali Mohamadi, Ph.D.</td>
</tr>
<tr>
<td>Drug Product</td>
<td>Suresh Dadiboyena, Ph.D.</td>
</tr>
<tr>
<td>Process/Facility</td>
<td>Mohanraj Manangeeswaran, Ph.D.</td>
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<tr>
<td>OBP Review</td>
<td>Helen Ngai, Ph.D.</td>
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<td>Microbiology Review</td>
<td>Sang Chung, Ph.D.</td>
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<tr>
<td>Clinical Pharmacology Review</td>
<td>Justin Earp, Ph.D.</td>
</tr>
<tr>
<td>Pharmacometrics</td>
<td>Yasmin Choudhry, M.D.</td>
</tr>
<tr>
<td>IRT CSS</td>
<td>Christine Garnett, PharmD.</td>
</tr>
<tr>
<td>DPMH</td>
<td>Carrie Ceresa, PharmD.</td>
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<tr>
<td>OPDP</td>
<td>Meena Savani, PharmD.</td>
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<tr>
<td>OSI</td>
<td>Cynthia Kleppinger, M.D.</td>
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<tr>
<td>OSE/DEPI I</td>
<td>Christian Hampp, Ph.D.</td>
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<tr>
<td>OSE/DMEPA – Human Factors</td>
<td>Jason Flint, M.B.A., PMP.</td>
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<tr>
<td>Proprietary Name</td>
<td>Sarah Vee, PharmD.</td>
</tr>
<tr>
<td>OSE/DMPP</td>
<td>Kelly Jackson, PharmD.</td>
</tr>
<tr>
<td>RPM</td>
<td>Martin White, M.S.</td>
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OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OBP=Office of Biotechnology Products
COA=Clinical Outcome Assessment
IRT CSS=Interdisciplinary Review Team for Cardiac Safety Studies
DPMH=Division of Pediatrics and Maternal Health
OPDP=Office of Prescription Drug Promotion
OSE=Office of Surveillance and Epidemiology
OSE/DEPI=Division of Epidemiology I
OSE/DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Promotions
RPM=Regulatory Project Manager
1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Obesity and overweight are conditions that increase the risk of chronic health outcomes, including hypertension, dyslipidemia, type 2 diabetes, cardiovascular disease, and certain cancers. Weight loss of 5-10% in patients through diet and exercise is generally accepted as beneficial on cardiometabolic risk factors. Lifestyle intervention with a reduced calorie diet and moderate exercise program is the standard-of-care but is usually not successful. Use of pharmacologic or surgical therapies is limited by factors including adverse effects, cost, and insurance coverage, and there remains an unmet medical need.

This application includes substantial evidence of effectiveness that semaglutide 2.4 mg injection, administered subcutaneously once weekly, results in clinically meaningful weight loss and improvement in anthropomorphic and cardiometabolic parameters in patients with obesity or overweight. The benefit of semaglutide (body weight loss) was demonstrated in the clinical trials. The observed placebo-adjusted weight loss was greater than the goal of 5% to 10% weight loss from baseline and can be expected to result in improvement in health outcomes.

The efficacy of semaglutide 2.4 mg was evaluated in three 68-week, randomized, double-blind, placebo-controlled trials, and one 68-week, randomized, double-blind, placebo withdrawal trial. The first randomized, placebo-controlled trial evaluated semaglutide as adjunctive therapy to a reduced calorie diet and exercise in patients without diabetes, the second evaluated semaglutide as an adjunct to diet and exercise in patients with type 2 diabetes, and the third evaluated semaglutide as an adjunct to an intensive diet and exercise program in patients without diabetes. In the randomized withdrawal trial, all enrolled patients received semaglutide during a 20-week dose escalation period, and those who achieved the 2.4 mg target dose were randomized to continue therapy with semaglutide or withdraw to placebo for an additional 48 weeks.

The estimated treatment effect of semaglutide versus placebo as an adjunct to a reduced calorie diet and exercise is an approximately 12% reduction in body weight from baseline compared to patients without type 2 diabetes. Over 80% of patients assigned to semaglutide treatment achieved at least 5% weight loss and approximately two-thirds of patients achieved 10% weight loss compared to baseline. The estimated treatment effect versus placebo as an adjunct to an intensive diet and exercise program was about 10% weight loss from baseline. In patients with type 2 diabetes, the estimated treatment effect of semaglutide as an adjunct to a reduced calorie diet and exercise is about a 6% reduction in body weight compared to placebo. Approximately two-thirds of patients assigned to semaglutide lost at least 5% of baseline body weight compared to baseline. Although modest compared to the weight-loss observed in the non-diabetes population, 6% weight loss is nonetheless clinically meaningful.

The observed treatment effect in the randomized withdrawal trial is challenging to interpret. Choice of baseline (week 0 pre-treatment or week 20 randomization) affects the estimate size. Furthermore, because the randomized population was a subset of the enrolled population, results for this subgroup are not generalizable to patients starting treatment who have never been exposed to semaglutide previously. Nevertheless, continued treatment with semaglutide for an additional 48 weeks as an adjunct to a reduced calorie diet and exercise, was superior to randomized withdrawal to placebo. Weight
regain was considerable in patients who withdrew to placebo at week 20. There does not appear to be a role for the short-term use of semaglutide (20 weeks or fewer) as an adjunct to a reduced calorie diet and exercise for chronic weight management.

Semaglutide was effective among patients who tolerated escalation to the target dose of 2.4 mg once weekly. Effectiveness was not assessed at other dose levels. Semaglutide should be discontinued in patients who do not achieve the target dose following recommended dose escalation.

The trials results were clinically meaningful and statistically robust. Overall trial quality, including low proportions of treatment discontinuation and missing data, strongly support the validity of the results. The trials clearly distinguished the treatment effect of semaglutide on body weight from other influences and provide a quantitative estimate of the treatment effect of semaglutide under the conditions of use.

The safety profile of semaglutide 2.4 mg for chronic weight management is similar to that of other glucagon-like peptide-1 (GLP-1) receptor agonists and semaglutide products approved for diabetes indications. There were no new safety issues identified in the weight management development program. The most frequent adverse events observed with semaglutide and greater than placebo were gastrointestinal disorders. Other frequent adverse events included headache, fatigue, back pain, and increased heart rate. Acute kidney injury, hypotension and syncope, and injection site reactions occurred infrequently.

Gallbladder disorders, hypoglycemia, and diabetic retinopathy complications are previously identified risks with GLP-1 receptor agonists. In the semaglutide program, the risk of gallbladder events appeared greater in association with greater weight loss. The risk of hypoglycemia is greater in patients with type 2 diabetes on insulin or insulin secretagogues, especially following initiation and dose escalation. Diabetic retinopathy complications occurred in association with rapid improvement in glucose control in a cardiovascular outcomes trial of patients with type 2 diabetes, and the risk was greater in patients with diabetic retinopathy at baseline. The potential risk is under further evaluation in patients with diabetes, and its relevance to the conditions of use for weight management is unclear. Other safety issues associated with GLP-1 receptor agonists, such as acute pancreatitis, neoplasms, and suicidal behavior are infrequent or unconfirmed signals from nonclinical data, postmarketing reports, or related medications. These risks are addressed in current labeling of approved GLP-1 receptor agonists, and some will be evaluated in postmarketing studies. Semaglutide is contraindicated in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia, type 2 (MEN 2) because of the nonclinical signal for thyroid C-cell tumors.

In nonclinical studies, semaglutide was associated with fetal abnormalities coinciding with maternal weight loss. Pregnancy loss (in rabbits) and fetal malformations (in rats and rabbits) occurred at clinical exposures, while early pregnancy loss, decreased infant body weight, and sporadic fetal abnormalities occurred in monkeys above predicted human exposure based on area-under-the-curve concentrations. The potential risk in pregnancy can be addressed in labeling.

In summary, the weight-loss benefit of semaglutide 2.4 mg once weekly outweighs the potential risks in the intended population. The treatment effect on weight loss is clinically meaningful and expected to improve health outcomes in patients with obesity and overweight. The most common adverse reactions primarily impact tolerability. Other risks, including less common, but serious, safety issues are adequately mitigated with labeling.

Semaglutide is safe for use in the indicated population under the proposed conditions of use, as an adjunct to a reduced calorie diet and exercise for chronic weight management. Semaglutide should not be used in combination with other GLP-1 receptor agonists or other products intended for weight loss.
## Benefit-Risk Dimensions

<table>
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<tr>
<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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| Analysis of Condition | - Obesity is a chronic, relapsing health condition.  
- Obesity and overweight increase the risk of chronic health outcomes, including hypertension, dyslipidemia, type 2 diabetes, cardiovascular disease, and certain cancers.  
- Weight loss of 5-10% in patients through diet and exercise is generally accepted as beneficial on cardiometabolic risk factors.  
- The cardiovascular benefit of pharmacologic-induced weight loss has not been demonstrated in clinical trials to date. | Current FDA guidance recommends evaluating drugs intended for chronic weight management in patients with obesity (BMI $\geq 30$ kg/m$^2$) and those with overweight (BMI $\geq 27$ kg/m$^2$) and at least one co-morbid condition. Effects on weight should be evaluated after at least one year. |
| Current Treatment Options | - Lifestyle intervention, typically consisting of a reduced calorie diet and moderate exercise is the standard-of-care treatment.  
- Bariatric surgery is effective, but is indicated for patients with extreme obesity (BMI $\geq 40$ kg/m$^2$) or patients with BMI $\geq 35$ kg/m$^2$ (Class 2 obesity) and one or more obesity-related co-morbidities is reserved for patients with morbid obesity  
- Use of approved medications for chronic weight management is limited by issues such as modest treatment effects, early treatment discontinuation, and cost/lack of insurance coverage | Lifestyle interventions are not effective in most patients. Use of pharmacologic therapy and bariatric surgery are limited. There is unmet medical need. |
| Benefit            | - Semaglutide was evaluated in three randomized, placebo-controlled trials consisting of a 16-week blinded dose escalation period and a 52-week treatment period. Patients were adults with obesity (BMI $\geq 30$ kg/m$^2$) or overweight (BMI $\geq 30$ kg/m$^2$) with at least one co-morbid condition.  
- The estimated treatment effect of semaglutide was a 10% to 12% reduction in body weight from baseline to week 68 compared to placebo in patients without diabetes. Over 80% of patients achieved at least 5% weight loss and about 66% achieved 10% weight loss.  
- In patients with diabetes at baseline, the estimated treatment effect was a 6% reduction in body weight compared to placebo. About 67% of patients achieved at least 5% weight loss and 44% achieved 10% weight loss. | The three randomized, placebo controlled, Phase 3 clinical trial results represent substantial evidence of effectiveness that semaglutide 2.4 mg injection, administered subcutaneously once weekly results in clinically meaningful weight loss and improvement in anthropomorphic and cardiometabolic parameters in patients with obesity and overweight, with and without type 2 diabetes.  
The randomized withdrawal trial demonstrated substantial evidence of a clinically meaningful |
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<tbody>
<tr>
<td></td>
<td>• Weight loss with semaglutide was associated with improvements in glycemia, blood pressure, and lipid parameters.</td>
<td>benefit of continued therapy over withdrawal to placebo at 20 weeks.</td>
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<td></td>
<td>• In a randomized withdrawal trial, patients who reached the target dose during a 20-week dose escalation period were randomized to continued treatment with semaglutide or withdrawal to placebo. Continued treatment with semaglutide was superior to withdrawal to placebo. Short-term use of semaglutide (20 weeks or fewer) appeared to have limited utility as an adjunct to a reduced calorie diet and exercise.</td>
<td>The benefit of semaglutide was demonstrated in a population of patients that is adequately representative of the intended U.S. population, including demographic groups and patients with common co-morbid conditions. Patients who do not tolerate semaglutide 2.4 mg once weekly should discontinue treatment. Substantial evidence was not demonstrated for any other dose level.</td>
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<td></td>
<td>• Cardiovascular or other outcomes benefit of semaglutide for weight management has not yet been evaluated in patients with obesity or overweight. Long-term benefits (beyond 68 weeks) are unknown.</td>
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<tr>
<td>Risk and Risk Management</td>
<td>• There were no new issues identified in the semaglutide weight management program that were not previously seen with GLP-1 receptor agonists.</td>
<td>The safety database was adequate to support the proposed indication. Investigations included adequate tests to demonstrate that semaglutide is safe for use under the conditions of use recommended in labeling.</td>
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<td></td>
<td>• Serious potential risks, such as acute pancreatitis, neoplasms, diabetic retinopathy complications, and suicidal behavior are unconfirmed and have occurred only rarely in patients exposed to semaglutide.</td>
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<tr>
<td></td>
<td>• Gallbladder disease, hypoglycemia, acute kidney injury, increased HR, and hypotension and syncope occurred in clinical trials.</td>
<td>Serious risks are rare. Gallbladder disease, acute pancreatitis, and hypoglycemia may be adequately addressed in labeling and PMRs. The risk of MTC will be included in a boxed warning based on the risk of thyroid C-cell tumors identified in rodents.</td>
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<td></td>
<td>• The risk of pregnancy loss and fetal abnormalities was identified in animals in association with maternal toxicity.</td>
<td>Common adverse reactions may be adequately addressed in labeling.</td>
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<tr>
<td></td>
<td>• Risks may be addressed in labeling, including a boxed warning for the potential risk of medullary thyroid cancer (MTC). Some risks are the subject of postmarketing requirements (PMRs).</td>
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<td></td>
<td>• Common adverse events including gastrointestinal disorders resolved without discontinuation of semaglutide in most patients.</td>
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2. Background

Obesity and overweight are chronic, relapsing physical conditions characterized by excess body fat. Excess body fat increases the risk of cardiovascular and all-cause mortality and the incidence of major co-morbid conditions, such as type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease. Obesity affects over 40% of American adults and is difficult to treat. The purpose of medical weight loss is long-term reduction in fat mass, with a goal of reduction in morbidity and mortality.

In some observational studies of individuals with overweight and obesity, weight loss of 5% to 10% through diet and exercise has been associated with improvement in cardiovascular risk factors and a reduced risk of cardiovascular disease. The 2007 FDA draft Guidance for Industry – Developing Products for Weight Management recommends that weight-loss medications may be approved on the basis of their effect on body weight and cardiovascular risk factors; nevertheless, medication-induced weight loss has not been shown to reduce the risk of cardiovascular events in a controlled trial.1

Currently, four pharmaceutical agents are approved in the U.S. as an adjunct to a reduced calorie diet and exercise for chronic weight management in patients with obesity, or overweight with at least one co-morbid condition: orlistat, phentermine/topiramate, naltrexone/bupropion, and liraglutide.2 Use of these medications is limited by issues such as modest treatment effects and cost/lack of insurance coverage. The median duration of therapy is approximately 1 to 3 months according to drug utilization data.3

Additionally, several amphetamine congeners (such as phentermine, phendimetrazine, and diethylpropion), are approved as short-term (a few weeks) adjuncts in a regimen of weight reduction based on exercise, behavioral modification, and caloric restriction in the management of exogenous obesity. These drugs were approved in the U.S. prior to the 1962 Kefauver-Harris amendments to the U.S. Food Drugs and Cosmetics Act, which established the current efficacy standard requiring substantial evidence of effectiveness consisting of adequate and well-controlled investigations.4 The drugs remained on the market following review under the Drug Efficacy Study Implementation (DESI), but the indications were restricted to short-term use in 1973.5 Although this class of drugs is the most frequently used for prescription weight loss, the utility of drugs intended for short-term use for medical weight loss is unclear.

Regulatory

Ozempic (semaglutide) injection, at doses of 0.5 and 1 mg once weekly subcutaneously (SC), and Rybelsus (semaglutide) tablets, at doses of 7 and 14 mg once daily orally, are approved in

1 [https://www.fda.gov/regulatory-information/search-fda-guidance-documents](https://www.fda.gov/regulatory-information/search-fda-guidance-documents)
2 [https://www.accessdata.fda.gov/scripts/cder/daf/](https://www.accessdata.fda.gov/scripts/cder/daf/)

CDER Deputy Division Director Summary Review

*NDA 215256 Wegovy (semaglutide) injection, for subcutaneous use*
the U.S. for glycemic control in patients with type 2 diabetes. Ozempic is also indicated to reduce major adverse cardiovascular (CV) events in patients with type 2 diabetes and established CV disease.

The NDA applicant and IND sponsor (Novo Nordisk, Inc.) submitted IND 126360 in June 2015 to evaluate semaglutide for weight management. The initial clinical protocol was a Phase 2, placebo-controlled, dose-finding trial NN9536-4153 (Trial 4153).

An end-of-phase 2 meeting was held on October 23, 2017. Major topics included Phase 3 trial design, eligibility criteria, endpoints, cardiovascular safety, and assessment of immunogenicity.

A pre-NDA teleconference was held on August 11, 2020. The applicant submitted the NDA on December 4, 2020.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends approval, including approval for all facilities listed in the application. Refer to the OPQ Integrated Quality Assessment authored by the Application Technical Lead, Dr. Muthukumar Ramaswamy, and the individual discipline reviews, for details. The product is a drug-device combination product. Recommendations from the Center for Devices and Radiologic Health (CDRH) are also summarized in this of this section. I concur with the conclusions and recommendations of the OPQ and CDRH reviewers.

The drug substance reviewer, Dr. Daniel Jansen, concluded that the application is adequate to support approval. Refer to his review for details of the drug substance review. Data pertinent to labeling are summarized here.

Semaglutide (NN9536) is an analog of human glucagon-like peptide-1, GLP-1(7-37) with two amino acid substitutions (Ala8 to Aib8 [2-aminoisobutyric acid], Lys34 to Arg34) and Lys26 acylated with a fatty diacid moiety. The chemical name for semaglutide is N6.26-{18-[N-(17-carboxyheptadecanoyl)-L-γ-glutamyl]-10-oxo-3,6,12,15-tetraoxa-9,18-diazaoctadecanoyl]-[8-(2-amino-2-propanoic acid), 34-L-arginine] human glucagon-like peptide 1 (7-37). This application cross-references NDA 209637 Ozempic (semaglutide) injection, also held by Novo Nordisk, for all drug substance information.

The drug product reviewer, Dr. Ali Mohamadi, concluded that the proposed specification is adequate to support the quality of the proposed product. Refer to his review for details. Data pertinent to labeling are summarized here.

The proposed drug product, Wegovy (semaglutide) injection is a clear, colorless, sterile aqueous solution provided as a single dose pre-filled syringe assembled in a mL single-dose pen injector in five strengths (0.25 mg/0.5 mL, 0.5mg/0.5mL, 1.0 mg/0.5mL, 1.7 mg/0.75mL, and 2.4 mg/0.75mL). Each mL of Wegovy contains 1.42 mg of disodium phosphate dihydrate, 8.25 mg of sodium chloride and water for injection, adjusted to pH 7.4 with hydrochloric acid or sodium hydroxide.

The container closure components proposed for use are known for use in approved products. The applicant provided leachable study assessment to assure the safety of the proposed system. Dr. Mohamadi reviewed and recommends approval of the final carton and container labeling, agreed upon with the applicant.

Reference ID: 4806089
The applicant sought exemption from environmental impact analysis, and Dr. Mohamadi granted categorical exclusion from this requirement.

The microbiology reviewer, Dr. Helen Ngai, concluded that the proposed microbiological controls are adequate to support approval. Refer to her review for details.

The process reviewer, Dr. Suresh Dadiboyena, concluded that the proposed control strategy is adequate to assure the quality of the product. Dr. Dadiboyena reviewed the facility compliance information in consultation with the Office of Regulatory Affairs (ORA) and the CDRH reviewer, Dr. Dunya Karimi, and concluded that the facilities associated with the application are adequate to support approval.

Dr. Ramaswamy recommends that the Wegovy drug product should be stored at 2°C to 8°C (36°F to 46°F) for up to 24 months protected away from light in the carton. During shelf-life, each Wegovy single dose pen may be stored unrefrigerated at 8°C to 30°C (46 F to 86F) for 28 days in the commercial packaging.

In summary, Dr. Ramaswamy and the individual discipline reviewers all support approval of the application, and I concur with their recommendations.

**Device Review**

The CDRH reviewer, Dr. Dunya Karimi, reviewed the device component of the combination product and recommends approval. There were no unresolved information requests or deficiencies at the end of the review. Dr. Karimi recommends post-approval inspections for two manufacturing sites, because a recent medical device inspection has not been performed for either. I concur with these recommendations.

**Human Factors**

The Division of Medication Error Prevention and Analysis (DMEPA) reviewer, Mr. Jason Flint, concluded that the human factors validation study provided by the applicant demonstrated that representative users could use the product safely and effectively. The DMEPA review also provided recommendations for the carton and container labeling and the Instructions for Use. I concur with the recommendations.

**Immunogenicity Review**

The Office of Biotechnology Products (OBP) reviewer, Dr. Mohanraj Manangeeswaran, concluded that the screening and confirmatory assays used in monitoring the anti-drug antibody (ADA) response were validated and suitable for their intended purpose, but that the assay used to assess neutralizing activity lacked sufficient sensitivity in the presence of residual levels of semaglutide.

FDA had previously issued postmarketing commitments (PMCs) to the applicant for the Ozempic (semaglutide) injection and Rybelsus (semaglutide) oral tablets products approved for diabetes indications to improve assay sensitivity. The applicant had made a good-faith effort but was unable to develop a sufficiently sensitive assay. In this application, there were no safety or efficacy concerns with semaglutide in patients who develop ADA. The overall incidence of ADA in the semaglutide weight management program was 2.9% (50/1709), ADA titers were low, and there was no apparent impact on PK, PD, safety, or efficacy. Dr.
Manangeeswaran supports approval of the application from an immunogenicity perspective and concluded that a PMC is not required for this application. I concur with these recommendations.

4. Nonclinical Pharmacology/Toxicology

The FDA nonclinical reviewer, Dr. Elena Braithwaite, supports approval of the application. The applicant submitted two pharmacology studies to investigate the mechanism of weight loss but did not submit any new toxicology studies. The applicant had previously conducted a nonclinical program under IND 079754 and submitted with NDA 209637 in support of the diabetes indication for semaglutide. Refer to Dr. Braithwaite’s review for details. Major findings relevant to labeling are summarized here.

Semaglutide binds and activates the human GLP-1 receptor (GLP-1R), which is expressed both in the brain and peripheral tissues. In mice, single subcutaneous-dose administration led to increased brain expression of c-Fos, a gene induced by GLP-1R. With repeat subcutaneous dosing, fluorescently tagged semaglutide distributed to areas of the brain involved in food regulation, including areas of the hypothalamus protected by the blood-brain barrier.

In rats, semaglutide demonstrated treatment-related effects on the central nervous system and urinary system up to 8 hours post-dose at the clinical exposure. There were no adverse effects on respiratory function in rats. Semaglutide did not adversely affect the cardiovascular system in vitro, and there were no ECG changes in monkeys following single doses.

In monkeys, semaglutide subcutaneous injection had a bioavailability of 86% and was >99% bound to plasma proteins, primarily albumin. The volume of distribution was 0.2 L/kg, indicating that semaglutide distributes to plasma and peripheral tissues to the same extent as albumin. In rats, semaglutide was detected in all tissues (with the exception of the lens of the eye) after subcutaneous administration. Semaglutide is metabolized by degradation of the peptide backbone and the fatty octadecanedioic acid before being eliminated predominately in the urine and feces. In rats, semaglutide was secreted in the milk at day 10 post-partum at levels 3- to 12-fold lower than in maternal plasma.

The toxicity profile of semaglutide was evaluated in mice, rats, and monkeys for up to 3, 6, and 12 months in duration, respectively. In mice, the primary histopathological microscopic finding was focal C-cell hyperplasia and C-cell nests in the thyroid, and dilated ultimobranchial ducts in all semaglutide-treated groups at 6-fold clinical exposure based on area-under-the-curve-concentration (AUC). Liver findings were considered secondary to the pharmacodynamic activity. A no-observed-adverse-effect level (NOAEL) could not be established in mice. In rats, findings were considered non-adverse. The NOAEL in rats was the highest dose examined, 10-fold the maximum recommended human dose (MRHD). In monkeys, chronic left bundle branch block occurred in one female at 5-fold the MRHD, and multifocal myocardial vacuolation and degeneration, with karyomegaly, in the left ventricle occurred in one male at 10- to 12-fold the MRHD. The NOAEL was 2-fold the MRHD based on AUC.

In a combined fertility and embryo-fetal development study in rats, no effects were observed on male fertility. In females, an increase in estrus cycle length was observed at all dose levels.
and reduction in numbers of corpora lutea at clinical exposure associated with decreased food consumption and body weight.

In the embryo-fetal development component of the rat study, visceral (cardiovascular) and skeletal fetal abnormalities were observed at clinical exposures associated with decreased maternal food consumption and body weight gain. In an embryo-fetal development study in pregnant rabbits, reductions in maternal body weight gain and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (renal, hepatic) and skeletal fetal abnormalities were observed at clinical exposures. In an embryo-fetal development study in pregnant cynomolgus monkeys, marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities at greater than or equal to 2-times human exposure.

In a pre- and postnatal development study in pregnant cynomolgus monkeys, initial maternal body weight loss and reductions in body weight gain and food consumption at human exposure coincided with an increase in early pregnancy losses and decreased infant body weight at birth at 3-times human exposure.

In juvenile rats, administration of semaglutide resulted in reduced food consumption, body weight gain, and delayed sexual maturation in all treated groups at the clinical exposure but did not have an adverse impact on estrous cyclicity, mating performance, or fertility at doses 8-fold the MRHD based on AUC.

Semaglutide was not genotoxic in standard in vitro and in vivo assays.

In 2-year carcinogenicity studies in mice, a statistically significant increase in thyroid C-cell adenomas and a numerical increase in C-cell carcinomas was observed in males and females at clinical exposures. In a 2-year carcinogenicity study in rats, a statistically significant increase in C-cell adenomas was observed in males and females at clinical exposures, and a statistically significant increase in C-cell carcinomas was observed in males at clinical exposures.

5. Clinical Pharmacology

The FDA clinical pharmacology review team recommends approval, and I concur with the recommendation. Refer to the Office of Clinical Pharmacology review, authored by Dr. Sang Chung and Dr. Justin Earp for details. Major findings are summarized here.

Body weight percent change from baseline with semaglutide compared to placebo at Week 68 was statistically significant in the Phase 3 trials. The most common adverse events were gastrointestinal, and there were no new or unexpected safety observations. Refer to the Clinical Efficacy and Safety sections of this review for details.

The therapeutic and maintenance dose of semaglutide injection for weight management is 2.4 mg administered subcutaneously once weekly. The dose should be administered subcutaneously into the abdomen, thigh, or upper arm, and the injection sites should be changed. Dose escalation is used to mitigate gastrointestinal adverse events. The starting dose is 0.25 mg followed by a dose-escalation regimen consisting of dose increases every 4 weeks (interim doses of 0.5, 1.0, and 1.7 mg once weekly) until the target dose, 2.4 mg once weekly, is reached. The dose can be temporarily decreased to 1.7 mg weekly, for a maximum of 4 weeks, if a patient does not tolerate the maintenance 2.4 mg dose. There is no specific dosing for any patient subgroup because of intrinsic or extrinsic factors.
The to-be-marketed drug product (single-dose pen-injector [DV3396] with formulation D) was bridged to the clinical product (multi-dose cartridge-based PDS290 pen-injector with formulation B) in a pivotal pharmacokinetic (PK) bioequivalence (BE) trial (NN9536-4590). Bioequivalence was demonstrated between the formulations and presentations.

Semaglutide is a long-acting GLP-1 receptor agonist, which consists of human GLP-1 analog, C18 fatty di-acid, and a hydrophilic spacer. Semaglutide has prolonged plasma half-life compared to endogenous GLP-1 because of increased stability against the dipeptidyl peptidase 4 (DPP-4) enzyme from the amino acid substitution and increased protein binding from both the fatty acid side chain and spacer. The long half-life supports once-weekly administration.

**Absorption, Distribution, and Elimination**

In clinical PK studies at steady state in subjects with overweight or obesity, the maximum plasma concentration ($C_{\text{max}}$) was reached at a median time of 24 hours with range of 3 to 48 hours. The area-under-the-curve concentration-time profile (AUC$_{0-7\text{days}}$) was 5729 nmol*h/L, and $C_{\text{max}}$ was 46.3 nmol/L. Steady-state was reached approximately 4 to 5 weeks following once weekly administration. PK was approximately dose-proportional at steady state between 1 mg and 2.4 mg once weekly.

The volume of distribution ($V_{\text{ss/F}}$) was 9.8 L.

The elimination half-life was 155 hours. Clearance ($CL/F$) was 0.04 L/h. The primary elimination involves known protein catabolism, and there is no significant dose- or time-dependent change in disposition.

**Dose**

The exposure-response information from the Phase 2 dose-finding trial supports the dosing regimen. Exposure modeling supports the proposed administration instructions in the event of a missed dose. If one dose is missed and the next scheduled dose is more than 2 days away (48 hours), the dose may be administered. If one dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the patient should resume dosing on the regularly scheduled day of the week.

**QT Evaluation**

The applicant did not conduct a dedicated QT/QTc trial following the proposed therapeutic dose of 2.4 mg once weekly and instead referenced results of the previously conducted thorough QTc (TQT) trial following 1.5 mg once weekly in healthy subjects conducted as part of the diabetes program. The TQT trial showed that there was no prolongation of the QTc interval and no concentration-QTc relationship. The applicant concluded that results were adequate to support the weight management indication with the proposed therapeutic dose of 2.4 mg once weekly based on estimated population average exposure ($C_{\text{avg}}$) comparability between the TQT trial and the weight management Phase 3 trials for the target populations. In a previous consult review dated October 5, 2017, the FDA Interdisciplinary Review Team (IRT) for Cardiac Safety Studies agreed with the IND sponsor’s proposal. In a follow-up memorandum dated May 21, 2021, and authored by Dr. Christine Garnett, the IRT confirmed that the applicant’s approach appeared reasonable.
**Immunogenicity**

The proportion for subjects with positive ADA at any time post-baseline was 2.9% (N=50) in trials with antibody assessments, and approximately half of positive ADA were transient. Neutralizing antibody (NAb) cross-reacting with endogenous GLP-1 were present in 1.6% (N=28) of patients exposed to semaglutide. Overall, ADA and NAb detection rates were low, and there was no apparent impact on PK.

**Drug-Drug Interactions**

The applicant referenced information in Ozempic labeling for drug-drug interactions. In addition, the sponsor conducted a drug interaction study with paracetamol (acetaminophen) with the 2.4 mg dose, which showed a statistically significant effect of semaglutide on paracetamol PK (8% difference in paracetamol). The applicant conducted a post hoc analysis using body weight adjusted paracetamol PK, which indicated that there was no apparent effect on gastric emptying.

**6. Clinical Microbiology**

The FDA microbiology reviewer, Dr. Helen Ngai, concluded that the proposed microbiological controls are adequate to support approval. Refer to Section 3 – Product Quality of this review, and Dr. Ngai’s review for details.

**7. Clinical/Statistical-Efficacy**

This section discusses the major design features of the Phase 3 clinical trials, the analysis of the primary endpoint, and analyses of secondary endpoints pertinent to labeling. For in-depth discussion of the trials and endpoints not immediately relevant to approval or labeling, refer to the FDA clinical review by Dr. Julie Golden. For details of the statistical methods, refer to the FDA statistical review by Dr. Kyunghee Song.

The efficacy of semaglutide as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with obesity or overweight in the presence of at least one weight related co-morbid condition was evaluated in three 68-week, randomized, double-blind, placebo-controlled trials and one 68-week, randomized, double-blind, placebo withdrawal trial.

Both Dr. Golden and Dr. Song recommend approval of semaglutide as an adjunct to a reduced calorie diet and exercise for chronic weight management in the proposed population. I agree with their conclusions.

The data from these trials represent substantial evidence of effectiveness consisting of adequate and well-controlled trials. The randomized, double-blind, placebo-controlled design allowed the reviewers to distinguish the treatment effect of semaglutide on body weight from other influences and provide a quantitative estimate of the treatment effect of the drug as an adjunct to a reduced calorie diet and exercise in patients without and with type 2 diabetes, and as an adjunct to an intensive diet and exercise program in patients without diabetes. Although the design of the fourth trial, a randomized withdrawal, limits interpretability of the observed treatment effect somewhat, the trial nevertheless demonstrated the superiority of continued treatment with semaglutide compared to discontinuation in patients who achieved the target dose after 20 weeks of treatment.
**Trial Design – Overview**

Studies NN9536-4373 (STEP 1, Trial 4373), NN9536-4374 (STEP 2, Trial 4374), and NN9536-4375 (STEP 3, Trial 4375) consisted of a 16-week dose-escalation period, during which semaglutide or placebo was escalated to 2.4 mg subcutaneous weekly (blinded), followed by a 52-week maintenance-dose treatment period. During dose escalation, patients took each of the following dose levels – once weekly for 4 weeks each at 0.25 mg, 0.5 mg, 1 mg, and 1.7 mg – before increasing to the maintenance dose.

Study NN9536-4376 (STEP 4, Trial 4376) consisted of a 20-week open-label, run-in period during which the dose of semaglutide was escalated to 2.4 mg once weekly following the same escalation schedule used for the other three trials, followed by a randomized withdrawal; patients who reached 2.4 mg were randomized to either continued treatment with semaglutide or matching placebo for a 48-week treatment period.

In Trials 4373, 4374, and 4376, patients received instruction for a reduced calorie meal diet (approximately 500 kcal/day deficit) and increased physical activity counseling (recommended minimum of 150 min/week) beginning with the first dose of study medication or placebo. In Trial 4375, patients received instruction for an initial 8-week low-calorie diet (total energy intake 1000 to 1200 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). Refer to the FDA clinical review authored by Dr. Golden for details.

Statistical methods were similar across trials. Refer to the FDA statistical review by Dr. Kyunghee Song for details. Major principles are described here.

In all trials, the primary estimand quantified the treatment effect in all randomized subjects regardless of adherence to treatment or initiation of other anti-obesity therapies (i.e., treatment policy estimand). The full analysis set (FAS) included all randomized subjects according to the intention-to-treat principle. The analysis model for continuous variables was an analysis of covariance model (ANCOVA). The analysis model for categorical endpoints was a logistic regression. The type I error rate for secondary endpoints was controlled by a sequential testing approach.

The last available and eligible observation at or before randomization was used as the baseline value when baseline data were missing. For Trial 4376, the baseline values were values at week 20 (at randomization). All available data at Week 68 were used and missing values at Week 68 were imputed. The primary imputation approach was a multiple imputation. Missing values for non-retrieved dropouts were imputed using available assessments from retrieved dropouts in each randomized treatment arm. Missing values for patients on-treatment were imputed using available assessments on randomized treatment in the same arm.

Dr. Song concluded that there were no major statistical issues with the submission.

**Individual Trials**

**Trial 4373**

Trial 4373 was a multicenter, multinational, randomized, double-blind, parallel-arm, placebo-controlled trial to evaluate the effect of semaglutide 2.4 mg on body weight as an adjunct to a reduced calorie diet and exercise in adult patients with obesity or overweight. The trial consisted of a 68-week treatment period (including 16-week blinded dose-escalation), a 7-
week off-treatment follow-up period, and an open-label, 52-week, off-treatment, extension period (not reported with this submission). Refer to Dr. Golden’s review for details of the trial. The results are summarized here.

The trial enrolled 1961 patients at least 18 years of age with obesity (BMI greater than or equal to 30 kg/m2) or with overweight (BMI 27-29.9 kg/m2) and at least one weight-related comorbid condition (treated or untreated hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease). Patients with diabetes mellitus and patients with body weight change >5 kg within 90 days before screening were excluded. Patients were randomized in a 2:1 ratio to either semaglutide or placebo. A subpopulation of 140 patients in the U.S. with BMI ≤ 40 kg/m2 at screening were enrolled in a body composition study using dual x-ray absorptiometry (DXA) scanning.

The two co-primary endpoints were:

- Mean percent change in body weight from baseline to week 68
- Proportion of patients achieving a weight loss of ≥ 5% from baseline to week 68

The secondary endpoints were: proportion of patients achieving ≥ 10% weight loss, proportion of patients achieving ≥ 15% weight loss, change in waist circumference, change in systolic blood pressure, change in SF-36 Physical Functioning score, and change in Impact of Weight on Quality of Life-Lite for Clinical Trials v. 3.0 (IWQoL-Lite-CT) Physical Function score, all assessed from baseline (week 0) to week 68.

All randomized patients (1306 semaglutide and 655 placebo) were exposed to treatment and included in the full analysis set. Approximately 95% of patients in the semaglutide arm and 93% of patients in the placebo arm completed the trial. Approximately 83% of patients in the semaglutide arm and 78% of patients in the placebo arm remained on treatment. The most frequently reported reason for permanent treatment discontinuation in the semaglutide arm was an adverse event.

Demographic characteristics were similar between arms. At baseline, the mean age was 46 years (range 18-86), 74% of patients were female, and 39% were from the U.S. About 75% identified as White race, 13% as Asian, and 6% as Black; 12% were Hispanic or Latino ethnicity.

Baseline characteristics were similar between arms. Mean baseline body weight was 105.3 kg, mean BMI was 37.9 kg/m², mean waist circumference was 114.7 cm, and mean HbA1c was 5.7%.

Treatment with semaglutide 2.4 mg weekly resulted in statistically significant and clinically meaningful weight loss compared to placebo. Table 1 summarizes the primary endpoint, mean percent change in weight from baseline. Figure 1 presents the mean percent change in body weight over time.

The FDA statistical reviewer, Dr. Song, confirmed the results of the primary endpoint and concluded that the multiple prespecified sensitivity analyses were consistent with the primary analysis. Additionally, she concluded that tipping point analyses supported the robustness of the conclusion derived from the primary analysis. Refer to the FDA statistical review for additional details.
Table 1: Percent Body Weight Change from Baseline to Week 68, NN9536-4373, Full Analysis Set

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline Mean (SD) (kg)</th>
<th>Week 68 Mean (SD) In-trial (kg)</th>
<th>% Change from Baseline ANCOVA RD-MI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semaglutide</td>
<td>1306</td>
<td>105.4 (22.1)</td>
<td>89.0 (22.7)</td>
<td>-14.85</td>
</tr>
<tr>
<td>Placebo</td>
<td>655</td>
<td>105.2 (21.5)</td>
<td>101.9 (22.0)</td>
<td>-2.41</td>
</tr>
<tr>
<td>Semaglutide vs. Placebo</td>
<td></td>
<td>Estimated treatment difference (95% CI) (%)</td>
<td>p-value</td>
<td>-12.44 (-13.37, -11.51)</td>
</tr>
</tbody>
</table>

Abbreviations: N=number of patients randomized, SD=standard deviation, CI=confidence interval, ANCOVA RD-MI= analysis of covariance retrieved-dropout multiple imputation.

Model based estimates using an analysis of covariance model included treatment as a fixed effect and baseline value as a covariate. Missing values imputed using retrieved-dropout multiple imputation.

Source: Trial 4373 CSR, Tables 14.2.2 and 14.2.9 and FDA Clinical Review.

Figure 1: Percent Body Weight Change from Baseline by Week, Trial NN9536-4373, Observed Data

Table 2 summarizes the co-primary and first two secondary endpoints in the testing hierarchy, the proportions of patients achieving ≥5%, ≥10%, and ≥15% body weight loss from baseline. Figure 2 presents the cumulative distribution for percent change in body weight by treatment arm.
Table 2: Proportion of Patients Achieving Weight Loss Thresholds from Baseline to Week 68, NN9536-4373, Full Analysis Set

<table>
<thead>
<tr>
<th>Percent Weight Loss</th>
<th>N</th>
<th>Proportion of Patients Achieving Weight Loss (%)</th>
<th>Estimated treatment difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≥ 5%</td>
<td>≥ 10%</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>1306</td>
<td>83.5</td>
<td>66.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>47.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>655</td>
<td>31.1</td>
<td>12.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td>Semaglutide vs. Placebo</td>
<td></td>
<td>52.4 (48.1, 56.8)</td>
<td>54.1 (50.4, 57.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>43.1 (39.8, 46.3)</td>
</tr>
</tbody>
</table>

Abbreviations: N=number of patients randomized, CI=confidence interval. Model based estimates using a logistic regression with treatment as a factor and baseline body weight (kg) as a covariate. P<0.0001 for all.

Source: Applicant M5.3.5.3 [ISE] Appendices 6.3.42, 6.3.45, 6.3.46

Figure 2: Body Weight Percent Change from Baseline to Week 68 – Cumulative Distribution by Treatment Arm, NN9536-4373, Observed Data

All secondary endpoints (in addition to the two categorical endpoints, addressed above) were evaluated from baseline to week 68 and were statistically significant per the prespecified testing procedure to control the type I error rate. Secondary endpoints are presented in the prespecified order in the testing hierarchy. Refer to Dr. Golden’s review for details of the
clinical relevance of these analyses and to Dr. Song’s review for details of the statistical methods and confirmation of the analyses. Patient-reported outcomes and other parameters included among the secondary endpoints are discussed later in this review.

Mean waist circumference (WC) at baseline was 114.7 cm. Mean changes from baseline in WC were -4.1 cm for placebo and -13.5 cm for semaglutide 2.4 mg. The estimated treatment difference between semaglutide and placebo was -9.4 cm.

Mean systolic blood pressure (SBP) at baseline was 126 mmHg. Mean changes from baseline in SBP were -1.1 mmHg for placebo and -6.2 mmHg for semaglutide, for an estimated difference of -5.1 mmHg.

Mean Short Form 36 v2.0 (SF-36) physical functioning score was 50.9 at baseline. The range of possible scores is 19.03 to 57.60, with higher scores indicating better function. Mean changes from baseline were +0.4 for placebo and +2.2 for semaglutide. The estimated difference was +1.8.

Mean IWQoL-Lite-CT score was 65.0 at baseline. The range of possible scores is 0 to 100. Mean changes from baseline were +5.2 for placebo and +14.7 for semaglutide, for an estimated difference of +9.4.

Supportive secondary endpoints included assessment of cardiometabolic risk factors including changes in diastolic blood pressure (DBP), HbA1c, and lipid parameters. Treatment with semaglutide was associated with nominally significant improvement in all parameters. For DBP, the estimated difference between semaglutide and placebo was -2.41 mmHg. The estimated difference in HbA1c was -0.29%. Semaglutide was associated with mean percent change in low-density lipoprotein cholesterol (LDL-C) of -3.8% compared to placebo. Changes in total cholesterol (TC), high-density lipoprotein (HDL-C), and triglycerides (TG) were all favorable in the semaglutide arm compared to placebo.

Body composition assessments by DXA in a subset of patients suggested a decrease in total fat mass (-6.99 kg) along with a smaller decrease in lean body mass (-3.43 kg) versus placebo. Refer to the FDA clinical review for details and relevance of these endpoints.

**Trial 4374**

Trial 4374 was a multicenter, multinational, randomized, double-blind, double-dummy, three-arm, placebo-controlled, trial to evaluate the effect of semaglutide 2.4 mg once weekly on body weight as an adjunct to a reduced calorie diet and exercise in adult patients with obesity or overweight with concomitant type 2 diabetes. The trial consisted of a 68-week treatment period (including 16-week blinded dose escalation) and a 7-week off-treatment follow-up period. Refer to the FDA clinical review for additional details. Trial results are summarized here.

The trial enrolled 1210 patients at least 18 years of age with type 2 diabetes and BMI greater than or equal to 27 kg/m². Patients included in the trial had HbA1c 7% to 10% and were treated with either diet and exercise alone or up to three oral anti diabetic agents (metformin, sulfonylurea, thiazolidinedione, or sodium-glucose co-transporter 2 [SGLT2] inhibitor). Patients with a body weight change >5 kg within 90 days before screening, renal impairment (estimated glomerular filtration rate [eGFR] value of < 30 mL/min/1.73 m² or <60 mL/min/1.73 m² in subjects treated with SGLT2 inhibitor), or uncontrolled and potentially
unstable diabetic retinopathy or maculopathy were excluded. Patients were randomized 1:1:1 to semaglutide 2.4 mg, semaglutide 1 mg, or placebo.

The primary and secondary endpoints tested semaglutide 2.4 mg versus placebo, unless otherwise specified. The two co-primary endpoints were:

- Mean percent change in body weight from baseline to week 68
- Proportion of patients achieving a weight loss of ≥ 5% from baseline to week 68

The secondary endpoints were: proportion of patients achieving ≥ 10% weight loss, proportion of patients achieving ≥ 15% weight loss, change in waist circumference, percent change in body weight between semaglutide 2.4 mg and semaglutide 1 mg, change in systolic blood pressure, change in SF-36 Physical Functioning score, and change in IWQoL-Lite-CT Physical Function score, all assessed from baseline (week 0) to week 68.

A total of 1210 patients were randomized (full analysis set) and 1207 were exposed to treatment (safety analysis set). Approximately 97% of patients in each of the two semaglutide arms and 95% of patients in the placebo arm completed the trial. Approximately 88% of patients in each of the two semaglutide arms and 86% of patients in the placebo arm remained on treatment. The most frequently reported reason for treatment discontinuation in the semaglutide arms was an adverse event.

Demographic characteristics were similar between arms. At baseline, the mean age was 55 years (range 19-84), 51% of patients were female, and 30% were from the U.S. About 62% identified as White race, 26% as Asian, and 8% as Black or African American; about 13% were Hispanic or Latino ethnicity.

Baseline characteristics were similar between arms. Mean baseline body weight was 99.8 kg, mean BMI was 35.7 kg/m², mean waist circumference was 114.6 cm, and mean HbA1c was 8.1%. Mean duration of diabetes was 8 years.

Treatment with semaglutide 2.4 mg weekly in patients with type 2 diabetes resulted in statistically significant and clinically meaningful weight loss compared to placebo. Table 3 summarizes the primary endpoint, mean percent change in body weight from baseline between semaglutide 2.4 mg and placebo, and the fourth secondary endpoint, mean percent change in body weight between semaglutide 2.4 mg and semaglutide 1 mg. The estimated treatment effect versus placebo in this trial was numerically smaller than that observed in Trial 4373, suggesting that the expected clinical effect in patients with type 2 diabetes is smaller. Nevertheless, this cross-trial comparison should be interpreted cautiously. Differences in patient population, including mean baseline weight and allowed concomitant medications could impact the results.

Dr. Song confirmed the results of the primary endpoint and concluded that the data were statistically robust. Refer to the FDA statistical review for additional details.
Table 3: Percent Body Weight Change from Baseline to Week 68, NN9536-4374, Full Analysis Set

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline Mean (SD) (kg)</th>
<th>Week 68 Mean (SD) In-trial (kg)</th>
<th>% Change from Baseline ANCOVA RD-MI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semaglutide 2.4 mg</td>
<td>404</td>
<td>99.9 (22.5)</td>
<td>89.6 (21.0)</td>
<td>-9.64</td>
</tr>
<tr>
<td>Semaglutide 1 mg</td>
<td>403</td>
<td>99.0 (21.1)</td>
<td>92.3 (20.7)</td>
<td>-6.99</td>
</tr>
<tr>
<td>Placebo</td>
<td>403</td>
<td>100.5 (20.9)</td>
<td>96.8 (20.3)</td>
<td>-3.42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimated treatment difference (95% CI) (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semaglutide 2.4 mg vs. Placebo</td>
<td>-6.21 (-7.28, -5.15)</td>
</tr>
<tr>
<td>Semaglutide 2.4 mg vs. 1 mg</td>
<td>-2.65 (-3.66, -1.64)</td>
</tr>
</tbody>
</table>

Abbreviations: N=number of patients randomized, SD=standard deviation, CI=confidence interval, ANCOVA RD-MI= analysis of covariance retrieved-dropout multiple imputation.
Model based estimates using an analysis of covariance model included treatment and stratification groups (oral anti-diabetic drug (OAD) treatment and HbA1c category) as fixed effects and baseline value as a covariate. Missing values imputed using retrieved-dropout multiple imputation.
Source: Study 4374 CSR, Tables 14.2.1 and 14.2.9 and FDA Clinical Review

Table 4 summarizes the co-primary and first two secondary endpoints, the proportions of patients achieving ≥5%, ≥10%, and ≥15% body weight loss from baseline. Figure 3 presents the cumulative distribution for percent change in body weight by treatment arm.

Table 4: Proportion of Patients Achieving Weight Loss Thresholds from Baseline to Week 68, NN9536-4374, Full Analysis Set

<table>
<thead>
<tr>
<th>Percent Weight Loss</th>
<th>N</th>
<th>Proportion of Patients Achieving Weight Loss (%)</th>
<th>Estimated treatment difference (95% CI) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≥ 5%</td>
<td>≥ 10%</td>
</tr>
<tr>
<td>Semaglutide 2.4 mg</td>
<td>404</td>
<td>67.4</td>
<td>44.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>403</td>
<td>30.2</td>
<td>10.2</td>
</tr>
<tr>
<td>Semaglutide 2.4 mg vs. Placebo</td>
<td>37.3 (30.7, 43.8)</td>
<td>34.3 (28.4, 40.2)</td>
<td>20.7 (15.7, 25.8)</td>
</tr>
</tbody>
</table>

Abbreviations: N=number of patients randomized, CI=confidence interval.
Model based estimates using a logistic regression with treatment and stratification groups (oral anti-diabetic drug (OAD) treatment and HbA1c category) as factors and baseline body weight (kg) as a covariate. \(^1\) P<0.0001 for all.
Source: Applicant M5.3.5.3 [ISE] Appendices 6.3.42, 6.3.45, 6.3.46
The remaining secondary endpoints were evaluated from baseline to week 68 and were statistically significant per the prespecified testing procedure. Refer to the clinical and statistical reviews for details.

Mean WC at baseline was 114.6 cm. Mean changes in WC from baseline were -4.52 cm for placebo and -9.40 cm for semaglutide 2.4 mg, for an estimated difference of -9.4 cm.

Mean HbA1c at baseline was 8.1%. Mean changes from baseline were -0.37 for in the placebo arm and -1.60% in the semaglutide 2.4 mg arm, and the estimated difference was -1.23%. There was no significant difference in HbA1c between semaglutide 2.4 mg and semaglutide 1 mg, although the trial was not powered to detect a difference.

Mean systolic blood pressure (SBP) at baseline was 130 mmHg. Mean changes from baseline in SBP were -0.5 mmHg for placebo and -3.9 mmHg for semaglutide. The estimated difference was -3.4 mmHg.

Mean SF-36 physical functioning score was 49.7 at baseline. Mean changes from baseline were +1.0 for placebo and +2.5 for semaglutide. The estimated difference was +1.5.

Mean IWQoL-Lite-CT score was 69.2 at baseline. Mean changes from baseline were +5.3 for placebo and +10.1 for semaglutide, for an estimated difference of +4.8 between semaglutide and placebo.
Exploratory analyses comparing semaglutide 2.4 mg and semaglutide 1 mg were associated with an improvement in WC (-2.7 cm) with semaglutide 2.4 mg. Changes in HbA1c and SBP were not significantly different between arms.

Changes in cardiometabolic parameters (DBP, TC, and LDL-C) among patients randomized to semaglutide 2.4 mg were not significantly different from placebo or semaglutide 1 mg.

**Trial 4375**

Trial 4375 was a multicenter, randomized, double-blind, placebo-controlled trial, conducted in the U.S. to evaluate the effect of semaglutide 2.4 mg on body weight, as an adjunct to an intensive diet and exercise intervention, in adult patients with obesity or overweight. The trial consisted of a 68-week treatment period (including 16-week dose escalation) and a 7-week, off-treatment follow-up period. Results are summarized here. Refer to the clinical review for details.

The trial enrolled 611 patients with obesity (BMI greater than or equal to 30 kg/m²) or with overweight (BMI 27-29.9 kg/m²) and at least one weight-related comorbid condition; patients with diabetes mellitus or body weight change >5 kg within 90 days before screening were excluded. Patients were randomized in a 2:1 ratio to receive either semaglutide or placebo as an adjunct to an intensive diet and exercise intervention.

The two co-primary endpoints were:
- Mean percent change in body weight from baseline to week 68
- Proportion of patients achieving a weight loss of ≥ 5% from baseline to week 68

The secondary endpoints included: proportion of patients achieving ≥ 10% weight loss, proportion of patients achieving ≥ 15% weight loss, change in waist circumference, change in systolic blood pressure, and change in SF-36 Physical Functioning score, all assessed from baseline (week 0) to week 68.

All randomized patients (407 semaglutide and 204 placebo) were exposed to treatment and included in the full analysis set. Approximately 92% of patients randomized to semaglutide and 94% of patients randomized to placebo completed the trial. Approximately 83% of semaglutide and 81% of placebo patients remained on-treatment; the most frequently reported reason for treatment discontinuation in the semaglutide arm was an adverse event.

At baseline, the mean age was 46 years, 81% of patients were women, 76% identified as White race, 19% as Black or African American, 2% as Asian, and 20% as Hispanic or Latino ethnicity. Mean baseline body weight was 105.8 kg and mean BMI was 38.0 kg/m².

Demographic characteristics were similar between arms, except for sex. Females comprised about 77% of the semaglutide group compared to 88% of the placebo group. Mean age was 46 years. All patients were from the U.S. About 76% of patients identified as White race, and 19% as Black or African American; about 20% were Hispanic or Latino ethnicity.

Baseline characteristics were similar between arms. Mean body weight was 105.8 kg, mean BMI was 38.0 kg/m², mean waist circumference was 113.0 cm, and mean HbA1c was 5.7%.

Treatment with semaglutide 2.4 mg weekly as an adjunct to an intensive diet and exercise regimen resulted in statistically significant and clinically meaningful weight loss compared to placebo. Table 5 summarizes the primary endpoint, mean percent change in weight from
baseline. Refer to the FDA statistical review by Dr. Song for her review of the primary endpoint, sensitivity analysis, and tipping point analyses.

The percent change from baseline with semaglutide was numerically slightly greater than that observed in Trial 4373, but the estimated treatment effect (the effect versus placebo) was numerically lower. This cross-trial comparison should be interpreted cautiously.

Table 5: Percent Body Weight Change from Baseline to Week 68, NN9536-4375, Full Analysis Set

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline Mean (SD) (kg)</th>
<th>Week 68 Mean (SD) In-trial (kg)</th>
<th>% Change from Baseline ANCOVA RD-MI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semaglutide</td>
<td>407</td>
<td>106.9 (22.8)</td>
<td>88.4 (21.5)</td>
<td>-15.97</td>
</tr>
<tr>
<td>Placebo</td>
<td>204</td>
<td>103.7 (22.9)</td>
<td>98.3 (23.6)</td>
<td>-5.70</td>
</tr>
<tr>
<td>Semaglutide vs. Placebo</td>
<td></td>
<td>Between treatment difference (95% CI) (%)</td>
<td>p value</td>
<td>-10.27 (-11.97, -8.57)</td>
</tr>
</tbody>
</table>

Abbreviations: N=number of patients randomized, SD=standard deviation, CI=confidence interval, ANCOVA RD-MI= analysis of covariance retrieved-dropout multiple imputation.

Model based estimates using an analysis of covariance model included treatment as a fixed effect and baseline value as a covariate. Missing values imputed using retrieved-dropout multiple imputation.

Source: Study 4375 CSR, Tables 14.2.2 and 14.2.9 and FDA Clinical Review

Table 6 summarizes the co-primary and first two secondary endpoints, the proportion of patients achieving ≥5%, ≥10%, and ≥15% body weight loss from baseline. Figure 4 presents the cumulative distribution for percent change in body weight by treatment arm.

Table 6: Proportion of Patients Achieving Weight Loss Thresholds from Baseline to Week 68, NN9536-4375, Full Analysis Set

<table>
<thead>
<tr>
<th>Percent Weight Loss</th>
<th>N</th>
<th>Proportion of Patients Achieving Weight Loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≥ 5%</td>
</tr>
<tr>
<td>Semaglutide 2.4 mg</td>
<td>407</td>
<td>84.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>204</td>
<td>47.8</td>
</tr>
<tr>
<td>Semaglutide vs. Placebo</td>
<td></td>
<td>Estimated treatment difference (95% CI)$^1$ (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37.0 (28.9, 45.2)</td>
</tr>
</tbody>
</table>

Abbreviations: N=number of patients randomized, CI=confidence interval.

Model based estimates using a logistic regression with treatment as a factor and baseline body weight (kg) as a covariate. $^1$P<0.0001 for all.

Source: Applicant M5.3.5.3 [ISE] Appendices 6.3.42, 6.3.45, 6.3.46
The remaining secondary endpoints were evaluated from baseline to week 68. Changes in WC and SBP were statistically significant per the prespecified testing procedure, but the endpoint evaluating change in SF-36 physical functioning failed to exclude the null hypothesis. Refer to the FDA clinical review and statistical review for clinical interpretation and statistical conclusions, respectively.

Mean WC at baseline was 113.0 cm. Mean changes from baseline in WC were -6.27 cm for placebo and -14.61 cm for semaglutide 2.4 mg, for an estimated difference of -8.34 cm.

Mean systolic blood pressure (SBP) at baseline was 124 mmHg. Mean changes from baseline in SBP were -1.6 mmHg for placebo and -5.6 mmHg for semaglutide, and the estimated difference was -3.9 mmHg.

Mean SF-36 physical functioning score was 51.9 at baseline. Mean changes from baseline were +1.6 for placebo and +2.4 for semaglutide. The estimated difference between treatment was +0.8 and was not statistically different from placebo.

Changes in cardiometabolic parameters (DBP, HbA1c, TC, LDL-C, HDL-C, and TG) among patients randomized to semaglutide were favorable. Observed mean change in DBP compared to placebo was -2.24 mmHg, mean change in HbA1c was -0.24%, and mean change in LDL-C was -7.1 mg/dL.
Trial 4376
Study 4376 was a multicenter, multinational, randomized, double-blind, placebo-controlled, withdrawal trial to assess the effect of continued treatment with semaglutide on body weight as an adjunct to reduced calorie diet and exercise in adult patients with obesity or overweight who achieved the 2.4 mg once weekly dose during dose escalation. The trial consisted of a 20-week open-label run-in period (including dose escalation), a 48-week randomized treatment period, and a 7-week off-drug follow-up period. The results are summarized here. Refer to the FDA clinical review for details.

The trial enrolled 902 patients with obesity (BMI greater than or equal to 30 kg/m²) or with overweight (BMI 27-29.9 kg/m²) and at least one weight-related comorbid condition; patients with diabetes mellitus or body weight change > 5 kg within 90 days of screening were excluded. All patients received semaglutide during the run-in period. Patients who attended the randomization visit at week 20, had escalated to the target (2.4 mg weekly) dose, and remained on the target dose at week 20 were randomized in a 2:1 ratio to either continue on semaglutide or receive placebo.

The primary endpoint was the change in body weight from randomization (week 20) to week 68. The secondary endpoints were change in waist circumference, change in systolic blood pressure, and change in SF-36 Physical Functioning score from randomization (week 20) to week 68.

Of the 902 enrolled patients, 803 (89%) reached 2.4 mg once weekly and were randomized (535 semaglutide, 268 placebo). About 98% of patients randomized to semaglutide completed the trial and 94% remained on treatment. In the placebo arm, 97% completed the trial and 88% remained on treatment. The most frequently reported reason for discontinuation of semaglutide (during both run-in and blinded treatment) was an adverse event.

Demographic characteristics were similar between randomized treatment arms. Among randomized patients, the mean age was 46 years, 79% of patients were women, and 39% were from the U.S. About 84% identified as White race, 13% as Black or African American, 2.4% as Asian; about 8% were Hispanic or Latino ethnicity.

Mean body weight at baseline (week 0) was 107.2 kg and mean BMI at baseline (week 0) was 38.4 kg/m². Mean body weight at randomization (week 20) was 96.1 kg and mean BMI at was 34.4 kg/m². Baseline characteristics were similar between treatment arms.

Among patients who achieved semaglutide 2.4 mg once weekly during titration, continued treatment with semaglutide 2.4 mg once weekly from randomization (week 20) to week 68 resulted in statistically significant and clinically meaningful weight loss compared to withdrawal to placebo. Table 7 summarizes the mean percent change in weight from baseline. Refer to the FDA statistical review for interpretation of the supplementary analyses.
Table 7: Percent Body Weight Change from Baseline to Week 68, NN9536-4375, Full Analysis Set

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline (Week 20) Mean (SD) (kg)</th>
<th>Week 68 Mean (SD) In-trial (kg)</th>
<th>% Change from Baseline ANCOVA RD-MI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semaglutide</td>
<td>535</td>
<td>96.5 (22.5)</td>
<td>89.0 (24.5)</td>
<td>-7.88</td>
</tr>
<tr>
<td>Placebo</td>
<td>268</td>
<td>95.4 (22.7)</td>
<td>100.6 (22.7)</td>
<td>+6.87</td>
</tr>
<tr>
<td>Semaglutide vs. Placebo</td>
<td></td>
<td><strong>Between treatment difference (95% CI) (%)</strong></td>
<td><strong>p value</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-14.75 (-16.00, -13.50)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Source: Study 4376 CSR, Tables 14.2.2 and 14.2.9

The observed treatment effect in this trial must be interpreted with caution. It does not represent an estimate of the experience of patients with no previous exposure to semaglutide, who are initiating therapy for the first time. The randomized population (N=803) was a subgroup of the population enrolled at the start of the run-in period (N=902) and includes individuals who both tolerated the dose-escalation and achieved the target dose. Patients who discontinued or did not escalate to the target dose, including those who discontinued or interrupted dose titration because of adverse events, were not eligible for evaluation.

Choice of baseline affects the observed percent change from baseline versus placebo. The week 20 baseline used as the denominator to calculate percent change baseline may overstate the estimate of the treatment effect, because it represents a substantial decrease (approximately 10%) from pre-treatment baseline.

For an alternate comparison, the applicant also analyzed the change from the start of the run-in period (week 0) to week 68, to attempt to better represent the experience of patients not previously exposed to semaglutide. Figure 5 presents the mean percent change in body weight by week for randomized patients, beginning at week 0.

The mean body weight among the subset of randomized patients (N=803) at week 0 was 107.2 kg. Mean percent change in body weight from week 0 to week 68 was baseline was -5.02% on placebo and -17.38% on semaglutide, for an estimated treatment difference of -12.36%.

Although the week 0 baseline value is probably a better estimate of the pre-treatment baseline, analysis of the change from baseline could only be conducted in the subset of patients who achieved the target dose and were randomized in the trial. Analysis of a subset of the enrolled population limits generalizability of the results.
Categorical endpoints were not included among the primary and key secondary endpoints and are not presented in this review. The study design issues described above limit interpretation of the categorical endpoints as well. Refer to the FDA clinical review by Dr. Golden for additional details of these analyses.

The secondary endpoints were evaluated from randomization (week 20 baseline) to week 68, comparing continued treatment with semaglutide to withdrawal to placebo, and were statistically significant per the prespecified testing procedure. Interpretation of these endpoints is limited by the same issues raised for the primary analysis. Refer to the FDA clinical review for details of these analyses.

Mean WC at week 20 was 105.3 cm. Mean changes from baseline in WC were +3.31 cm for placebo and -6.43 cm for semaglutide, for an estimated difference of -9.74 cm.

Mean systolic blood pressure (SBP) at week 20 was 121 mmHg. Mean changes from baseline in SBP were +4.4 mmHg for placebo and +0.5 mmHg for semaglutide, for an estimated difference of -3.9 mmHg.
Mean SF-36 physical functioning score was 53.9 at week 20. Mean changes from baseline were -1.46 for placebo and +1.0 for semaglutide. The estimated difference was +2.45.

Changes in cardiometabolic parameters (DBP, HbA1c, TC, LDL-C, HDL-C, and TG) among patients randomized to semaglutide were favorable. Observed mean change in DBP was -0.5 mmHg, mean change in HbA1c was -0.24%, and mean change in LDL-C was -6.0 mg/dL, for continued semaglutide treatment compared to withdrawal to placebo.

**Stopping Rule**

In Trial 4376, the applicant conducted analyses of a stopping rule for patients who are unable to achieve a certain threshold of weight loss. Because so few patients were non-responders, Trial 4376 supports continued use in patients who are able to tolerate escalation to the target dose (2.4 mg once weekly).

Of 902 enrolled patients in Trial 4376, 803 patients achieved escalation to the target dose and were randomized at week 20, and approximately 90% of randomized patients (719/803) achieved 5% or greater weight loss at week 20. In the FDA statistical review, Dr. Song conducted an exploratory analysis of patients with available data at week 20 and week 68. Table 8 summarizes response rates by weight loss achieved during the run-in period.

Among patients randomized to semaglutide, approximately 94% of week 20 responders (defined as 5% or greater weight loss from baseline) maintained 5% or greater weight loss at week 68. Among the 62 patients who had not responded by week 20, 52% nonetheless achieved at least 5% weight loss by week 68.

In contrast, among patients randomized to placebo, only 50% of week 20 responders maintained at least 5% weight loss at week 68 (as expected, given withdrawal of active treatment), and only 12% of placebo non-responders achieved 5% weight loss by week 68 on the background reduced calorie diet and exercise.

Most of the randomized non-responders had lost between 2% and <5% weight loss by week 20, and the data support continued treatment with semaglutide in this subset. Too few patients had achieved less than 2% weight loss at week 20 to make meaningful comparisons between randomized arms or define a stopping rule contingent on weight loss in this subset.

The trial reaffirmed the efficacy of semaglutide in patients who are able to tolerate dose escalation to the 2.4 mg once weekly dose. A stopping rule recommending discontinuation of semaglutide in patients who fail to achieve the target dose following the recommended escalation schedule is appropriate, as the Phase 3 trials were not designed to demonstrate substantial evidence of effectiveness at any other dose level.
Table 8: Weight Loss Responder Analysis by Run-in Weight Loss, NN9536-4376, Available Data

<table>
<thead>
<tr>
<th>% Change from Week 0 to Week 20</th>
<th>Semaglutide during randomized withdrawal period</th>
<th>Placebo during randomized withdrawal period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=520 Response rate¹</td>
<td>N=250 Response rate</td>
</tr>
<tr>
<td>No loss or gain</td>
<td>3 0 (0%)</td>
<td>0 0</td>
</tr>
<tr>
<td>&lt;1% loss</td>
<td>5 0 (0%)</td>
<td>1 0 (0%)</td>
</tr>
<tr>
<td>&lt;2% loss</td>
<td>11 1 (9.1%)</td>
<td>1 0 (0%)</td>
</tr>
<tr>
<td>&lt;3% loss</td>
<td>20 8 (40.0%)</td>
<td>5 0 (0%)</td>
</tr>
<tr>
<td>&lt;4% loss</td>
<td>40 16 (40.0%)</td>
<td>10 0 (0%)</td>
</tr>
<tr>
<td>&lt;5% loss</td>
<td>62 32 (51.6%)</td>
<td>17 2 (11.8%)</td>
</tr>
<tr>
<td>5% or more loss</td>
<td>458 429 (93.7%)</td>
<td>233 117 (50.2%)</td>
</tr>
</tbody>
</table>

¹Proportion of subjects who achieved 5% or more weight loss; cell contents are frequencies with relative frequencies in parentheses; missing data not assessed

Source: Adapted from FDA Statistical Review, Table 17

Clinical Outcomes Assessments

The FDA clinical outcomes assessments reviewer, Dr. Yasmin Choudhry, evaluated the use of the instruments in the Phase 3 program. Refer to her review for details of these analyses. The major conclusions are summarized here.

The secondary analyses of Trials 4373 and 4374 demonstrated statistically significant differences with semaglutide compared to placebo. The applicant proposed that Dr. Chowdhury observed, however, that there were minimal or no score changes – which she described as one category change on the raw score scale (i.e. non-normalized and non-transformed data) – at the item- and domain-level raw score scale data. Additionally, she noted that the changes in normalized and transformed scores were also minimal, evidenced by minimal separation between treatment arms on cumulative distribution function plots.

I concur with the recommendation.

Efficacy Summary

The data from the Phase 3 trials represent substantial evidence of effectiveness consisting of adequate and well-controlled trials to support approval of semaglutide 2.4 mg as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with overweight and at least one weight-related comorbid condition or obesity. The FDA clinical reviewer, Dr. Golden, supports approval on the basis of these trials, and I agree with her conclusions.
The three randomized, double-blind, placebo-controlled trials clearly distinguished the treatment effect of semaglutide on body weight from other influences, such as placebo effect, biased observation, or other factors. These trials provide a quantitative estimate of the treatment effect of the drug as an adjunct to a reduced calorie diet and exercise in patients without diabetes (Trial 4373), in patients with type 2 diabetes (Trial 4374), and as an adjunct to an intensive diet and exercise program in patients without diabetes (Trial 4375). The FDA statistical reviewer, Dr. Song, concluded that the trials provided evidence of a robust treatment effect for the study population. Furthermore, she observed that efficacy was supported by the secondary endpoints in each trial. I agree with her conclusions.

The effects of semaglutide versus placebo represent a 10% to 12% reduction in body weight compared to placebo in patients without type 2 diabetes at baseline. As an adjunct to a reduced calorie diet in Trial 4373, the estimated treatment effect was 12% weight loss versus placebo; over 80% of patients assigned to semaglutide treatment achieved at least 5% weight loss and approximately two-thirds achieved 10% weight loss compared to baseline. As an adjunct to an intensive diet and exercise program (Trial 4375), the observed weight change with semaglutide from baseline was slightly greater (as were the proportions of patients achieving various thresholds of weight loss), but the estimated treatment effect (10.3% weight loss) compared to placebo was slightly lower. Nevertheless, the results were clinically meaningful and statistically robust.

The estimated treatment effect observed in these trials is substantially greater than that observed in any comparable weight loss trial conducted to support approval for other approved products, although such a cross-study comparisons should be interpreted cautiously. Nevertheless, the overall trial quality (relatively low proportion of treatment discontinuation, high participant retention, low proportion of missing data, and appropriate handling of missing data) strongly support the validity of these findings.

In patients with type 2 diabetes, the estimated treatment effect of semaglutide as an adjunct to a reduced calorie diet and exercise represents about a 6% reduction in body weight compared to placebo. Approximately two-thirds of patients assigned to semaglutide lost at least 5% of baseline body weight, and 44% lost at least 10% compared to baseline. The effects were clinically meaningful and statistically robust.

It would appear that semaglutide has a more modest effect on body weight in patients with type 2 diabetes compared to patients without diabetes, similar to a reduced effect observed with other medicines. The results of Trials 4373 and 4374 are not directly comparable, as evidenced by differences in baseline characteristics (older mean age, higher proportion of male patients, and lower baseline body weight and BMI). Additionally, SGLT2 inhibitors were an allowed concomitant medication in Trial 4374, and these drugs represent a possible confounder, as they are associated with modest weight loss in the treatment of type 2 diabetes.

Currently approved products for chronic weight management were studied prior to the approval of SGLT2 inhibitors and long-acting GLP-1 receptor agonists; thus, the results of 4374 cannot be compared meaningfully to older trials, which were conducted in patients with diabetes on a background of sulfonylureas, meglitinides, and thiazolidinediones, all known to be associated with weight gain.

The estimated treatment effect in Trial 4376, the randomized withdrawal, is challenging to interpret. As discussed previously, use of the week 20 baseline (after 10% weight loss from
week 0 baseline had occurred) as the denominator to calculate percent change from baseline may overestimate the estimate of the treatment effect versus placebo. The week 0 baseline may represent a more accurate estimate of pre-treatment baseline, but it still excludes patients who were not eligible for randomization. Regardless of the baseline value used, the randomized population is a subset of the originally enrolled population that excludes patients who discontinued treatment or did not reach the target dose during the 20-week run-in. Results for this subgroup are not generalizable to patients starting treatment who have never been exposed to semaglutide previously.

Nevertheless, the results of Trial 4376 are informative. Continued treatment with semaglutide for an additional 48 weeks (68 weeks total) as an adjunct to a reduced calorie diet and exercise, was superior to randomized withdrawal to placebo. The estimated effect size between continued treatment and withdrawal to placebo was clinically meaningful and statistically robust. Weight regain in the placebo group was considerable. Thus, there does not appear to be a role for the short-term use of semaglutide (20 weeks or fewer) as an adjunct to a reduced calorie diet and exercise for chronic weight management.

In the FDA statistical review, Dr. Song confirmed the results of the analyses of Trial 4376, and she supports its inclusion in labeling. Dr. Golden also supports inclusion of data from this trial in labeling, with language discussing interpretation of the observed treatment effect to providers. I agree with the reviewers’ conclusions.

In summary, the trials support the primary indication:

*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/m² or greater (obesity) or
- 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)

The data support inclusion of descriptions of all four Phase 3 studies in Section 14 of labeling. Trials 4373 and 4374 represent the estimated treatment effect of semaglutide as an adjunct to a reduced calorie diet and exercise in patients without and with type 2 diabetes, respectively. Trial 4375 represents the estimated treatment effect of semaglutide as an adjunct to an intensive diet and exercise intervention (a relevant subset of the condition of use in labeling). Trial 4376 represents the effect of the drug under the conditions of use recommended in labeling, for chronic weight management at the 2.4 mg once-weekly dose (as compared to treatment discontinuation). The trial suggests that short-term use, simulated by randomized withdrawal at week 20, is not an appropriate condition of use in clinical practice.

I agree with including trial descriptions and weight loss results in section 14, including tabular descriptions of the primary and secondary weight loss endpoints, cumulative distribution plots for Trials 4373 and 4374 (categorical endpoints were not secondary endpoints for trial 4376), and figures depicting change from baseline over time, similar to labeling for other approved weight management products. Additionally, it is appropriate to include changes in anthropometric and cardiometabolic parameters, such as waist circumference, blood pressure, heart rate, HbA1c, and lipid parameters, which are supportive of the favorable effects of weight loss. Trial data indicate similar results across important subgroups, including age, sex, race, ethnicity, and baseline body weight.
The FDA clinical outcomes assessment reviewer, Dr. Yasmin Choudhry, concluded that the relevance of the items used was unclear, and that the minimal changes observed, both in raw data and in transformed, normalized data, limited their interpretability.

8. Safety

In the FDA clinical review, Dr. Golden concluded that the most common risks with semaglutide are monitorable and may be mitigated with labeling. Semaglutide is thus safe for use under the conditions of use recommended. I agree with her assessment.

Summary of Safety Issues

The safety profile of semaglutide 2.4 mg administered subcutaneously as an adjunct to diet for chronic weight management in patients with obesity and overweight is generally similar to that of other approved GLP-1 receptor agonists, including semaglutide products approved for diabetes indications – Ozempic (semaglutide) injection and Rybelsus (semaglutide) tablets – and the other GLP-1 receptor agonist approved for chronic weight management, liraglutide. There were no new safety issues identified in this development program.

The most frequent adverse events (AEs) observed with semaglutide, gastrointestinal disorders, may be mitigated in most patients with dose titration. These reactions are monitorable, and severe events are reversible with treatment discontinuation. Other common adverse reactions, such as headache, fatigue, and increased heart rate are self-limited. Infrequent events include volume depletion, acute kidney injury, hypotension, and syncope.

Gallbladder disorders known are a previously identified risk with GLP-1 receptor agonists. In the semaglutide program, the risk of gallbladder events appeared greater in association with increased weight loss.
Hypoglycemia is a risk with GLP-1 receptor agonists, especially following initiation and dose escalation. The risk is greater in patients with T2D on insulin or insulin secretagogues, but it may be monitored and mitigated with medication adjustment in these patients.

Other safety issues associated with GLP-1 receptor agonists are infrequent or unconfirmed. In general, these signals were identified in nonclinical studies, postmarketing data, or with related products. These risks are addressed in current labeling of approved GLP-1 receptor agonists, and in some cases are the subject of ongoing postmarketing studies.

Acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis, has been reported with semaglutide. Randomized trials have not confirmed a drug-associated risk of acute pancreatitis. In the semaglutide weight management program, the incidence of acute pancreatitis was small, but there was a small numerical imbalance in events among patients assigned to semaglutide compared to placebo.

Neoplasms, particularly thyroid C-cell tumors, are a signal identified in nonclinical programs of all GLP-1 receptor agonists. The relevance of thyroid C-cell tumors in rodents to humans in unclear. There is an ongoing registry to evaluate the risk across all approved products in the class. GLP-1 receptor agonists are contraindicated in patients with multiple endocrine neoplasia syndrome, type 2 (MEN 2) and patients with a personal or family history of medullary thyroid cancer. Communication of the risk includes a boxed warning in labeling.

An increased risk of retinopathy complications was identified in a 2-year cardiovascular outcomes trial with semaglutide in patients type 2 diabetes. Because rapid improvement in glycemic control is associated with temporary worsening of diabetic retinopathy, a 5-year trial to evaluate the effect of long-term glycemic control with semaglutide is ongoing in the diabetes program. Even if confirmed in the diabetes population, the relevance of this risk to the conditions of use for the weight management product are unclear.

Suicidal behavior and ideation have been reported with other centrally acting weight management products. There were no observed imbalances in psychiatric disorders in the semaglutide weight management program.

Immunogenicity, evidenced by the presence of ADA, occurred at low frequency in the semaglutide weight management program. There was no apparent impact of positive ADA on PK, efficacy, or safety.

Serious hypersensitivity reactions have been reported with semaglutide and other GLP-1 receptor agonists. There was no imbalance in hypersensitivity reactions or allergic reactions in the semaglutide weight management program. Injection site reactions were self-limited and occurred at low rates overall but were reported more frequently with semaglutide compared to placebo.

In nonclinical studies, semaglutide was associated with a risk of pregnancy loss and fetal malformations at clinical exposures associated with maternal weight loss. The risk may be mitigated with labeling. FDA will issue postmarketing requirements to evaluate the risks of exposure to semaglutide during pregnancy.

Rare cases consistent with drug-induced liver injury (DILI) have been reported postmarketing with GLP-1 receptor agonists, including semaglutide. There were no signals related to liver safety in the semaglutide weight management program, including no imbalances in hepatic enzyme elevations and no Hy’s Law cases. FDA recently opened a Newly Identified Safety
Signal (NISS) to assess DILI with the GLP-1 receptor agonist class. Because the safety issue is in the evaluation phase, no changes to GLP-1 labeling are currently warranted.

Refer to the FDA clinical review authored by Dr. Golden for details of the safety evaluation. The major safety topics and important risks are summarized here.

**Safety Database**

The safety profile of semaglutide 2.4 mg injection for weight management was primarily characterized in the three randomized, placebo-controlled, Phase 3 trials. This group included 2116 patients randomized to semaglutide 2.4 mg for 68 weeks compared to 1261 randomized to placebo. The Phase 3 dose-escalation pool included Trials 4373, 4375, and the semaglutide 2.4 mg arm in trial 4374 (in addition to placebo). Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1. Safety data in this review describes events occurring in the Safety Population (defined as all randomized patients exposed to at least one dose of trial product) during the on-treatment period (defined as 2 weeks after the last administered dose for ECG, labs, physical examination, and heart rate, and 7 weeks after the last administered dose for adverse events, adjudicated events, and hypoglycemia) or the in-trial period (defined as the time from date of randomization to date of last contact) for long latency events (deaths, neoplasms), unless otherwise specified. For patients completing the trial, the date of last contact would correspond to the final safety visit at week 75 (7 weeks after the final dose of trial product).

Supportive safety data included Trial 4376, the randomized withdrawal trial, which included an additional 534 patients randomized to semaglutide (completers exposed to 68 weeks of semaglutide, including open-label dose escalation). Safety data from this trial is challenging to interpret, because all patients were exposed to 20 weeks of treatment with semaglutide prior to randomization. This trial is thus excluded from many of our analyses comparing semaglutide versus placebo (such as assessments of AEs). The applicant conducted pooled safety analyses on the “Phase 3 Pool” which included all four trials (4373, 4374, 4375, and 4376). Use of this population is noted, where applicable. Additional supportive safety data came from other studies submitted with the application. Refer to Dr. Golden’s review for details.

In the three randomized, controlled trials, the mean age was 48 years, 71% of patients were women, 72% identified as White race, 9% as Black or African American, 14% as Asian, and 14% as Hispanic or Latino ethnicity. Common co-morbid conditions included dyslipidemia (43%), hypertension (42%), and type 2 diabetes (19%).

**General Safety Topics**

Refer to Dr. Golden’s review for detailed analysis. This section presents a summary and focuses on issues related to approvability and labeling.

**Adverse Events**

There were too few deaths to identify meaningful trends. In Trials 4373, 4374, and 4375, there were 2 deaths in the semaglutide 2.4 mg group, both classified as cardiovascular deaths, 1 death in the semaglutide 1 mg arm of Trial 4374, and 2 deaths in the placebo group, both classified as death due to malignancy. Refer to the clinical review for details.
The most frequent serious adverse events (SAEs) were consistent with the overall safety profile and the trial population. In the applicant’s analysis of the Phase 3 pool (which included Trial 4376), a greater proportion of patients randomized to semaglutide experienced SAEs compared to patients randomized to placebo (9.3% versus 6.4%, respectively). The most frequently reported AEs in the semaglutide arm were in the MedDRA System Organ Classes (SOCs) Infections and infestations, Gastrointestinal disorders, and Hepatobiliary disorders.

A higher proportion of patients assigned to semaglutide experienced AEs leading to permanent treatment discontinuation (5.7% versus 3.0%) in the applicant’s analysis of the Phase 3 pool. The most frequently reported AEs leading to discontinuation in the semaglutide arm were gastrointestinal disorders (nausea, vomiting, diarrhea, abdominal pain, and constipation).

A higher proportion of patients assigned to semaglutide (88.5%) experienced one or more AEs during the in-trial period compared to patients assigned to placebo (83.6%). The most frequently reported AEs in the semaglutide arm were gastrointestinal disorders (nausea, diarrhea, constipation, vomiting), nasopharyngitis, and headache. Table 8 summarizes the proportion of patients with one or more AEs with incidence of 2% or greater and more frequently than placebo.

Table 9: Adverse Reactions Occurring in > 2% of Semaglutide-treated Patients and More Frequently than with Placebo, Dose-escalation pool, Safety Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo N = 1261</th>
<th>Semaglutide N = 2116</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>16.1%</td>
<td>43.9%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15.9%</td>
<td>29.7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.3%</td>
<td>24.5%</td>
</tr>
<tr>
<td>Constipation</td>
<td>11.1%</td>
<td>24.2%</td>
</tr>
<tr>
<td>Abdominal Pain(^a)</td>
<td>10.0%</td>
<td>19.7%</td>
</tr>
<tr>
<td>Headache</td>
<td>9.9%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Fatigue(^b)</td>
<td>5.1%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3.2%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.8%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Abdominal Distension</td>
<td>5.1%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Eructation</td>
<td>0.4%</td>
<td>7.4%</td>
</tr>
<tr>
<td>Hypoglycemia in patients with type 2 diabetes(^c)</td>
<td>2.5%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>4.2%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>4.5%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Gastroesophageal Reflux Disease</td>
<td>2.5%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Gastroenteritis Viral</td>
<td>2.8%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Gastritis(^d)</td>
<td>1.3%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Hair Loss</td>
<td>1.4%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

\(^a\)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 in patients with type 2 diabetes not on concomitant insulin (Study 2, semaglutide N=403, placebo N=402).

\(^d\)Includes chronic gastritis, gastritis, gastritis erosive, and reflux gastritis

Source: adapted from draft Prescribing Information
**Gastrointestinal disorders**

Gastrointestinal adverse events (nausea, diarrhea, vomiting, constipation) were the most commonly reported AEs in the semaglutide arm of Phase 3 clinical trials and the most frequently reported AEs leading to treatment discontinuation among patients assigned to semaglutide. Most events were of categorized as mild or moderate severity. In some cases, gastrointestinal adverse events led to volume depletion, orthostatic hypotension or syncope, dehydration, electrolyte disturbances, and acute kidney injury (discussed later in this section of the review).

In Phase 3 trials, gastrointestinal adverse events were most frequently reported during dose escalation. Figure 6 presents time-to-event analyses demonstrating this phenomenon. In the Phase 2 dose finding trial, the incidence of gastrointestinal adverse events was somewhat dose related, and the frequency and severity of these events was greater with faster dose escalation.

Nausea, vomiting, and diarrhea were generally self-limited. The median duration of these events in the semaglutide arm were 8 days, 2 days, and 3 days, respectively. The median duration of adverse events of constipation, in contrast, was 47 days in the semaglutide arm. Refer to Dr. Golden’s review for additional details.

**Figure 6: Gastrointestinal Adverse Events by Time, Phase 3 Dose-Escalation Group, On Treatment**

![Gastrointestinal Adverse Events by Time, Phase 3 Dose-Escalation Group, On Treatment](image)
Infrequent Adverse Events

Hypotension and Syncope
Hypotension and orthostatic hypotension were infrequent events reported more frequently in patients randomized to semaglutide compared to placebo. AEs related to hypotension (hypotension, orthostatic hypotension, decreased blood pressure) were reported in 1.3% of patients randomized to semaglutide compared to 0.8% of patients randomized to placebo. Syncope was reported in 0.8% of patients randomized to semaglutide versus 0.2% of patients assigned to placebo. These AEs occurred more frequently in patients on concomitant antihypertensive medications at baseline.

Appendicitis
Appendicitis (including perforated appendicitis) was reported in 10 patients (0.5%) randomized to semaglutide and 2 patients randomized to placebo (0.2%).

Injection Site Reactions
Injection site reactions (injection site pruritus, erythema, inflammation, induration, and irritation) were reported in 1.4% of patients randomized to semaglutide and 1.0% of patients randomized to placebo.

Laboratory, Vital Signs, and ECG
Relevant findings affecting approval and labeling are discussed among safety issues of special interest, the next section of this review. For details of these evaluations, refer to the FDA clinical review by Dr. Golden.

Safety Issues of Special Interest:
This section summarizes important safety issues relevant to approval, labeling, and postmarketing studies, and is not intended to be comprehensive. Where applicable, findings in the semaglutide weight management program are discussed in the context of previously identified safety issues for GLP-1 receptor agonists. For details of the overall semaglutide safety evaluation, refer to Dr. Golden’s review.

Acute Kidney Injury
Acute kidney injury (AKI) was an infrequent AE reported at a higher incidence in patients randomized to semaglutide compared to placebo. AKI was reported in 7 patients (0.4 cases per 100 patient-years) randomized to semaglutide and 4 patients (0.2 case per 100 patient-years) among patients randomized to placebo. In some cases, AKI was associated with gastrointestinal AEs or dehydration. Mean eGFR and serum creatinine were essentially unchanged in both the semaglutide and placebo arms over the course of the trial.

Gallbladder disorders
Obesity and rapid weight loss are associated with increased risk for gallstone formation.6 GLP-1 receptor agonists are also associated with gallstone formation, independent of weight change. Gallbladder events in the semaglutide weight management program were generally consistent with previous data. In the three randomized, controlled, Phase 3 trials, cholelithiasis was

reported as an adverse event in 1.6% of patients randomized to semaglutide compared to 0.7% of patients randomized to placebo. Cholecystitis was reported in a greater proportion of patients in the semaglutide arm compared to placebo (0.6% versus 0.2%). The incidence of gallbladder disorders reported as AEs was greatest in both the semaglutide and placebo arms in Trial 4375 (4.9% versus 1.5%, respectively), in which semaglutide or placebo were studied as an adjunct to an intensive diet and exercise program. Nevertheless, the increased risk of gallbladder disorders was present, even when accounting for weight loss. Refer to Dr. Golden’s review for additional analyses and discussion.

**Pancreatitis**
Acute pancreatitis has been reported in patients taking GLP-1 receptor agonists. In the semaglutide program, the overall incidence of pancreatitis events was low in Phase 3 pool. Four subjects exposed to semaglutide (0.2%) experienced five events of adjudicated pancreatitis compared to one event in one patient assigned to placebo (<0.1%). Events were associated with gallstones in 2 of the 4 semaglutide patients and the placebo patient.

In the semaglutide arms of the Phase 3 trials, mean concentrations of amylase and lipase increased 16% and 39%, respectively compared to no change in the placebo arm. The clinical significance of these mild elevations is unclear.

**Hypoglycemia**
GLP-1 receptor agonists stimulate insulin secretion in a glucose-dependent manner and may increase the risk of hypoglycemia in patients taking insulin or insulin secretagogue. Hypoglycemia in this section uses the American Diabetes Association (A.D.A.) 2018 definitions.

In Trial 4374, 6.2% of patients in the semaglutide 2.4 mg arm and 6.7% of patients in the semaglutide 1 mg arm experienced at least one episode of clinically significant (Level 2) hypoglycemia (defined as a plasma glucose less than 54 mg/dL) compared to 2.5% of patients in the placebo arm. One patient in the semaglutide 2.4 mg arm experienced one event of severe (Level 3) hypoglycemia (defined as severe cognitive impairment requiring external assistance for recovery). The incidence of clinically significant hypoglycemia was 10.7 events per 100 patient-years in the semaglutide 2.4 mg arm, 7.2 events per 100 patient-years in the semaglutide 1 mg arm, and 3.2 events per 100 patient-years in the placebo arm.

The risk of hypoglycemia was increased among patients taking sulfonylureas.

Time-to-event analysis indicated that the patients in the two semaglutide arms had a similar risk of having an event, but patients assigned to semaglutide 2.4 mg were more likely to have more than one event of clinically significant hypoglycemia. Figure 7 illustrates these findings in time-to-onset of first event and time-to-onset of any event of hypoglycemia plots in Trial 4374. Refer to Dr. Golden’s review for details and additional analyses of hypoglycemia.
Hypoglycemia was not systematically evaluated in patients without type 2 diabetes in the Phase 3 clinical program. AE reporting in Trials 4373 and 4375 did not demonstrate any consistent imbalances in the proportion of patients reporting AEs of hypoglycemia. Overall, the proportion of patients reporting one or more events of hypoglycemia was less than 1.0%. Refer to Dr. Golden’s review for details of hypoglycemia AE data in patients without diabetes.

In a pediatric weight management trial of liraglutide in patients without diabetes, patients were provided with blood glucose meters and monitored for hypoglycemia. Clinically significant hypoglycemia occurred in 1.6% of patients assigned to liraglutide compared to 0.8% patients assigned to placebo. These data suggest that hypoglycemia is probably underreported in trials of GLP-1 receptor agonists in patients without diabetes, and information from the pediatric liraglutide trial should be included in labeling. Nevertheless, the clinical significance of hypoglycemia in adult patients without type 2 diabetes is unclear.

**Neoplasms**

There was no evidence of an increased risk of malignancies and no evidence of an increased risk of any individual malignancy in the semaglutide weight management program. In Trials 4373, 4374, and 4375, the proportion of patients reporting one or more AEs in the MedDRA SOC *Neoplasms benign, malignant, and unspecified* was numerically smaller than the
proportion of patients in the placebo arms reporting at least one event, in both pooled analyses and in each trial individually. The proportion of patients reporting at least one malignant AE was lower in the pooled semaglutide arms compared to placebo. There were no events of medullary thyroid cancer and no events of pancreatic cancer reported in the semaglutide weight management program. Refer to Dr. Golden’s review for additional details.

**Retinal Disorders**
In a cardiovascular outcomes trial (CVOT) with mean follow-up time of 2.1 years evaluating semaglutide 0.5 mg and 1 mg once weekly in patients with type 2 diabetes, there was an increased incidence of adjudicated diabetic retinopathy complications with semaglutide compared to placebo, and the risk was higher in patients with a history of diabetic retinopathy at baseline. The implication of these findings is unclear, however, because rapid improvement in glucose control is associated with transient worsening of diabetic retinopathy. A randomized, placebo-controlled trial to evaluate the effect of semaglutide on diabetic retinopathy over 5 years is ongoing.

In Trial 4374, 85 AEs of retinal disorders were identified using a pre-defined MedDRA search. A greater proportion of patients randomized to semaglutide 2.4 mg or semaglutide 1 mg (6.9% and 6.2%, respectively) experienced events compared to patients randomized to placebo (4.2%). The majority of events were the MedDRA preferred terms **Diabetic retinopathy** (4.0%, 2.7%, and 2.7%, respectively) and **Non-proliferative retinopathy** (0.7%, 0%, and 0%, respectively). No SAEs of retinal disorders were reported.

Eye examinations were conducted at baseline and at the end of treatment in Trial 4374. Few patients had clinically significant findings at any time, and few patients with normal findings or abnormal-but-not-clinically significant findings at baseline developed clinically significant findings at the end of treatment. Refer to Dr. Golden’s review for details.

**Heart Rate Increases**
Heart rate (HR) increases are associated with GLP-1 receptor agonists. A treatment difference in HR of approximately 1 to 4 beats per minute (bpm) greater in the semaglutide arm than placebo was observed in the Phase 3 trials. Maximum HR change from baseline ≥ 20 bpm occurred in 26% of patients randomized to semaglutide versus 16% of patients randomized to placebo. There was no apparent dose-dependent HR effect.

**Psychiatric disorders**
Suicidal ideation and behaviors have been reported in clinical trials of centrally acting weight management products. There was no apparent increase in suicidal ideation, suicidal behaviors, or AEs of psychiatric disorders with semaglutide compared to placebo. Refer to the clinical review for additional details.

**Immunogenicity**
Semaglutide is a peptide with a potential risk for immunogenicity. ADA (anti-drug antibodies) were evaluated in Trials 4373 and 4374. In these trials, 50 patients randomized to semaglutide (2.9%) experienced ADAs on the screening assay that were confirmed positive, and 29 patients (1.6%) of the trial population had persistent ADA.
In the Phase 3 trials, semaglutide plasma concentrations were similar in subjects with confirmed positive ADA compared to patients with who were ADA negative. Patterns of weight loss were similar among patients with confirmed positive ADA compared to ADA-negative patients. There was no apparent difference in the incidence of AEs between patients who were ADA positive and those who were ADA negative.

Refer to the FDA clinical review by Dr. Golden for details of efficacy and safety analyses and ADA. Refer to the FDA clinical pharmacology review by Dr. Chung for details of PK analyses and ADA. Refer to the Immunogenicity review by Dr. Manangeeswaran for details of the ADA assays.

**Other Safety Issues**

**Pregnancy**
In the semaglutide weight management program, there were 37 pregnancies across five Phase 2 and Phase 3 trials (29 semaglutide and 8 placebo). Pregnancy outcomes in patients exposed to semaglutide and patients randomized to placebo were generally consistent with the relatively higher risk patient population (including healthy outcome, ongoing pregnancy, spontaneous abortion, and elective abortion). There were no reported major fetal malformations among patients exposed to semaglutide (one newborn was reported to have a congenital anomaly of “left ear fold” which resolved).

**Major adverse cardiovascular events (MACE)**
In a randomized, double-blind, placebo-controlled, CVOT of semaglutide 0.5 mg or 1 mg once-weekly injection as concomitant therapy to standard therapy in 3297 patients with type 2 diabetes and atherosclerotic cardiovascular disease, semaglutide reduced the risk of the primary composite MACE endpoint, which comprised cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The estimated hazard ratio for time to first MACE was 0.74 (95% CI: 0.58, 0.95). The total number of patients experiencing a component of the primary MACE endpoint was 108 (6.6%) in the semaglutide arms and 146 (8.9%) in the placebo arm.

These results support the cardiovascular safety of semaglutide in weight management, but the efficacy results at these lower doses used for glycemic control in patients with type 2 diabetes cannot be extrapolated to the use of semaglutide 2.4 mg injection once weekly for chronic weight management in patients with obesity or overweight, especially patients without diabetes at baseline.

In the semaglutide weight-management program, adjudicated 3-component MACE (composed of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) was analyzed in the randomized Phase 3 pool (Trials 4373, 4374, 4375, and 4376). The number of events observed was too few to infer the risk of MACE in this population. The estimated hazard ratio for time to first MACE compared to placebo was 0.991 (95% CI: 0.400, 2.456). A total number of 20 patients experienced a MACE, 0.5% of patients in each treatment group. Refer to Dr. Golden’s review for additional analyses and discussion.
Liver Safety
There was no signal of hepatic toxicity in the semaglutide weight management program. The proportions of patients reporting hepatic AEs was similar between semaglutide and placebo. Rare serious AEs were associated with confounders. In Trials 4373, 4374, and 4375, the proportions of patients experiencing transaminase elevations above the upper limit of normal (ULN) or higher thresholds (>3× ULN, >5× ULN) and the proportions of patients experiencing bilirubin elevations (>ULN, >1.5× ULN, >2× ULN) were lower in the semaglutide arms than in the placebo arms. Mean transaminase values (AST, ALT) decreased from baseline among patients randomized to semaglutide versus placebo, and mean total bilirubin increased slightly (15%) in the semaglutide arm versus placebo.

There were no reports of biochemical Hy’s law (ALT/AST >3× ULN concurrent with total bilirubin >2× ULN) in the weight management program observed in the central laboratory through routine monitoring. Events identified in local laboratory monitoring in AE narratives were associated with alternative etiologies, such as gallbladder disease.

Safety Summary
The safety profile of semaglutide 2.4 mg for chronic weight management is similar to that of other approved GLP-1 receptor agonists and semaglutide products approved for diabetes indications. There were no new safety issues identified in the weight management development program.

The most frequent AEs observed with semaglutide occurring more frequently than in the placebo arm were gastrointestinal disorders. Other frequent adverse events included headache, fatigue, dyspepsia, dizziness, and increased heart rate. Acute kidney injury, electrolyte disorders, hypotension and syncope, and injection site reactions occurred infrequently. These reactions are monitorable and may be mitigated with appropriate labeling.

Gallbladder disorders are a previously identified risk with GLP-1 receptor agonists. In the semaglutide program, the risk of gallbladder events appeared higher in association with greater weight loss. The risk may be addressed in labeling.

Hypoglycemia is a risk with GLP-1 receptor agonists, especially following initiation and dose escalation. The risk is greater in patients with type 2 diabetes on insulin or insulin secretagogues. Prescribers may consider decreasing the doses of insulin or insulin secretagogues when initiating or escalating the dose of semaglutide to reduce the risk.

Diabetic retinopathy complications occurred in association with rapid improvement in glucose control in a cardiovascular outcomes trial of patients with type 2 diabetes. The relevance of this signal to the conditions of use for weight management is unclear. Labeling is adequate to mitigate the risk.

Other safety issues associated with GLP-1 receptor agonists, such as acute pancreatitis, neoplasms, and suicidal behavior, are infrequent or unconfirmed. These risks are addressed in current labeling of approved GLP-1 receptor agonists. FDA will issue a postmarketing requirement (PMR) to evaluate the risk of pancreatitis, gallbladder disorders, renal safety, serious hepatic events, malignant neoplasms, serious hypoglycemia, and serious gastrointestinal disorders in the ongoing weight management CVOT. Labeling includes a
boxed warning for the potential risk of medullary thyroid cancer. Semaglutide will be contraindicated in patients with a personal or family history of medullary thyroid cancer or MEN 2. FDA will issue a PMR for a medullary thyroid cancer registry study. In nonclinical studies, semaglutide was associated with a risk of pregnancy loss and fetal malformations at clinical exposures associated with maternal weight loss and these findings should be labeled. FDA will issue postmarketing requirements to evaluate the risks of exposure to semaglutide during pregnancy.

9. Advisory Committee Meeting
An Advisory Committee Meeting was not convened for this application. The Division and the Applicant agreed on the components of the development program and the key design features of the clinical trials during development, and the development program was consistent with the FDA draft Guidance for Industry – Developing Products for Weight Management. No new efficacy or safety issue arose during review of this application.

10. Pediatrics
Safety and efficacy in pediatric patients have not been established. The application is subject to Pediatric Research Equity Act (PREA) requirements because weight management is a new indication for the active ingredient. The applicant requested a partial waiver for pediatric studies in patient aged <6 years because the product fails to represent a meaningful therapeutic benefit over existing therapies for this age group. The applicant requested a deferral of pediatric studies in patients aged 6 to <18. The Pediatric Research Committee (PeRC) agreed with the partial waiver and deferral. FDA will issue a postmarketing requirement for pediatric studies with the approval of this application.

11. Other Relevant Regulatory Issues

Clinical Inspections
The Office of Scientific Investigations (OSI) reviewer, Dr. Cynthia Kleppinger, concluded that the inspectional findings support validity of the data reported in this application, and supports approval. I concur with the recommendation.

The original assignment issued to the Office of Regulatory Affairs (ORA) was to conduct good clinical practice (GCP) inspections of five sites covering Trials 4375 and 4376. The ongoing COVID-19 global pandemic has limited ORA’s ability to conduct on-site inspections. Planned inspections of three sites were not able to be conducted before the action date.

Inspection of Dr. Domenica M. Rubino’s clinical site in Arlington, VA, identified discussion items related to reporting of adverse events, concomitant medications, protocol deviations, investigational product storage, and documentation practices, but the deviations were not expected to affect analyses. The inspection revealed adequate adherence to the regulations and the investigations plan. No Form-483, Inspectional Observations, was issued.

Inspection of Dr. Andrew P. Brockmyre’s clinical site in Bristol, TN, revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued.
Financial Disclosure
The applicant reported disclosable financial interests for 8 clinical studies, including the 4 Phase 3 trials. In studies NN9536-4588, 4590, and 4455, no investigators had disclosable interests, while 1 of 327 investigators in Trial 4153, 17 of 614 investigators in Trial 4373, 14 of 677 investigators in Trial 4374, 12 of 293 investigators in Trial 4375, and 8 of 359 investigators in Trial 4376 had a disclosable financial interest. Additionally, one investigator in each of Trials 4374 and 4376 was a Sponsor employee.

The investigators with disclosable interests in each trial are not mutually exclusive (i.e. one investigator may be counted in two or more trials), and in some cases more than one investigator at a single site had disclosable interests. Overall, the proportions of investigators with disclosable financial interests, sites with one or more investigators with disclosable financial interests, and patients enrolled at sites with one or more investigators with disclosable financial interests were small.

Proprietary Name
The DMEPA reviewer, Dr. Sarah Vee, concluded that the proposed proprietary name, Wegovy, is acceptable. In the proprietary name review, Dr. Vee concluded that the name would not misbrand the product, and that there were no safety concerns, such as orthographic, spelling, or phonetic similarities with other approved products. I concur with the recommendation.

12. Labeling
Prescribing Information
This section summarizes major changes to proposed labeling implemented during negotiations.

- INDICATIONS AND USAGE section:
  - Minor changes to Indication language
  - Minor changes to Limitation of Use language

- DOSAGE AND ADMINISTRATION section:
  - Revised 2.1 Patient Selection consistent with current guidance
  - Revised 2.2 Administration instructions to bulleted list for clarity
  - Revised dose-escalation schedule in 2.3 for readability

- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:
  - Discontinuation when pregnancy is recognized is still recommended in Section 8.1
  - Rearranged Warnings and Precautions for relevance to weight management (e.g. Diabetic Retinopathy section from diabetes labels moved down from 5.3 to 5.7)
  - Added sections regarding Acute Gallbladder Disease (5.3), Heart Rate Increase (5.8), and Suicidal Behavior and Ideation (5.9)

- ADVERSE REACTIONS section:
  - Revised Section 6.1 to use data from Trials 4373, 4374, and 4375.
Added information for infrequent, but relevant, Adverse reactions occurring more frequently in patients randomized to semaglutide than patients randomized to placebo, such as acute pancreatitis, acute gallbladder disease, acute kidney injury, acute appendicitis, and hypotension and syncope.

- **DRUG INTERACTIONS section:**
  - Revised risk information and recommendations for insulin secretagogues and insulin
  - Revised description of gastric emptying studies for clarity

- **USE IN SPECIFIC POPULATIONS section:**
  - Refer to FDA nonclinical review and DPMH consult review for revisions to pregnancy, lactation, and patients of reproductive potential sections.

- **CLINICAL PHARMACOLOGY section:**
  - Minor edits to other sections (Renal Impairment, Hepatic Impairment, Drug Interactions)

- **CLINICAL STUDIES section:**
  - Revised description of Trial 4376 (randomized withdrawal)
  - Addressed interpretability of observed treatment effect in randomized withdrawal data because the randomized population represents a subset of enrolled patients. Patients who discontinued treatment during dose escalation and those who did not reach the target dose were not eligible for randomization.

The Office of Prescription Drug Promotion (OPDP) reviewer, Dr. Meena Savani, provided labeling recommendations for the Prescribing Information, and discussed the recommendations with the review team.

The Division of Pediatric and Maternal Health (DPMH) reviewer, Dr. Carrie Ceresa, provided recommendations for the Pregnancy (8.1), Lactation (8.2), Females and Males of Reproductive Potential (8.3), and the relevant Patient Counseling (17) sections of the Prescribing Information. Refer to Dr. Ceresa’s review for details. DPMH recommends issuing a PMR to conduct a pregnancy exposure registry and a complementary study using a different design. I concur with the recommendations.

**Other Labeling**
Medication Guide, Instructions for Use, Carton and Container

- The Division of Medical Policy Promotions (DMPP) reviewer, Dr. Kelly Jackson, and the OPDP reviewer, Dr. Meena Savani, collaborated on review of the patient labeling,
which consists of the Medication Guide and Instructions for Use. The revisions ensured compliance with regulations, consistency with the Prescribing information, use of appropriate language to enhance patient comprehension. Refer to the Patient Labeling review for details.

- The drug product reviewer, Dr. Mohamadi, reviewed the carton and container labeling. Refer to the Product Quality section of this review and the OPQ Integrated Quality Assessment for details.
- The DMEPA reviewer, Mr. Flint, provided recommendations for the carton and container labeling and the Instructions for Use.
- The OPDP reviewer, Dr. Savani, provided recommendations for the carton and container labeling in the labeling review

13. Postmarketing

Postmarketing Risk Evaluation and Mitigation Strategies

The Division of Epidemiology (DEPI) I reviewer, Dr. Christian Hampp, concluded that the Sentinel Active Risk Identification and Analysis (ARIA) system is not sufficient to address the postmarketing requirement to evaluate the medullary thyroid cancer signal in humans because of insufficiency in exposure and study outcome, and that the ARIA system in not sufficient to address postmarketing requirements to detect a signal for major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, or preterm birth in pregnant patients, because necessary covariates are not reliably available, and because of the multiple outcomes targeted. Refer to the respective ARIA Sufficiency Assessments by Dr. Hampp for details.

The following list includes postmarketing requirements required under PREA and the Food and Drug Amendments Act of 2007 (FDAAA):

Postmarketing Requirements

1) Complete the ongoing 68-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of semaglutide for the treatment of obesity in pediatric patients ages 12 to less than 18.

   Study Completion:   April 2022
   Final Report Submission:   October 2022

2) Conduct a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy after 68 weeks of semaglutide for the treatment of obesity in pediatric patients ages 6 to less than 12. Compare the long-term (at least 2 years) safety and tolerability of semaglutide versus placebo for the treatment of obesity in both children and adolescents (ages 6 to less than 18 years). The trial may not be initiated until results from the semaglutide adolescent trial have been submitted to and reviewed by the Agency.
3) Conduct a prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to semaglutide during pregnancy to an unexposed reference population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

   Draft Protocol Submission: January 2022
   Final Protocol Submission: July 2022
   Interim Report Submission: August 2023, August 2024, August 2025, August 2026, August 2027, August 2028, August 2029, August 2030, August 2031, August 2032
   Study Completion: August 2032
   Final Report Submission: August 2033

4) Conduct an additional pregnancy study that uses a different observational design from the Pregnancy Exposure Registry, using claims or electronic medical record data, to assess the associations between semaglutide exposure during pregnancy with pregnancy outcomes and infant outcomes, including but not limited to major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age, preterm birth and postnatal growth and development.

   Draft Protocol Submission: January 2022
   Final Protocol Submission: July 2022
   Interim Report Submission: August 2023, August 2024, August 2025, August 2026, August 2027
   Study Completion: August 2027
   Final Report Submission: August 2028

5) Conduct a medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of semaglutide for the treatment of obesity into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to the use of semaglutide for the treatment of obesity.
Draft Protocol Submission: February 2022
Final Protocol Submission: August 2022
Study Completion: February 2038
Final Report Submission: February 2039

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.

Trial Completion: December 2023
Final Report Submission: August 2024
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
06/03/2021 10:16:04 PM