CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209637Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	(see electronic signature)
From	William H. Chong
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 209637
Applicant	Novo Nordisk Inc.
Date of Submission	December 5, 2016
PDUFA Goal Date	December 5, 2017
Proprietary Name / Non-Proprietary Name	OZEMPIC (semaglutide)
Dosage form(s) / Strength(s)	Once weekly subcutaneous injection (0.5 mg, or 1 mg)
Applicant Proposed Indication(s)/Population(s)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	*Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus*

Review Team:

Drug Substance Reviewer	Joseph Leginus
Drug Product Reviewer	Muthukumar Ramaswamy
Quality Microbiology Reviewer	Elizabeth Bearr
Quality Process Reviewer	Chaoying Ma
Facilities Reviewers	Vidya Pai (CDER) and Christopher Brown (CDRH)
Quality Technical Lead	Suong Tran
Nonclinical Reviewer	Federica Basso
Carcinogenicity Statistics Reviewer (DB-VI)	Hepei Chen
QT-IRT	Janell Chen
Clinical Pharmacology Reviewers	Shalini Wickramaratne Senarath Yapa and Justin Earp
Clinical Reviewer	Andreea Lungu
Efficacy Statistics Reviewer (DB-II)	Jiwei He
Safety Statistics (DB-VII)	Ya-Hui Hsueh
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CDRH/GHDB Consultant	Sarah Mollo
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DPMH Reviewer	Jane Liedtka
DRISK Reviewer	Till Olickal
DMPP Reviewer	Sharon Williams
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1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Type 2 diabetes mellitus (T2DM) is a condition of chronic impaired glucose homeostasis that results in chronic hyperglycemia and increases the risk for microvascular and macrovascular complications. Therapies for T2DM have focused on improving glycemic control as assessed by change in hemoglobin A1c (HbA1c), as better glycemic control has been correlated with better clinical outcomes. While there are multiple drug products approved both as individual drugs and as fixed combination drug products (FCDP), many patients are unable to achieve glucose targets. Thus, patients and prescribers have been advocating for additional therapeutic options to facilitate individualization of therapy in hopes that this will improve patients' ability to achieve glycemic control.

Semaglutide is a once weekly glucagon-like peptide-1 (GLP-1) receptor agonist that has been developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). In controlled clinical trials, use of semaglutide 0.5 mg or 1 mg once weekly resulted reduction in HbA1c (treatment difference compared to placebo of -1.1% to -1.6% at 30 weeks). Additional findings which may be desirable for patients include a reduction in body weight (treatment difference compared to placebo of -2.2 to -4.7 kg at 30 weeks).

Safety findings from the semaglutide development program were generally consistent with what would be expected for a long-acting GLP-1 receptor agonist. The most common adverse reactions are nausea and vomiting. The inherent risk for hypoglycemia with semaglutide appears to be low, but this is increased when co-administered with insulin (and likely to be increased when co-administered with insulin secretagogues, such as sulfonylureas). While no difference in the incidence of pancreatitis was seen in the development program, patients treated with semaglutide had increases in serum amylase and lipase. No notable difference in malignancies (including for medullary thyroid cancer) was seen in the development program, but duration of exposure was relatively short and may not be sufficient to fully exclude an increased risk. Nonclinical findings support that the concern for MTC with long-acting GLP-1 receptor agonists also applies to semaglutide. As a peptide product, it is expected that semaglutide will carry some risk for anti-semaglutide antibody formation and hypersensitivity reactions. The observed incidence and titer of anti-semaglutide antibodies was relatively low, and no apparent increased risk for clinically significant hypersensitivity events was seen.

In support of the semaglutide new drug application (NDA), the applicant has also completed a cardiovascular outcomes trial (CVOT) designed to exclude excess cardiovascular risk. This trial ran for two years and accrued a total of 254 first major adverse cardiovascular events (MACE). Based on this trial, the applicant has adequately established that there is no excess cardiovascular risk with semaglutide.

An unexpected finding from the CVOT was an increased risk for diabetic retinopathy complications. This was seen early in the trial and the increased risk persisted through the two-year observation period of the trial. The patients at greatest risk were those with diabetic retinopathy at

baseline. Though the definitions and means by which events were identified were considered inadequate had the applicant been pursuing an indication of reduced risk for diabetic retinopathy progression, the finding is nevertheless concerning given that improving glycemic control is expected to reduce the risk for complications of diabetes. The applicant has posited that this finding is a result of the glucose lowering effect of semaglutide and that it is consistent with what would be expected based on findings from other large clinical trials (i.e., the Diabetes Control and Complications Trial [DCCT]). While adjusting for change in HbA1c does attenuate the observed hazard ratio, it may not fully explain the observed finding. The FDA ophthalmology consultant acknowledged that the finding does raise some concerns, but that this observation would be expected and that it does not adversely impact the benefit-risk. A public Advisory Committee meeting was convened to discuss the benefits and risks of semaglutide, including the diabetic retinopathy findings. The external ophthalmology experts and other Advisory Committee panel members expressed opinions similar to that of the FDA ophthalmology consultant.

The finding of increased risk for diabetic retinopathy complications is concerning, but I do not believe it results in an unfavorable benefit-risk. Diabetic retinopathy is but one of several diabetic complications that is expected to be favorably impacted by improved glycemic control. Data from the semaglutide development program have not suggested that these other clinical outcomes are similarly adversely impacted. Additionally, the data on semaglutide for diabetic retinopathy complications are limited. The longest exposure to semaglutide was two years, and it is notable that in the DCCT there was an early worsening of diabetic retinopathy progression with intense glycemic control which reversed after approximately three years. Whether longer term treatment with semaglutide would similarly result in a reduced risk of diabetic retinopathy progression is unknown, but it may not be feasible or ethical to conduct such a study. While this uncertainty remains, it is reassuring to note that diabetic retinopathy can be monitored and that there are effective therapies to treat it such that serious adverse clinical outcomes (e.g., blindness) can be avoided with proper ophthalmologic care. The patients at greatest risk were those with diabetic retinopathy at baseline, and those patients would generally be expected to have closer ophthalmology follow-up.

In summary, I believe that semaglutide has a favorable benefit-risk profile. The findings from the development program demonstrate the ability of semaglutide to improve glycemic control, and the safety profile is generally consistent with other member of the class. Further, the cardiovascular safety of semaglutide has been adequately established. Though there was a finding for increased risk of diabetic retinopathy complications, I do not believe that it is so substantial as to outweigh the benefits. While the finding raises some question as to the benefit of semaglutide with respect to reducing the risk for diabetic retinopathy progression, improved glycemic control should convey a reduced risk for other diabetic complications (e.g., diabetic nephropathy, diabetic neuropathy). Further, diabetic retinopathy can be monitored and treated to prevent serious clinical outcomes (e.g., blindness).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Type 2 diabetes mellitus (T2DM) is a condition of chronic impaired glucose homeostasis leading to chronic hyperglycemia and an increased risk for microvascular (e.g., retinopathy, nephropathy) and macrovascular (e.g., myocardial infarction, stroke) complications. The Center for Disease Control estimates that there are over 29 million patients with type 2 diabetes mellitus in the United States.	Type 2 diabetes mellitus is a serious and life threatening condition that if left untreated leads an increased risk for morbidity and mortality.
Current Treatment Options	• Based on the results of the Diabetes Control and Complication Trial and the United Kingdom Prospective Diabetes study, improved glycemic control (as measured using hemoglobin A1c [HbA1c]) is believed to result in improved clinical outcomes (i.e., reduced microvascular complications). • There are currently 12 classes of medications (generally with multiple members in each class), approved to improve glycemic control in patients with T2DM. Many of these medications are also approved as fixed combination drug products (FCDPs). • There are different safety concerns for each class. Metformin is often considered first-line therapy with the choice of subsequent therapies individualized by prescribers based on the patient. • While approved antidiabetic agents have been shown to improve glycemic control, data on the ability of individual agents to improve clinical outcomes are limited in terms of drug products and studied populations.	Despite the many available treatment options, many patients continue to have difficulty with achieving the desired degree of glycemic control. Further, T2DM is a progressive disorder and patients typically need additional agents as the course of the disease progresses.
Benefit	• Use of semaglutide improved glycemic control with treatment difference compared to placebo in mean HbA1c of -1.1 to -1.6% at 30 weeks. • Subjects treated with semaglutide were also found to have a treatment difference compared to placebo in mean body weight ranging from -2.2 to -4.7 kg.	Semaglutide has demonstrated the ability to improve glycemic control. Other findings that may be desirable for patients include a reduction in body weight.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The most common adverse reactions were gastrointestinal events (i.e., nausea/vomiting). • Class safety concerns include pancreatitis, medullary thyroid tumors, and acute kidney injury. Findings from the development program do not change these concerns • No evidence of increased cardiovascular risk. • Finding of increased risk of progression of diabetic retinopathy was seen in the two year cardiovascular outcomes trial, primarily in subjects with retinopathy at baseline. Whether this will ultimately reverse (as would be expected based on the DCCT and other large clinical trials) or persist is unknown.	The safety profile of semaglutide is generally consistent with other long-acting GLP-1 receptor agonists. The cardiovascular safety of semaglutide has been adequately established. An increased risk for diabetic retinopathy complications was seen with semaglutide in the CVOT which is contrary to what would be expected with a therapy that improves glycemic control. While it is unknown whether long-term therapy with semaglutide will lead to a reduced risk for progression of diabetic retinopathy (which is what would be expected based on large, prospective clinical trials such as the DCCT), it is worth noting that a reduced risk of diabetic retinopathy progression is not the only clinical benefit expected with improved glycemic control. Additionally, diabetic retinopathy can be monitored and there are effective therapies to prevent serious adverse clinical outcomes (e.g., blindness). This risk can be managed and does not by itself result in an unfavorable benefit-risk assessment.
Risk Management	• The identified risks for semaglutide are generally consistent with the other members of the class. Labeling should be similar to other long-acting GLP-1 receptor agonists. • The approval of other GLP-1 receptor agonists has included a communication plan REMS for purposes of informing prescribers of the risk for MTC and pancreatitis. The assessment of the data from these REMS has suggested that this risk has been sufficiently communicated for the class. Thus, no REMS is recommended for semaglutide.	The risks associated with semaglutide can be handled with adequate labeling. Given the extensive experience with other long-acting GLP-1 receptor agonists and their communication plan REMS for MTC and pancreatitis, the risk appears to have been adequately communicated for the class and I do not recommend a REMS for semaglutide. The finding of increased risk for diabetic

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The increased risk for diabetic retinopathy complications is unexpected and of some concern. Whether this will be a short-term risk or remain a long-term safety concern is unknown. However, diabetic retinopathy can be monitored and managed. This risk can be managed through labeling.	retinopathy complications was unexpected and of some concern, but this can be monitored and there are effective treatments. Routine diabetic ophthalmologic care should be sufficient to mitigate this risk, and I believe that communication of this risk can be handled with labeling.

2. Background

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia. There are two main types of diabetes mellitus: type 1 diabetes mellitus (T1DM; characterized by autoimmune destruction of pancreatic β-cells and loss of insulin secretion) and type 2 diabetes mellitus (T2DM; characterized by resistance to insulin activity with inadequate insulin production to maintain euglycemia). Chronic hyperglycemia in turn leads to an increased risk for microvascular (e.g., retinopathy, nephropathy) and macrovascular (e.g., myocardial infarction, stroke) complications. Based on the results of the Diabetes Control and Complication Trial (DCCT) [1] and the United Kingdom Prospective Diabetes study (UKPDS) [2], improved glycemic control (as measured using hemoglobin A1c [HbA1c]) is believed to result in improved clinical outcomes.

The development of therapies to treat T2DM has focused on developing agents that can improve glycemic control as assessed by the ability to reduce HbA1c, and this has served as the basis for approval of antidiabetic agents. Recently, studies of some antidiabetic drugs have reported improved clinical outcomes in patients with T2DM. These findings are limited to a few drug products [3, 4] and were conducted in a population with high cardiovascular risk. Whether these findings can be generalized to the entire population of patients with T2DM is unknown.

There are currently 11 classes of antidiabetic drugs with most classes having multiple members (Table 1). Many of these drug products are also available as FCDPs.

Table 1: Summary of FDA approved drugs to improve glycemic control in diabetes

Drug Class	Drug Products
Insulin and insulin analogs	Multiple products including basal, prandial, and mixed insulin products
Biguanides	Metformin (as an immediate release and an extended release formulation)
Sulfonylureas	Chlorpropamide, Glimepiride, Glipizide, Glyburide
Thiazolidinediones	Rosiglitazone, Pioglitazone
Meglitinides	Repaglinide, Nateglinide
Alpha glucosidase inhibitors	Acarbose, Miglitol
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin
Glucagon-like peptide-1 (GLP-1) receptor agonists	Exenatide (as a twice daily and as a once weekly), Liraglutide, Albiglutide, Dulaglutide, Lixisenatide

[1] The Diabetes Control and Complications Trial Research Group. "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus". NEJM, 1993; 329 (14): 977-986.
[2] UK Prospective Study Group. "Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)". Lancet, 1998; 352 (9131): 837-853.
[3] Zinman B, et al. "Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes". NEJM, 2015; 373: 2117-2128.
[4] Marso SP, et al. "Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes". NEJM, 2016; 375: 311-322.

Drug Class	Drug Products
Sodium glucose cotransporter-2 (SGLT2) inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin
Amylin analogs	Pramlintide
Bile acid sequestrants	Colesevelam
Dopamine agonists	Bromocriptine

Despite the number of available therapies, many patients with T2DM continue to have difficulty in achieving glycemic targets. While reasons for this are likely multifactorial, it has been suggested that more therapeutic options are needed to allow for better individualization of therapy.

Novo Nordisk (hereafter referred to as the applicant) has submitted a new drug application (NDA) seeking approval for semaglutide, a once weekly GLP-1 receptor agonist. Semaglutide would be the seventh GLP-1 receptor agonist drug product to be marketed in the United States, and the fourth once weekly GLP-1 receptor agonist.

The applicant (b) (4) proposed (b) (4) for semaglutide. (b) (4) "… as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." (b) (4)

The applicant has proposed two therapeutic doses for semaglutide (0.5 mg once weekly and 1 mg once weekly) as well as a titration dose of 0.25 mg once weekly. The titration dose is to be administered for the first four weeks followed by an increase to the 0.5 mg dose. If additional glycemic control is required, patients can increase to the 1 mg dose. The drug product will be available in pre-filled, multi-dose pens for subcutaneous injection. One pen will allow for selection of the two different dosage strengths (i.e., 0.25 mg, and 0.5 mg). The other pen will deliver only the 1 mg dose.

3. Product Quality

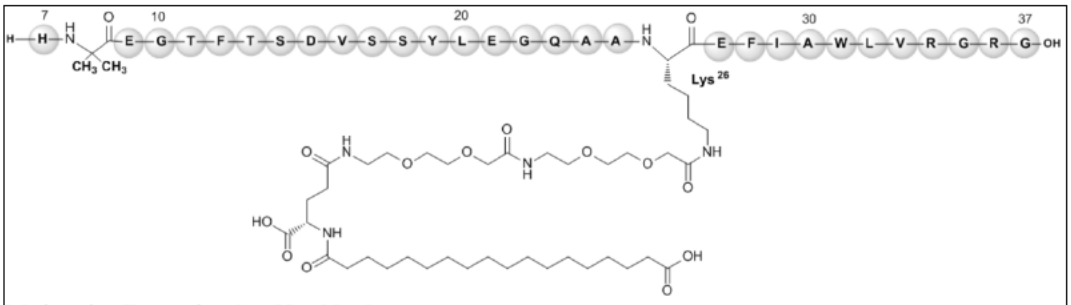
Drug Substance:

Semaglutide is a (b) (4) peptide that is an analog of glucagon-like peptide-1 (GLP-1) which differs from endogenous GLP-1 through three modifications:

(1) Substitution of arginine for lysine at position 34
(2) Attachment of a long fatty acid derivative at position 26, and
(3) Modification of position 8 of the peptide backbone, substituting amino-isobutyric acid for alanine

These modifications are intended to result in slowed degradation and reduced renal clearance, thus contributing to the prolonged half-life and allowing for once-weekly subcutaneous administration.

The molecular formula and chemical structure of semaglutide are shown below:

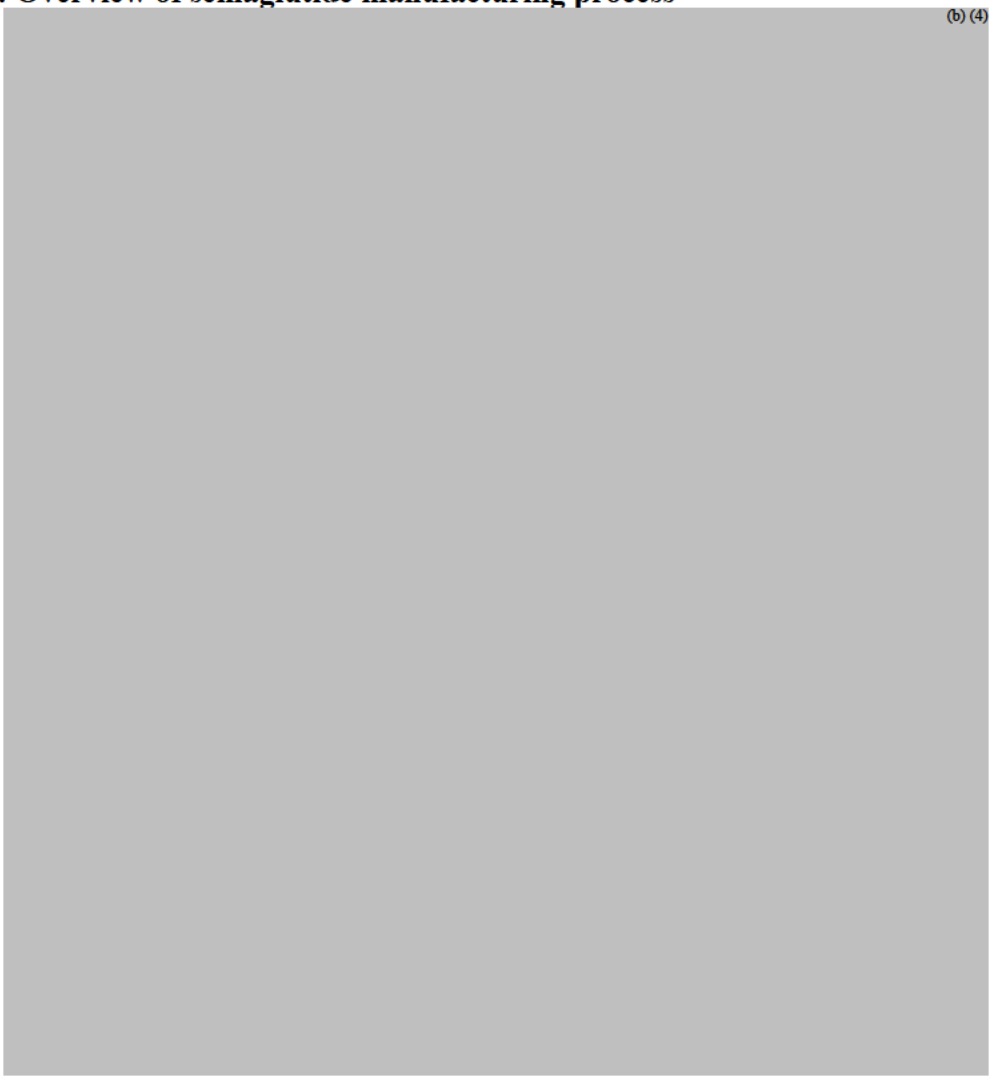


Molecular Formula: $C_{187}H_{291}N_{45}O_{59}$

Source: Excerpted from section 5.1 of Dr. Leginus' Drug Substance Review

Manufacturing of semaglutide is (b) (4) (Figure 1).

Figure 1: Overview of semaglutide manufacturing process



Source: Excerpted from section 5.2 of Dr. Leginus' Drug Substance review

For detailed discussion of the semaglutide drug substance manufacturing, see Dr. Leginus' review. The available data on the manufacturing process including characterization of product-related and process-related impurities is acceptable and support approval.

Drug Product:

The semaglutide drug product consists of semaglutide in a clear, colorless solution at a concentration of 1.34 mg/mL. The semaglutide solution will be packaged in a 1.5 mL glass

cartridge that is subsequently incorporated into a pen injector delivery system. This section of the review will focus on the drug product manufacturing through the primary container closure system (i.e., the 1.5 mL glass cartridge). Discussion of the pen injector is found below, under "Device".

The drug product is manufactured by (b) (4). Dr. Ma has found the manufacturing process and in-process controls to be adequate.

Table 2: Composition of semaglutide drug product

Name of ingredients	Quantity per ml	Function	Reference to standards
Active substance			
Semaglutide	1.34 mg	Active drug substance	Novo Nordisk A/S
Excipients			
Disodium phosphate, dihydrate	1.42 mg	(b) (4)	USP/Ph. Eur.
Propylene glycol	14.0 mg		USP/JP/Ph. Eur.
Phenol	5.50 mg[a]		USP/JP/Ph. Eur.
Hydrochloric acid	q.s[b]	pH adjustment	USP/JP/Ph. Eur.
Sodium hydroxide	q.s[b]	pH adjustment	USP/JP/Ph. Eur.
Water for injections	(b) (4)	(b) (4)	USP/JP/Ph. Eur.

[a] (b) (4)

[b] To reach pH 7.4

Source: Excerpted from P.3 of Dr. Ma's review

The primary container closure consists of a chemically inert, 1.5 mL cartridge made of colorless glass that is sealed with a (b) (4) rubber disc and rubber plunger. The rubber disc consists of (b) (4) rubber (non-contact side) and (b) (4) rubber (contact side). The rubber plunger is made of (b) (4) rubber. Compatibility of the semaglutide drug product with the primary container closure is supported by 36 months of real-time stability data. Leachable and extractable data were also adequate.

Of note, photostability testing demonstrated that the drug product is sensitive to light (Table 3). When exposed to light (i.e., 1.4 million lux hours and 585 Wh/m^2 over 26 hours), semaglutide content was noted to decrease and impurity content (primarily high molecular weight proteins) increased. When the drug product is stored in the pen injector with the cap in place, no such degradation was noted.

Table 3: Photo stability results

Test item	Dark control	1.5 ml cartridge	PDS290 pen-injector	Comments
Macroscopy	Colorless or almost colorless liquid free from turbidity and essentially free from particulate matter			Drug product packaged in pen injector (with cap) on is protected from degradation. Exposure to light resulted in an increase in HMWP content.
pH	7.40	7.39	7.38	
Content of semaglutide, mg/mL	1.34	1.26	1.34	
High molecular weight proteins	(b) (4)			
Hydrophilic impurities				
Hydrophobic impurities 1				
Hydrophobic impurities 2				
Sum of impurities				
Phenol, mg/mL				

Source: Excerpted from section P.2 of the Drug Product Review

Based on the provided stability data, Dr. Ramaswamy agrees with the applicant's proposed 36-month shelf-life when stored at 5°C, and the proposed 56 day in-use period when stored at 5 to 30°C. The semaglutide pen injector should be stored with the cap on as the secondary packaging is adequate to protect against degradation due to light exposure.

The manufacturing process was found to be adequate. For detailed discussion of the drug product manufacturing process and the drug product in its primary container closure, see Dr. Ma's and Dr. Ramaswamy's reviews.

Microbiology:

(b) (4). Antimicrobial effectiveness testing of (b) (4) at the lower specification limit demonstrated that it meets the USP<51> acceptance criteria.

(b) (4)

The manufacturing processes were found to be adequate to assure microbiological quality.

Device:

Semaglutide is to be marketed in a PDS290 pen injector that will contain 1.5 mL of semaglutide 1.34 mg/mL. Two pen injectors are proposed. The initial proposal was to have one pen injector labeled to deliver doses of 0.25 mg, 0.5 mg, or 1 mg and the other labeled to deliver doses of 1 mg. Differences between the two pen injectors include the imprint on the drum displaying dose, the maximum dose stop, and color.

The to-be-marketed device was not used in the phase 3 clinical trials, however, differences between the device are cosmetic and do not alter the function of the device.

The design and performance of the proposed pen injector were reviewed. The design verification and dose accuracy testing comply with ISO 11608-1.

The assessment of the initial proposal identified user errors in selecting the correct pen injector. This was attributed to confusion from both pen injectors being labeled for administration of the 1 mg dose. Dr. Susan Rimmel from the Division of Medication Errors Prevention and Analysis felt that this error could be corrected by either marketing a single pen injector or by relabeling the pen injectors such that the 1 mg dose could not be selected with the pen injector labeled for multiple dosage strengths. The applicant has opted to pursue the latter approach and has resubmitted the proposed devices such that one is labeled for delivery of 0.25 mg or 0.5 mg, and the other is labeled for delivery of the 1 mg dose only. In review of the changes, Dr. Rimmel believes that these are self-evident and that no additional data are required. Dr. Rimmel also has additional labeling recommendations to promote the safe use of the product and to mitigate any confusion. See Dr. Rimmel's consult review for details.

Dr. Sarah Mollo from the Center for Devices and Radiologic Health has reviewed the proposed device and the performance characteristics. Based on the provided device data, the design and performance review of the pen injector supports approval.

Facilities:

No preapproval inspections were conducted, but the application and inspectional documents were reviewed. Based on this review, the facilities reviewers did not identify any manufacturing or facility risks which would preclude approval of semaglutide.

4. Nonclinical Pharmacology/Toxicology

The review of the submitted nonclinical data was completed by Dr. Federica Basso. Findings from Dr. Basso's review are summarized here. For detailed discussion, see Dr. Basso's nonclinical review.

Nonclinical pharmacology studies demonstrated that semaglutide binds to and activates the human GLP-1 receptor. In Wistar rats and diabetic db/db mice, this in turn led to an increase in glucose-stimulated plasma insulin, a decrease in blood glucose, and a decrease in body weight gain. Dose-related increases in glucose-dependent insulin secretion (along with decreases in glucose levels) were seen in rats, mice, and minipigs. Administration of semaglutide was also associated with reduced food intake.

Semaglutide was well absorbed following subcutaneous injection with a bioavailability of 86% in monkeys. Binding to plasma protein was high with albumin being the primary binding site. Following injection, semaglutide is found primarily in plasma/blood. In pigmented rats, semaglutide was also found in the bile ducts. Metabolites of semaglutide make up only a small proportion of semaglutide related materials in the circulation. Urine and feces are the main excretion routes for semaglutide related materials. Low amounts of intact semaglutide were detected in the urine or feces.

Toxicity studies of up to 3-, 6-, and 12-months duration were conducted in mice, rats, and monkeys, respectively. Dose-limiting reductions in food intake and body weight were seen in all species. Findings of C-cell hyperplasia were seen in mice starting at 17x the clinical exposure (MRHD). At 175x the clinical exposure, liver necrosis and centrilobular hypertrophy were observed in rats (primarily males). ECG abnormalities and myocardial vacuolation and degeneration were seen at 27x the clinical exposure. A no observed adverse effect level for cardiac effects was determined to be 5x the clinical exposure.

Two-year carcinogenicity studies were conducted in mice and rats. The increase in the incidence of C-cell adenomas and carcinomas was seen in both species (at an exposure equal to the clinical exposure in rats, and at 2x and 5x the clinical exposure in female and male mice, respectively). C-cell carcinomas were increased in male rats starting at 0.7x the clinical exposure.

Developmental and reproductive toxicology studies were conducted in rats, rabbits and monkeys. No effects were observed on male fertility. An increase in estrus cycle length and a reduction in the number of corpora lutea were observed in females. These findings were observed at the clinical exposure, and may be due to the pharmacologic effect of reducing food consumption and body weight. Decreases in maternal body weight gain, embryofetal growth retardation and mortality, and embryofetal skeletal and visceral malformations were observed in rats at clinical exposures. These may also be mediated by the pharmacologic effect on food consumption and body weight, though mechanistic studies showed that semaglutide causes embryotoxicity in rats through a GLP-1 receptor-mediated effect on the yolk sac.

Administration of semaglutide to juvenile rats resulted in reduced food consumption, reduced body weight gain, and delayed sexual maturation at the clinical exposure.

The nonclinical data for semaglutide is generally consistent with findings for other GLP-1 RAs. Based on the data reviewed, Dr. Basso recommends approval.

5. Clinical Pharmacology

The development program for semaglutide included 16 clinical pharmacology studies. Findings included characterization of the pharmacokinetic characteristics (see below, excerpted from section 2.1 of the Clinical Pharmacology review).

PK Parameters	Geometric Mean (CV%)
$t_{max,SS}$[1]	36 – 59.8 hr (1.5 – 2.5 days)
$t_{1/2,SS}$	149-150 hr (6.2 days)
CL/F_{SS}	0.051 – 0.052 L/hr
V_{SS}/F	11.24 – 13.92 L

[1]Median

The relatively long terminal $t_{1/2}$ allows for once weekly subcutaneous dosing.

The absolute bioavailability of semaglutide was estimated to be 89% after administration of a single 0.5 mg dose in healthy subjects.

Steady-state exposure to semaglutide increased with semaglutide dose, consistent with dose-proportionality. While steady-state exposure appeared to be lower in patients with T2DM compared to healthy subjects, this is likely due to higher body weight in the T2DM patients.

Semaglutide is metabolized by proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side chain. Semaglutide-related materials are primarily excreted in the urine (53%) and feces (18.6%).

Treatment with semaglutide increased insulin secretion (first phase more than second phase) in patients with T2DM. Concurrently, an increase in C-peptide levels was observed along with a decrease in glucagon levels. During meal stimulation tests, administration of semaglutide led to a decrease in glucose and glucagon levels.

In patients with renal impairment, the terminal $t_{1/2}$ was comparable between patients with normal renal function and patients with mild to moderate renal impairment (i.e., eGFR between 30 to 90 mL/min/1.73 m^2). Terminal $t_{1/2}$ was longer in patients with severe renal impairment and in patients with end-stage renal disease. Dialysis did not affect exposure to semaglutide. While noting these differences, Dr. Yapa does not believe that renal impairment impacts exposure to semaglutide in a clinically relevant manner. Consequently, Dr. Yapa does not recommend dose adjustment for patients with renal impairment.

Similarly, degree of hepatic impairment did not appear to impact the pharmacokinetic characteristics of semaglutide. Exposure to semaglutide was similar between patients with normal, mild, moderate, or severe hepatic impairment.

No clinically relevant drug-drug interactions were identified in the conducted drug-drug interaction studies. *In vitro* studies showed semaglutide to have a low potential to inhibit or induce cytochrome P450. Similarly, semaglutide has a low potential to inhibit drug transporters (i.e., P-gp, BCRP, OCT2, OAT1, and OAT3). Semaglutide did partially inhibit OATP1B1 and OATP1B3, however, the potential for a clinically relevant interaction is considered to be low.

In a thorough QT study, no significant prolongation of the QT interval was observed.

Based on the reviewed clinical pharmacology data, Dr. Yapa and Dr. Earp support approval of semaglutide as a once weekly injection.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The efficacy of semaglutide for improving glycemic control was reviewed by Dr. Jiwei He. I will summarize findings from the statistical review here. For a detailed discussion, see Dr. He's statistical review.

In support of this NDA, the applicant conducted eight phase 3 studies. Features of these studies are briefly summarized in Table 4. Study NN9535-3744 (hereafter referred to as SUSTAIN 6) was conducted to demonstrate cardiovascular safety and will not be discussed here. Findings from SUSTAIN 6 will be discussed in Section 8 of this review.

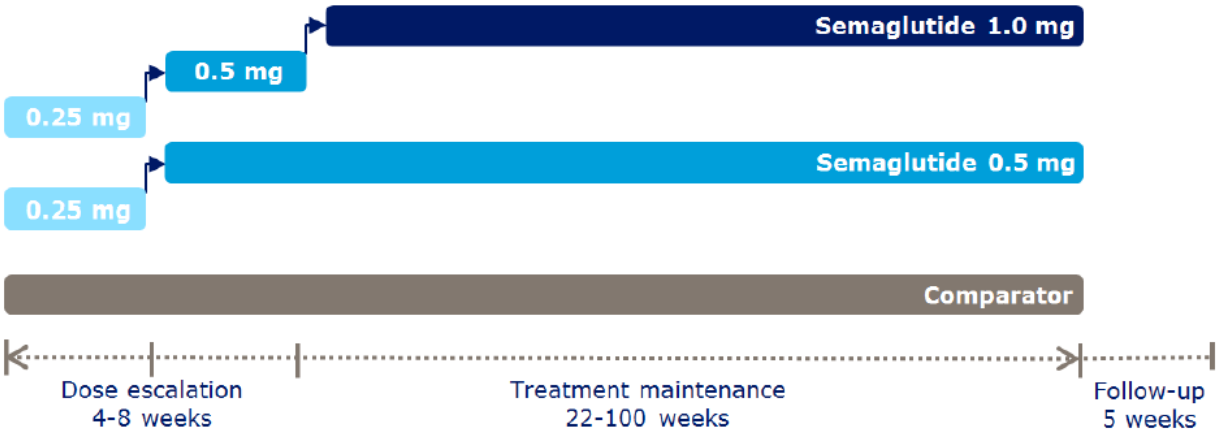
Table 4: Summary Description of Phase 3 Studies

Study ID	Population	Design	Duration	Treatment Arms
NN9535-3623 (SUSTAIN 1)	Adults with T2DM not on anti-diabetic drugs	Randomized, double-blind, placebo-controlled	30 weeks	• Semaglutide 0.5 mg once weekly • Semaglutide 1 mg once weekly • Placebo
NN9535-3626 (SUSTAIN 2)	Adults with T2DM on metformin and/or TZD	Randomized, double-blind, active-controlled	56 weeks	• Semaglutide 0.5 mg once weekly • Semaglutide 1 mg once weekly • Sitagliptin 100 mg once daily
NN9535-3624 (SUSTAIN 3)	Adults with T2DM on 1-2 oral anti-diabetic drugs	Randomized, open-label, active-controlled	56 weeks	• Semaglutide 1 mg once weekly • Exenatide LAR 2 mg once weekly
NN9535-3625 (SUSTAIN 4)	Adults with T2DM on metformin +/- sulfonylurea - Not previously treated with insulin	Randomized, open-label, active-controlled	30 weeks	• Semaglutide 0.5 mg once weekly • Semaglutide 1 mg once weekly • Insulin glargine (titrated)
NN9535-3627 (SUSTAIN 5)	Adults with T2DM on basal insulin +/- metformin	Randomized, double-blind, placebo-controlled	30 weeks	• Semaglutide 0.5 mg once weekly • Semaglutide 1 mg once weekly • Placebo
NN9535-4091	Japanese adults with T2DM on 1 oral anti-diabetic drug (sulfonylurea, glinide, alpha-glucosidase inhibitor, or TZD)	Randomized, open-label, active-controlled	56 weeks	• Semaglutide 0.5 mg once weekly • Semaglutide 1 mg once weekly • Additional oral anti-diabetic drug
NN9535-4092	Japanese adults with T2DM on diet and exercise or one oral anti-diabetic drug	Randomized, open-label, active-controlled	30 weeks	• Semaglutide 0.5 mg once weekly • Semaglutide 1 mg once weekly • Sitagliptin 100 mg once daily
NN9535-3744 (SUSTAIN 6)	Adults with T2DM and high cardiovascular risk - Variety of background therapies allowed	Randomized, double-blind, placebo-controlled	104 weeks	• Semaglutide 0.5 mg once weekly • Semaglutide 1 mg once weekly • Placebo

T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; LAR = long-acting release
Source: Adapted from the submitted "Tabular Listing of All Clinical Studies" in module 5.2 of NDA 209637

The focus of the discussion of efficacy will be the five multinational trials (i.e., SUSTAIN 1, 2, 3, 4, and 5). Two of these trials were placebo-controlled trials. The other three were active-controlled trials. The primary endpoint of all five trials was change in HbA1c from baseline to either 30 weeks (SUSTAIN 1, 4, and 5) or 56 weeks (SUSTAIN 2 and 3). Two doses of semaglutide (0.5 mg once weekly and 1 mg once weekly) were studied in four of the trials (SUSTAIN 1, 2, 4, and 5). Only the 1 mg dose was studied in SUSTAIN 3 (semaglutide vs. exenatide extended-release). Subjects randomized to semaglutide were started on a dose of 0.25 mg once weekly for 4 weeks. The dose was then increased to 0.5 mg once weekly. This dose was maintained for the remainder of the study (for patients randomized to the 0.5 mg once weekly dose) or used for an additional 4 weeks before increasing the dose further to 1 mg once weekly (for patients randomized to the 1 mg once weekly dose). See Figure 2 for an illustration of the dose titration used in the phase 3 studies.

Figure 2: Representative schematic of study design and semaglutide titration for phase 3 studies



Source: Excerpted from Figure 1-3 of the Summary of Clinical Efficacy

Study subject demographics were generally balanced in the trials (see Table 4 and Table 5 of Dr. He's statistical review). Overall, slightly more comparator treated subjects completed treatment (see Table 2 and Table 3 of Dr. He's statistical review, excerpted below). Premature discontinuation in the semaglutide arms was most commonly due to an adverse event. Rescue medication was used more frequently in comparator treated subjects in most of the trials. The one exception was SUSTAIN 4 where use of rescue was low overall and slightly higher with semaglutide.

Table 2 Summary of patient dispositions in placebo-controlled trials 3623 and 3627

Trial	3623				3627			
	Sema 0.5mg	Sema 1.0mg	Placebo 0.5mg	Placebo 1.0mg	Sema 0.5mg	Sema 1.0mg	Placeo 0.5mg	Placebo 1.0mg
Randomized, n	129	130	65	64	132	132	66	67
Randomized and Treated (FAS), n(%)	128 (99.2)	130 (100)	65 (100)	64 (100)	132 (100)	131 (99.2)	66 (100)	67 (100)
Completed Treatment[1], n(%)	111 (86.1)	114 (87.7)	57 (87.7)	58 (90.6)	118 (89.4)	115 (87.8)	59 (89.4)	61 (91.0)
Discontinued Treatment[1], n(%)	17 (13.3)	16 (12.3)	8 (12.3)	6 (9.4)	14 (10.6)	16 (12.2)	7 (10.6)	6 (9.0)
Adverse event	8	7	3	0	6	10	0	1
Protocol violation	4	2	0	1	1	0	2	0
Pregnancy	0	0	1	0	1	0	0	0
Other	5	7	4	5	6	6	5	5
Rescue medication during treatment[1], n(%)	6 (4.7)	6 (4.6)	14 (21.5)	13 (20.3)	3 (2.3)	1 (0.8)	12 (18.2)	9 (13.4)
Had HbA1c measurement at endpoint[1], n(%)	119 (93)	121 (93.1)	58 (89.2)	58 (90.6)	126 (95.5)	124 (94.7)	60 (90.9)	64 (95.5)
Missed HbA1c measurement at endpoint[1], n(%)	9 (7.0)	9 (6.9)	7 (10.8)	6 (9.4)	6 (4.5)	7 (5.3)	6 (9.1)	3 (4.5)
Retrieved dropouts[1], n(%)	11 (8.6)	12 (9.2)	4 (6.2)	2 (3.1)	12 (9.1)	15 (11.5)	5 (7.6)	8 (11.9)

1. The number and % are based on the randomized and treated population

Table 3 Summary of patient dispositions in active-controlled trials 3626, 3624 and 3625

Trial	3626				3624		3625		
	Sema 0.5mg	Sema 1.0mg	Sitagliptin +0.5mg Placebo	Sitagliptin +1.0mg Placebo	Sema 1.0mg	Exenatide	Sema 0.5mg	Sema 1.0mg	Insulin Glargine
Randomized, n	410	410	205	206	406	407	362	362	365
Randomized and Treated (FAS), n(%)	409 (99.8)	409 (99.8)	203 (99.0)	204 (99.0)	404 (99.5)	405 (99.5)	362 (100)	360 (99.4)	360 (98.6)
Completed Treatment[1], n(%)	356 (87.0)	348 (85.1)	182 (89.7)	193 (94.6)	322 (79.7)	320 (79.0)	313 (86.5)	305 (84.7)	334 (92.8)
Discontinued Treatment[1], n(%)	53 (13.0)	61 (14.9)	21 (10.3)	11 (5.4)	82 (20.3)	85 (21.0)	49 (13.5)	55 (15.3)	26 (7.2)
Adverse event	33	41	8	4	39	29	19	27	5
Protocol violation	4	4	1	5	15	21	12	13	2
Pregnancy	0	0	0	0	0	1	0	1	1
Other	16	16	12	2	28	34	18	14	18
Rescue medication during treatment[1], n(%)	25 (6.1)	10 (2.4)	45 (22.2)	40 (19.6)	28 (6.9)	48 (11.8)	14 (3.9)	9 (2.5)	5 (1.4)
Had HbA1c measurement at endpoint[1], n(%)	382 (93.4)	387 (94.6)	190 (93.6)	194 (95.1)	368 (91.1)	359 (88.6)	333 (92)	337 (93.6)	340 (94.4)
Missed HbA1c measurement at endpoint[1], n(%)	27 (6.6)	22 (5.4)	13 (6.4)	10 (4.9)	36 (8.9)	46 (11.4)	29 (8)	23 (6.4)	20 (5.6)
Retrieved dropouts[1], n(%)	33 (8.1)	47 (11.5)	15 (7.4)	8 (3.9)	55 (13.6)	51 (12.6)	31 (8.6)	48 (13.3)	13 (3.6)

1. The number and % are based on the randomized and treated population

The applicant's pre-specified primary analysis was a mixed-effect model repeated measures (MMRM) analysis using the on-treatment data without rescue (i.e., time from first dose of study drug up to 7 days after last dose of study drug, date of initiating rescue medication, or date of last study visit). Off-treatment measurements at scheduled visits were replaced with on-treatment measurements taken at the premature treatment discontinuation visit. Dr. He notes some issues with this approach including that missing data was assumed to be missing at random. At the pre-NDA meeting, the applicant was advised to perform a retrieved dropout analysis. This was conducted such that missing data was imputed based on values from subjects that discontinued

treatment but still had measurements at the endpoint visit. This last approach is Dr. He's preferred approach and is the focus of her efficacy review.

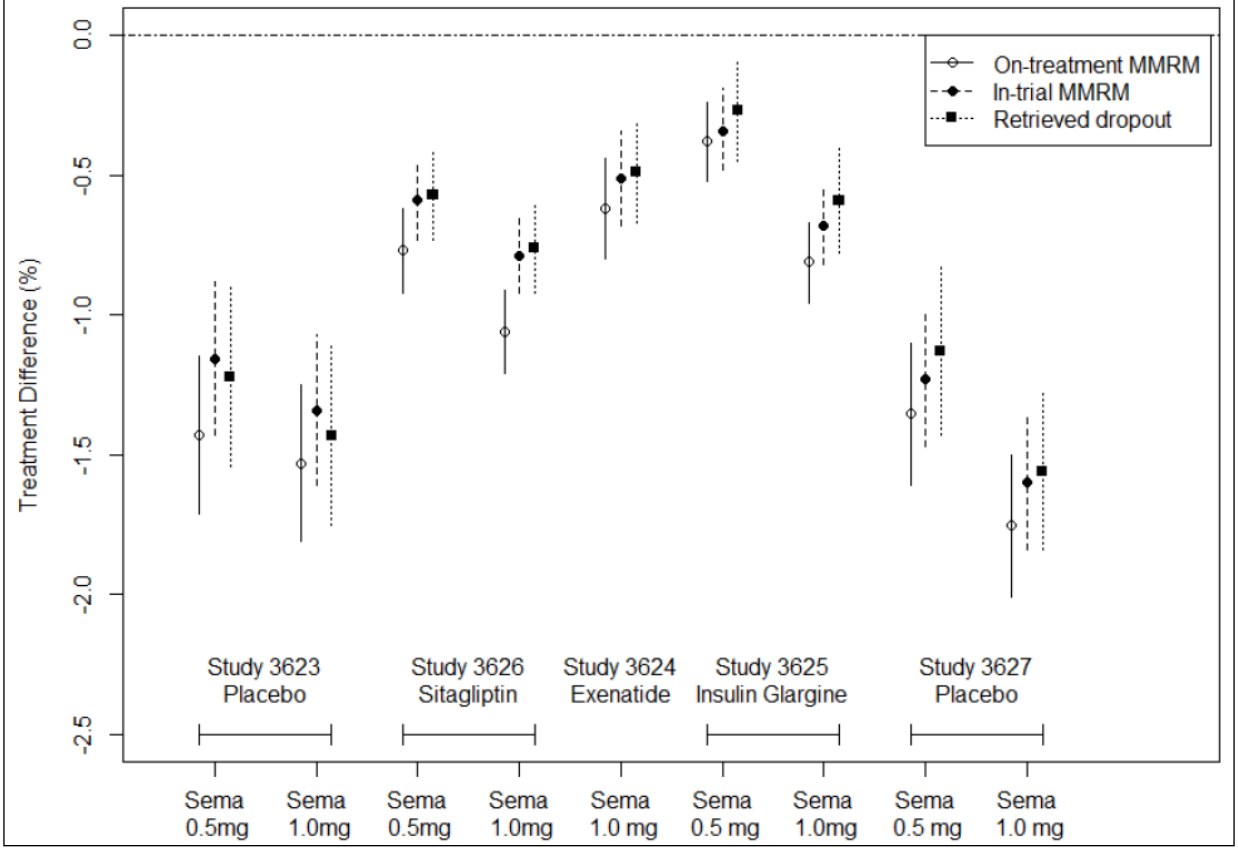
In all of the trials, treatment with semaglutide was found to result in a statistically significant greater reduction in HbA1c compared to comparator (see Table 6 from Dr. He's statistical review, excerpted below).

Table 6 Change in HbA1c (%) from baseline to the end of treatment period using multiple imputation based on retrieved dropouts in FAS[1]

Trial	Endpoint Visit/ Week	Treatment Arms	N	Baseline	Change from Baseline[2]		Treatment Difference (Semaglutide-Comparator)			Achieving HbA1c<7%	
				Mean	LS Mean	SE	LS Mean	95% CI	P-value	n	(%)
3623-SUSTAIN 1	30	Sema 0.5mg	128	8.09	-1.37	0.11	-1.22	[-1.54; -0.90]	<.0001	93	(73)
		Sema 1.0mg	130	8.12	-1.57	0.11	-1.43	[-1.75; -1.11]	<.0001	91	(70)
		Placebo	129	7.95	-0.15	0.12				36	(28)
3626-SUSTAIN 2	56	Sema 0.5mg	409	8.01	-1.29	0.06	-0.57	[-0.73; -0.41]	<.0001	269	(66)
		Sema 1.0mg	409	8.04	-1.48	0.05	-0.76	[-0.91; -0.61]	<.0001	300	(73)
		Sitagliptin	407	8.17	-0.72	0.06				165	(40)
3624-SUSTAIN 3	56	Sema 1.0mg	404	8.36	-1.39	0.07	-0.49	[-0.67; -0.30]	<.0001	249	(62)
		Exenatide	405	8.33	-0.91	0.07				163	(40)
3625-SUSTAIN 4	30	Sema 0.5mg	362	8.13	-1.16	0.06	-0.27	[-0.45; -0.08]	0.0047	200	(55)
		Sema 1.0mg	360	8.25	-1.48	0.06	-0.59	[-0.78; -0.40]	<.0001	237	(66)
		Insulin Glargine	360	8.13	-0.89	0.08				144	(40)
3627-SUSTAIN 5	30	Sema 0.5mg	132	8.36	-1.32	0.11	-1.13	[-1.43; -0.83]	<.0001	73	(56)
		Sema 1.0mg	131	8.31	-1.74	0.10	-1.56	[-1.84; -1.27]	<.0001	96	(73)
		Placebo	133	8.42	-0.19	0.11				17	(13)

The on-treatment MMRM analysis, the in-trial MMRM analysis, and the analysis using retrieved dropouts were generally consistent (see Figure 1 of Dr. He's statistical review, excerpted below).

Figure 1 Treatment difference of semaglutide minus comparator in terms of change in HbA1c (%) from baseline in the key efficacy trials



Secondary endpoints explored by the applicant included change in body weight from baseline, change in fasting plasma glucose from baseline, and proportion of subjects achieving HbA1c target. Subjects treated with semaglutide had a greater reduction in body weight, a greater reduction in fasting plasma glucose, and had a higher proportion reaching HbA1c targets compared to placebo and active comparator (see Dr. He's statistical review for details).

Based on review of the data, Dr. He concludes that both doses of semaglutide studied are effective in improving glycemic control in adults with T2DM. I agree with her conclusion.

While semaglutide was statistically superior to comparator for change in HbA1c, it is worth discussing the findings from SUSTAIN 4 in more depth. SUSTAIN 4 was a 30-week open-label trial comparing two doses of semaglutide to insulin glargine on a background of metformin with or without sulfonylurea. Subjects randomized to semaglutide escalated the dose as described in Figure 2. Subjects randomized to insulin glargine started insulin glargine at a dose of 10 units injected once daily. The dose was subsequently to be titrated based on the lowest fasting glucose value in the 3 days preceding a study visit/contact. Phone contact occurred at week 1, 2, 3, 6, 10, 14, 19, and 26. Study visits were to occur at week 4, 8, 12, 16, 23, and 30. The titration algorithm is shown below in Table 5, and the goal was a fasting glucose of 71 to 100 mg/dL.

Table 5 Insulin glargine titration algorithm in SUSTAIN 4

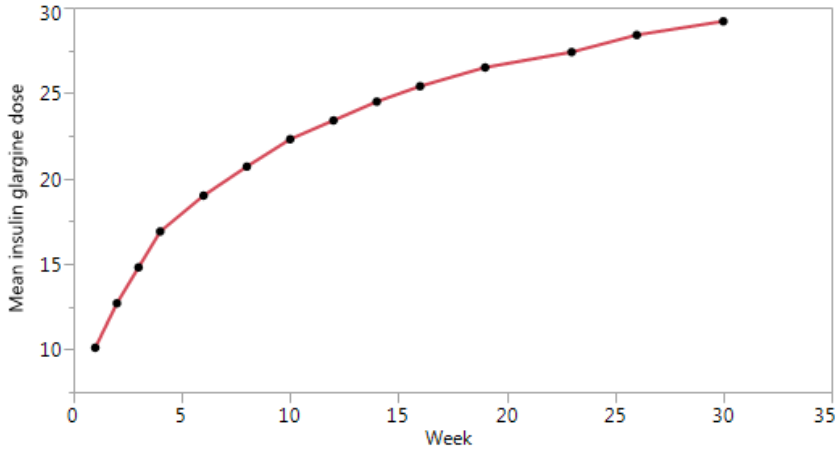
Fasting glucose (mg/dL) range	Change in insulin glargine dose
< 56	- 4 units (or reduction of 10% if dose is > 45 units)
≥56 to < 71	- 2 units (or reduction of 5% if dose is > 45 units)
≥ 71 to < 100	No change
≥ 100 to < 120	+ 0 to 2 units (at the discretion of the investigator)
≥ 120 to < 140	+ 2 units
≥ 140 to < 180	+ 4 units
≥ 180	+ 6 to 8 units (at the discretion of the investigator)

Titration based on lowest fasting glucose in the 3 days preceding study visit/contact
Source: Adapted from Table 9-2 and Table 9-3 of the study report for trial NN9535-3625

With insulin therapy, the dose is titrated to effect and, theoretically, there is no limit to the amount of insulin that can be administered or to the amount of glucose lowering that can be seen. Given this, the statistical superiority of semaglutide to insulin glargine warrants additional consideration as it is possible that the comparison between the two arms was not a fair comparison.

The first item to consider is whether the HbA1c at week 30 accurately reflects the insulin glargine dose at week 30. The insulin glargine dose appears to gradually increase over time, even up through the end of the treatment period (Figure 1). As HbA1c is a reflection of mean glucose over the preceding 12 weeks, it is unclear whether the week 30 HbA1c is reflective of the week 30 dose or if it more reflective of an earlier timepoint.

Figure 3 Mean insulin glargine dose over time in SUSTAIN 4



Source: Reviewer generated based on data from Table 14.2.37 of the study report for NN9535-3625

The second point worth considering is whether the insulin was adequately titrated such that a fair comparison can be made. The mean dose at week 30 was 29.2 units (for a change from week 1 of 19.1 units, or an increase of 0.6 units per week). This small weekly increase is difficult to characterize as adequate titration or as being consistent with clinical practice. It may also be worth considering the insulin dose relative to weight (i.e., units/kg) as a way to assess adequacy of the insulin dose. The mean baseline body weight of the study population was 93.45 kg at baseline. Using the final mean insulin dose of 29.2 units, this yields a dose of 0.3 units/kg at 30 weeks. The mean final dose relative to weight (i.e., 0.3 units/kg) is low compared to what might

be expected for an insulin resistant population, such as the one studied in SUSTAIN 4. A different approach to insulin titration would likely lead to a higher mean insulin dose and to greater reductions in HbA1c for the insulin glargine arm. Notably, this has been seen in other clinical trials of similar duration (Table 6). A reduction in HbA1c on par with what was seen with semaglutide 1 mg (i.e., ~1.5%) was achieved in the EASIE trial and the INITIATE trial. It is entirely plausible that the observed HbA1c reduction with the insulin glargine arm in SUSTAIN 4 could have been improved had the insulin dose been titrated differently.

Table 6: Findings for HbA1c and insulin dose from other insulin titration trials

	Mean HbA1c at baseline	Initial Insulin Dose	Mean HbA1c at endpoint (weeks)	Final insulin dose
TITRATE Trial[1]	8%	Insulin detemir, 0.1-0.2 U/kg or 10 U	6.8% to 7% at 20 weeks	0.5-0.6 U/kg
EASIE Trial[2]	8.5%	Insulin glargine, 0.2 U/kg	~6.8% at 24 weeks	0.5 U/kg
INITIATE Trial[3]	8.7% -8.8%	Insulin glargine, 10 U (0.1 U/kg)	6.9% to 6.8% at 24 weeks	56 to 62 U (0.6 to 0.64 U/kg)

[1] Blonde L, et al. Diabetes, Obesity and Metabolism 2009; 11: 623-631; [2] Aschner P, et al. Lancet 2012; 379: 2262-2269; [3] Yki-Järvinen H, et al. Diabetes Care 2007; 30(6): 1364-1369
U = units

It could be argued that insulin dose titration was limited by hypoglycemia. Though the incidence of hypoglycemia was increased in the insulin glargine arm (Table 7), it is unclear how many of these events were truly dose-limiting. The open-label design may have introduced bias for reporting of hypoglycemia and this raises some question to the validity of hypoglycemia categories that rely on symptoms for identification. Other categories (i.e., asymptomatic and pseudo-hypoglycemia) are of unclear clinical relevance. This leaves 'severe hypoglycemia' as the most objective measure of hypoglycemia, and review of only events of 'severe hypoglycemia' suggests that the incidence and event rate with insulin glargine were not markedly different from semaglutide (particularly from semaglutide 1 mg). Additionally, the incidence was low for these types of events in all treatment arms. Whether the differences in the incidence and event-rate of hypoglycemia would be sufficient to limit insulin titration is unclear.

Table 7: Incidence and event-rate of hypoglycemia in SUSTAIN 4

	Sema 0.5 N=362, PYE=225.1		Sema 1 N=360, PYE=219.1		Insulin Glargine N=360, PYE=234.6	
	N (%)	Events (per 100)	N (%)	Events (per 100)	N (%)	Events (per 100)
2013 ADA classification	82 (22.7)	277 (123.0)	90 (25.0)	271 (124.0)	142 (39.4)	416 (177.0)
Severe[1]	2 (0.6)	4 (1.8)	5 (1.4)	11 (5.0)	5 (1.4)	5 (2.1)
Documented symptomatic[2]	41 (11.3)	119 (52.9)	50 (13.9)	119 (54.3)	77 (21.4)	202 (86.1)
Asymptomatic[3]	41 (11.6)	123 (54.7)	46 (12.8)	102 (46.5)	74 (20.6)	163 (69.5)
Probable symptomatic[4]	5 (1.4)	5 (2.2)	13 (3.6)	15 (6.8)	8 (2.2)	8 (3.4)
Pseudo-hypoglycemia[5]	15 (4.1)	26 (11.6)	15 (4.2)	24 (11.0)	22 (6.1)	37 (15.8)
Unclassifiable	0	0	0	0	1 (0.3)	1 (0.4)

	Sema 0.5 N=362, PYE=225.1		Sema 1 N=360, PYE=219.1		Insulin Glargine N=360, PYE=234.6	
	N (%)	Events (per 100)	N (%)	Events (per 100)	N (%)	Events (per 100)
Novo Nordisk defined hypoglycemia[6]	16 (4.4)	32 (14.2)	20 (5.6)	39 (17.8)	38 (10.6)	69 (29.4)

PYE = patient-years exposed; Per 100 = per 100 patient-years
[1] episode requiring assistance of another person to actively administer corrective action; [2] typical symptoms with glucose ≤ 70 mg/dL; [3] glucose ≤ 70 mg/dL without typical symptoms; [4] typical symptoms without measured glucose; [5] typical symptoms with glucose > 70 mg/dL; [6] combination of events of 'severe' hypoglycemia and events of typical symptoms with glucose < 56 mg/dL
Source: Adapted from Table 12-10 of the study report for trial NN9535-3625

Given these issues in considering the results of SUSTAIN 4, I believe that the data are inadequate to conclude that semaglutide is superior to insulin glargine. The finding is true in the context of the trial design constraints, but whether this would hold true in clinical practice is unclear. The prescribing information should either not include this study or include language such that the limitations of the study design and of insulin titration are included to provide relevant contextual information in interpreting the statistical results.

Overall, Dr. He concludes that the applicant has provided substantial evidence that both doses of semaglutide are effective in improving glycemic control. I agree with Dr. He's conclusions.

8. Safety

The assessment of overall safety was conducted by Dr. Andreea Lungu. Additional assessments on specific safety issues were conducted by the Division of Biostatistics-7 (DB-7) and by Dr. Wiley Chambers from the Division of Transplant and Ophthalmology Products. In my CDTL review, I will briefly discuss the overall safety findings and highlight some selected safety findings of concern (e.g., retinopathy). See Dr. Lungu's review for a detailed discussion of the safety findings.

Several safety pools were considered in the assessment of safety. These included the following:

Table 8: Description of Safety Pools

Pool	Included studies	Size of population (S 0.5/S 1/C)
CVOT	Study 3744	823/819/1644
All phase 3	Study 3623, 3624, 3625, 3626, 3627, 4091, 4092	1373/1777/1657
Multi-national phase 3	Study 3623, 3624, 3625, 3626, 3627	1031/1434/1434
Phase 3 with placebo comparator	Study 3623, 3627	260/261/262
Phase 3 with non-GLP-1 RA comparator	Study 3623, 3625, 3626, 3627, 4091, 4092	1373/1373/1252
Phase 3 with GLP-1 RA comparator	Study 3624	--/404/405
Phase 3 with non-incretin comparator	Study 3626, 3625, 3626, 3627, 4091	861/862/742
Phase 3 with incretin comparator	Study 3624, 3626, 4092	512/915/915

S 0.5 = semaglutide 0.5 mg once weekly; S 1 = semaglutide 1 mg once weekly; C = comparator
Source: Adapted from Table 1-2 of the Summary of Clinical Safety

Deaths:

Overall, there was no evidence of an increase in the risk for death with semaglutide. No deaths were reported in any of the two placebo-controlled trials. There were 16 deaths in the phase 3 pool (excluding the CVOT). A total of 10 patients (0.3%) randomized to semaglutide died, and 6 patients (0.4%) randomized to comparator products died. In SUSTAIN 6, all-cause mortality was similar between semaglutide and placebo arms (3.8% with semaglutide, 3.7% with placebo).

Serious Adverse Events:

In the placebo pool, a higher proportion of patients was reported with serious adverse events (SAEs) on semaglutide 1 mg (7.3%) compared to semaglutide 0.5 mg (5.8%), or placebo (5.3%). However, the number of SAEs was small, which limits the ability to draw definitive conclusions.

A similar finding was seen in the phase 3 pool (excluding the CVOT). The proportion of patients with SAEs was higher with semaglutide (6.6% with 0.5 mg and 6.7% with 1 mg) than with comparator products (5.8%). SAEs within the SOC of gastrointestinal disorders were reported by a higher proportion of patients with semaglutide 0.5 mg (1.3%) than with semaglutide 1 mg (0.7%) and comparator products (0.5%).

In SUSTAIN 6, the proportion of patients reporting SAEs during the trial was lower with semaglutide (0.5 mg: 32.1% of patients, 1.0 mg: 29.2% of patients) than with placebo (34.9% of patients). Most of the SAEs reported were in the cardiac disorders SOC. The proportion of patients reporting SAEs within this SOC was generally lower with semaglutide than placebo.

Common Adverse Events:

For discussion of common adverse events, I will focus on findings from the placebo pool as this pool is the least confounded by adverse reactions associated with active comparators. Gastrointestinal disorders were the most common adverse event and occurred more commonly with semaglutide (Table 9). By individual preferred term, the most common adverse events occurring with semaglutide were nausea, vomiting, and diarrhea (Table 10). These observations are generally in-line with what would expected for a GLP-1 receptor agonist.

Table 9: Adverse events by system organ class from placebo pool occurring in ≥ 5% of either semaglutide arm – Placebo pool

System Organ Class	Placebo N=262		Sema 0.5 N=260		Sema 1 N=261	
	N	%	N	%	N	%
Gastrointestinal disorders	34	(13.0)	79	(30.4)	88	(33.7)
Infections and infestations	64	(24.4)	62	(23.8)	49	(18.8)
Investigations	22	(8.4)	32	(12.3)	26	(10.0)
Metabolism and nutrition disorders	18	(6.9)	11	(4.2)	26	(10.0)
Musculoskeletal and connective tissue disorders	28	(10.7)	21	(8.1)	23	(8.8)
Nervous system disorders	19	(7.3)	32	(12.3)	19	(7.3)

System Organ Class	Placebo N=262		Sema 0.5 N=260		Sema 1 N=261	
	N	%	N	%	N	%
General disorders and administration site conditions	14	(5.3)	10	(3.8)	14	(5.4)
Respiratory, thoracic and mediastinal disorders	13	(5.0)	14	(5.4)	9	(3.4)
Skin and subcutaneous tissue disorders	7	(2.7)	14	(5.4)	8	(3.1)
Injury, poisoning and procedural complications	6	(2.3)	13	(5.0)	5	(1.9)

Source: Reviewer generated based on review of adae.xpt for the ISS

Table 10: Adverse events by preferred term from placebo pool occurring in > 2% of either semaglutide arm – Placebo pool

Preferred Term	Placebo N=262		Sema 0.5 N=260		Sema 1 N=261	
	N	%	N	%	N	%
Nausea	15	(5.7)	39	(15.0)	48	(18.4)
Vomiting	6	(2.3)	11	(4.2)	23	(8.8)
Diarrhea	4	(1.5)	19	(7.3)	22	(8.4)
Lipase increased	8	(3.1)	18	(6.9)	12	(4.6)
Nasopharyngitis	19	(7.3)	14	(5.4)	12	(4.6)
Headache	13	(5.0)	16	(6.2)	9	(3.4)
Decreased appetite	2	(0.8)	6	(2.3)	9	(3.4)
Constipation	4	(1.5)	13	(5.0)	8	(3.1)
Dyspepsia	2	(0.8)	9	(3.5)	7	(2.7)
Fatigue	4	(1.5)	3	(1.2)	6	(2.3)
Arthralgia	6	(2.3)	1	(0.4)	6	(2.3)
Abdominal pain	4	(1.5)	7	(2.7)	5	(1.9)
Back pain	5	(1.9)	6	(2.3)	5	(1.9)
Upper respiratory tract infection	5	(1.9)	11	(4.2)	4	(1.5)
Gastroenteritis	2	(0.8)	9	(3.5)	4	(1.5)
Dizziness	2	(0.8)	8	(3.1)	3	(1.1)
Eructation	0	(0)	7	(2.7)	3	(1.1)
Amylase increased	3	(1.1)	6	(2.3)	3	(1.1)

Source: Reviewer generated based on review of adae.xpt for the ISS

Adverse Events of Interest:

Adverse events of interest for semaglutide include pancreatitis, pancreatic cancer, medullary thyroid cancer, allergic/hypersensitivity reactions, acute kidney injury, and hypoglycemia. For these safety concerns, the data from the semaglutide development program are generally consistent with other members of the GLP-1 receptor agonist class. No increased risk for pancreatitis was seen, although patients treated with semaglutide had increases in serum amylase and lipase. Malignancies, including pancreatic and medullary thyroid, were generally balanced between treatment arms. The incidence of anti-drug antibody was ~2% and titers were generally low. No imbalance in allergic or hypersensitivity reactions were seen. No imbalance in adverse renal events was seen, though there was a small, acute decrease in eGFR in the semaglutide treated patients. Semaglutide appears to have a low inherent risk for hypoglycemia but when used in combination with insulin the risk increases. More detailed discussion of these safety concerns can be found in Dr. Lungu's clinical review.

In this section, I will be discussing two specific concerns for semaglutide that warrant further discussion. These are diabetic retinopathy complications and cardiovascular risk.

- **Diabetic Retinopathy Complications:**

In trial 3744 (i.e., SUSTAIN 6), the applicant conducted a systematic assessment for diabetic retinopathy which included funduscopic exams at baseline, year 1, and year 2. Possible diabetic retinopathy complications were referred for adjudication. Positively adjudicated events were further categorized based on the type of events. The categories were (1) need for retinal photocoagulation, (2) need for treatment with intravitreal agents, (3) vitreous hemorrhage, (4) onset of diabetes-related blindness. Based on these adjudicated events a finding of increased risk for diabetic retinopathy complications was seen in the subjects treated with semaglutide (see Table 11 of Dr. Hsueh's statistical review, excerpted below).

Table 11. Pre-Specified Analysis of Diabetic Retinopathy Complications

	Semaglutide N=1648 PY=3408.2	**Placebo** N=1649 PY=3401.1	**Hazard Ratio (95% CI)**
Diabetic Retinopathy Complications	50	29	1.76 (1.11, 2.78)
Need for Retinal Photocoagulation	38	20	
Vitreous Hemorrhage	16	7	
Need for Treatment with Intravitreal agents	16	13	
Onset of Diabetes-Related Blindness	5	1	

Source: Created by the reviewer

In exploring the potential reasons for this finding, the applicant has conducted a post hoc analysis which included treatment, change in HbA1c at week 16, and three risk factors for diabetic retinopathy as independent variables. By considering the change in HbA1c at week 16 as an independent variable, the estimated hazard ratio is reduced to 1.22 (95% CI 0.71 to 2.09). From this, the applicant concludes that the increased risk of diabetic retinopathy appeared to be mediated through the reduction in blood glucose due to semaglutide. Dr. Hsueh believes that the results of the post hoc analysis should be interpreted with caution as the change in HbA1c is a post-randomization variable and may result in imbalance between the subgroups defined by this post-randomization characteristic. Additionally, adjusting for an intermediate variable such as change in HbA1c may introduce overadjustment bias. Dr. Hsueh views this as hypothesis generating rather than as a conclusive explanation for the finding.

Dr. Hsueh also notes that patients with diabetic retinopathy at baseline were more likely to experience a diabetic retinopathy complication during the trial (see Table 16 of Dr. Hsueh's statistical review, excerpted below). While there was a similar increase in relative risk for the subgroup of patients with retinopathy at baseline and the subgroup of patients without retinopathy at baseline, the absolute risk increase was much larger for those patients with diabetic retinopathy at baseline.

Table 16. Diabetic Retinopathy Complications by Retinopathy at Baseline

Retinopathy at Baseline	Semaglutide N=1648 Events/N (%)	Placebo N=1649 Events/N (%)
Yes (N=969; 29%)	42/510 (8.2%)	24/459 (5.2%)
No/Unknown (N=2328; 71%)	8/1138 (0.7%)	5/1190 (0.4%)

Source: Created by the reviewer

Dr. Lungu has also evaluated the reported adverse events from SUSTAIN 6 for potential events of diabetic retinopathy. Based on the MedDRA coded events, there appears to be an increased risk with semaglutide along with some suggestion of dose dependence (7.6% of patients treated with placebo, 9% of patients treated with semaglutide 0.5 mg, and 10% of patients treated with semaglutide 1 mg).

The Division of Transplant and Ophthalmology Products was consulted to for an opinion on the finding. Dr. Wiley Chambers has reviewed the assessment of retinopathy events as well as the findings. While the methods for assessing retinopathy were considered inadequate, Dr. Chambers acknowledged that the findings suggest an increased risk. However, based on findings from previous large prospective trials such as the DCCT and UKPDS, Dr. Chambers believes that this observed increased risk is not a concern. An early progression would be expected with improved glycemic control and that better glycemic control will ultimately lead to improved clinical outcomes.

The findings for retinopathy were discussed at a public Advisory Committee meeting (see Advisory Committee Meeting, below, for more detailed discussion). While many panel members expressed concern with the finding, many also felt that it was likely due to the glucose lowering effect of semaglutide. Findings from previous trials supporting long-term benefit were also reassuring to some panel members, though several opined that longer-term data would have allayed some of the residual uncertainty.

In considering the retinopathy findings from SUSTAIN 6, I have considered the clinical reviewer's findings, the assessment by the statistical reviewer, the ophthalmology consultant's responses, and comments from the Advisory Committee meeting. Additionally, data from previously reported clinical trials have been considered.

The DCCT [5] showed a similar early risk in diabetic retinopathy progression with intensive insulin therapy compared to conventional insulin therapy but showed convergence by year 2 and a reduced risk with intensive insulin therapy (see Figure 2 from "The effect of intensive treatment of diabetes on the development and progression of long-term complication in insulin-dependent diabetes mellitus". NEJM. 1993; 329(14): 977-986, excerpted below). Other large prospective studies, such as the UKPDS, have also shown a long-term benefit (i.e., reduced risk for microvascular complications) with improved glycemic control. While the data from SUSTAIN 6 suggest an increased risk for retinopathy complications in the first 2 years and this

[5] The Diabetes Control and Complications Trial Research Group. "The effect of intensive treatment of diabetes on the development and progression of long-term complication in insulin-dependent diabetes mellitus". NEJM. 1993; 329(14): 977-986.

seems counter to the expectation that improved glycemic control should reduce the risk of these complications, the prior data from large prospective trials suggests that long-term improvement in glycemic control will lead to better clinical outcomes.

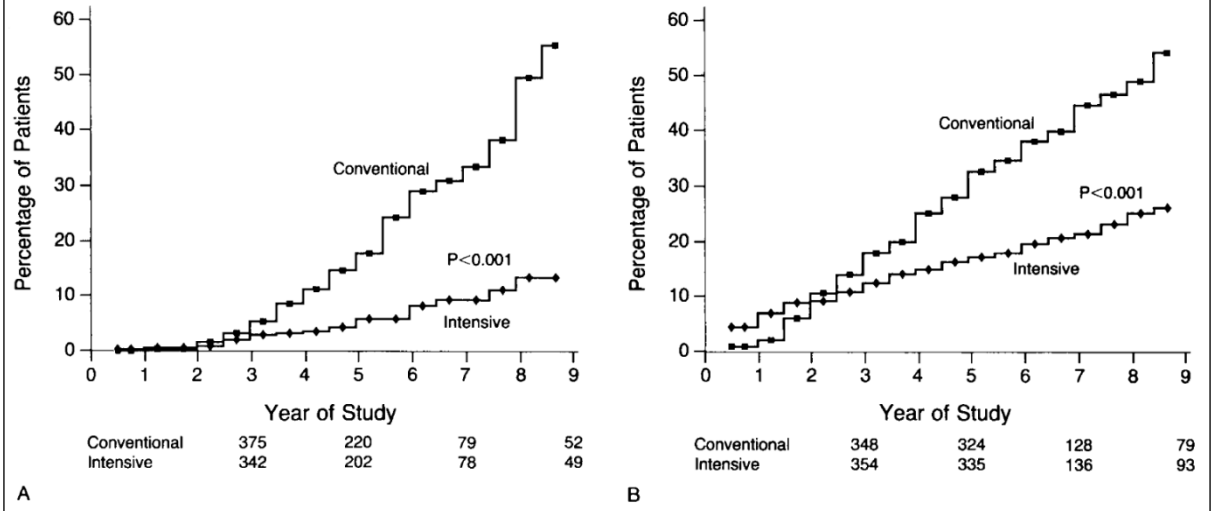


Figure 2. Cumulative Incidence of a Sustained Change in Retinopathy in Patients with IDDM Receiving Intensive or Conventional Therapy.

A sustained change in the severity of retinopathy was defined as a change observed by fundus photography of at least three steps from base line that was sustained for at least six months. In the primary-prevention cohort (Panel A), intensive therapy reduced the adjusted mean risk of the onset of retinopathy by 76 percent during the course of the study, as compared with conventional therapy (P<0.001). In the secondary-intervention cohort (Panel B), intensive therapy reduced the adjusted mean risk of progression of retinopathy by 54 percent as compared with conventional therapy (P<0.001). The numbers of patients in each therapy group who were evaluated at years 3, 5, 7, and 9 are shown below the graphs.

Though other CVOTs such as the LEADER trial and the EMPA-REG OUTCOMES trial assessed retinopathy and did not report a signal of increased risk, the methods used for identifying events differed. This limits the comparability and relevance of findings from these trials to the assessment of semaglutide. Additionally, the difference in glycemic control between the treatment arms for these trials was not as large as that seen in SUSTAIN 6.

Considering the totality of the data and the input of the panel members, I believe that the signal for increased risk of diabetic retinopathy complications does not present such a substantial risk that it precludes approval of semaglutide. I acknowledge that this finding is counterintuitive to what is expected with improved glycemic control, however I believe that the benefits of using semaglutide outweigh this risk for the following reasons:

- This observation is in-line with what has been described previously (i.e., early progression in diabetic retinopathy) and several long-term studies have shown that improved glycemic control leads to a reduced risk for clinical complications in the long run. Further, a reduced risk in diabetic retinopathy is not the only benefit expected with improved glycemic control. Better glycemic control is expected to also reduce the risk for diabetic nephropathy and diabetic neuropathy. Though the long-term effect of treatment with semaglutide on diabetic retinopathy is not known, I believe that improving glycemic control should convey a clinical benefit for patients through these other outcomes.

- While worsening of a diabetic complication is not a desirable development, progression of diabetic retinopathy can be identified early (i.e., before serious clinical outcomes occur) and there are effective therapeutic options that allow for intervention to prevent progression to serious clinical outcomes (e.g., blindness). If patients are being appropriately followed, it is likely that patients can be identified with asymptomatic progression and be treated to prevent further progression. This reduces my level of concern for this complication.

- **Cardiovascular Safety:**

The assessment of cardiovascular safety was based on SUSTAIN 6 and from pooling of the completed phase 3 studies. These two data streams were not combined. As SUSTAIN 6 provides the majority of the cardiovascular events, this was the focus of the cardiovascular (CV) risk assessment.

SUSTAIN 6 was a two-year randomized, double-blind, placebo-controlled trial comparing semaglutide vs. placebo as add-on to local standard of care. The study enrolled subjects with T2DM and high cardiovascular risk (defined as subjects ≥ 50 years of age with previous cardiovascular [CV] disease [e.g., prior myocardial infarction/stroke, prior arterial revascularization, ≥ 50% stenosis on angiography, positive test for coronary artery disease], or subjects ≥ 60 years of age with well-established CV risk factors [e.g., persistent microalbuminuria/proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, ankle-brachial index < 0.9]). These subjects were then randomized 1:1:2 to either semaglutide 0.5 mg once weekly, semaglutide 1 mg once weekly, or placebo.

A total of 254 first MACE occurred during the trial. Based on these events, the estimated hazard ratio for MACE with semaglutide compared to placebo was 0.74 with a 95% confidence interval of 0.58 to 0.95 (see Table 6 of Dr. Hsueh's statistical review, excerpted below). The results of this study excluded excess cardiovascular risk for semaglutide. For detailed discussion, see Dr. Ya-Hui Hsueh's statistical review.

Table 6. Primary Analysis of MACE – Number of Events

	Semaglutide N=1648 PY=3408.2	**Placebo** N=1649 PY=3401.1	**Hazard Ratio (95% CI)**
MACE (FAS)	108 [3.2]	146 [4.3]	0.74 (0.58, 0.95)
Cardiovascular death	44	46	0.98 (0.65, 1.48)
Non-fatal MI	47	64	0.74 (0.51, 1.08)
Non-fatal Stroke	27	44	0.61 (0.38, 0.99)

[] indicates incidence rate per 100 person-years
Source: Created by the reviewer

I agree with Dr. Hsueh that there is no evidence of increased cardiovascular risk with semaglutide. The applicant has provided sufficient data to support this conclusion and I do not believe that an additional post-marketing study should be required to further assess whether there is increased cardiovascular risk with semaglutide.

9. Advisory Committee Meeting

An Advisory Committee Meeting was held to discuss the risks and benefits of semaglutide for subcutaneous injection on October 18, 2017.

At the Advisory Committee Meeting, the benefits and risks of semaglutide were discussed including a discussion the cardiovascular risk assessment and the finding of an increased risk of diabetic retinopathy complications.

Discussion of Efficacy:
All the Advisory Committee members concluded that semaglutide was effective in improving glycemic control. Several members also commented on the magnitude of HbA1c lowering, the observed weight loss, and the sustained efficacy over 104 weeks.

Discussion of Safety (other than retinopathy and CV risk):
Advisory Committee members felt that the safety findings were generally consistent with other members of the GLP-1 receptor agonist class. Some panel members commented that the database was limited in terms of allowing for meaningful evaluation of rare events. One panel member noted that there was suggestion of an imbalance in breast cancer and heart failure that may warrant further monitoring.

Discussion of Retinopathy:
The assessment was felt to be inadequate. While evaluating retinopathy is probably worth doing, it was not done well in the semaglutide development program. The ophthalmologists on the panel stated that the approach to identifying events was not adequate. This could have introduced noise in the assessment which some panel members thought should have led to masking of a signal. For those members, this was a concern as they felt this suggested that the finding of a risk was more likely to be a true increased risk. It was noted that the worsening in diabetic retinopathy seen was consistent with previous trials with a similar degree of improvement in glycemic control, and that those trials ultimately showed a benefit. Several panel members commented that the duration of the study limited the ability to make strong conclusions and that longer-term data would have been more informative.

While the post-hoc analyses adjusting for glycemic control were consistent with the hypothesis that glucose lowering was the mediator of increased risk, several members expressed reservation that it was the only mediator. This uncertainty made several panel members uneasy with respect to concluding that a reduction in glucose was the only mediator of the effect. One panel member noted that an increased risk was also seen in the sub-group with small HbA1c changes.

The ophthalmologists on the panel were not concerned that the finding would translate into long term increased risk. Based on previous studies, the ophthalmologists stated that a better HbA1c is better for outcomes. Other panel members expressed some reservations but did not believe that the finding was very concerning as retinopathy can be managed. Still others noted that the increased risk is paradoxical to the expected benefit of improving glycemic control, and that the

long-term effect is unclear. One panel member felt that the message could be confusing (i.e., start a drug that should reduce the risk of retinopathy, but watch out for worsening retinopathy with this drug).

In discussing risk to patients, several panel members stated that it would be prudent to identify patients at risk (i.e., those with retinopathy). A baseline evaluation or knowledge of baseline retinopathy would be important in considering management. While there appears to be an increased risk, one panel member noted that there were not a lot of events and that this should not be a reason to withhold therapy from a patient. Many panel members noted that this finding serves as a reminder that patients with retinopathy should be screened/monitored when intensifying therapy and that patients should be seeing their ophthalmologists.

Some panel members expressed a moderate level of concern given the finding, but believed that the risk was small compared to the benefits of using semaglutide. The ophthalmologists on the panel expressed no concerns with the findings, noting that this is expected given data from previous large, prospective trials like the DCCT.

Discussion of CV Risk Assessment:
None of the panel members expressed a concern for increased cardiovascular risk with semaglutide. While some volunteered that the data suggested a benefit, others countered that they did not believe the data were adequate to conclude a cardiovascular benefit. One panel member expressed concern with the lack of diversity in the patient population and that since the patients were overwhelmingly white, the findings may not be generalizable to the entire population which includes a high proportion of patients from other ethnic and racial backgrounds. Overall, the panel did not believe that there was a signal of cardiovascular risk.

Voting Question: Do the available efficacy and safety data support approval of semaglutide 0.5 mg and 1 mg administered subcutaneously once weekly, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:

Vote: Yes – 16; No – 0; Abstain – 1

Panel members that voted yes commented that the efficacy results were impressive and that the safety profile was acceptable and in-line with other GLP-1 receptor agonists. None of the panel members raised concern of cardiovascular risk. While several panel members noted concerns with the retinopathy finding, none believed that the finding outweighed the benefits of using semaglutide. There were overall a small number of events, and retinopathy can be treated. Further, several members were reassured by the data from long-term trials like the DCCT. Other members wondered whether the DCCT data were relevant here, but none of these members stated that the observed increased risk for retinopathy outweighed the benefits. While several members expressed a desire for more data on the risk of retinopathy, only a few believed that such a study should be required from this applicant. Other members questioned the feasibility of conducting a study which would provide sufficient data to adequately evaluate the retinopathy finding. The majority of panel members felt that the risk could be managed through labeling.

The one member who abstained stated that he wanted to vote yes but that more information would have been ideal. This panel member struggled to describe what additional study would be feasible to allay concerns with the retinopathy finding, but noted that additional study should not be required.

10. Pediatrics

There are no data on the use of semaglutide in pediatric patients. The applicant's pediatric study plan was discussed with the Pediatric Review Committee on November 1, 2017. The applicant's plan to conduct a phase 3 trial in pediatric patients with T2DM was found to be acceptable. A postmarketing requirement will be issued for this study.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

Prescribing Information

The applicant currently proposes the following indication for semaglutide: 'adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus'. I agree that the submitted data support this indication and that the provided data support that semaglutide is safe and effective for this use.

The applicant has proposed two therapeutic dosage strengths: 0.5 mg and 1 mg. The provided data support that both doses are effective in improving glycemic control, and a numerically greater reduction in HbA1c was consistently seen with 1 mg compared to 0.5 mg. Additionally, there does not appear to be any serious dose-related safety concern for the 1 mg dose. The applicant has proposed that patients be titrated first to 0.5 mg and that further up-titration of dose occur if additional glycemic control is needed. Patients will start 0.25 mg once weekly for four weeks before increasing to 0.5 mg once weekly. If after at least four weeks on 0.5 mg once weekly additional glycemic control is needed, the applicant proposes that the dose can be increased to 1 mg. I agree with this.

The labeling includes a Boxed Warning describing the risk for medullary thyroid cancer which I believe is appropriate. This is also consistent with the other long-acting GLP-1 RAs. Warnings & Precautions include risk of thyroid C-cell tumors, pancreatitis, hypoglycemia, acute kidney injury, hypersensitivity, and diabetic retinopathy complications. I agree with inclusion of all of these. Aside from diabetic retinopathy complications, all of the listed Warnings & Precautions are consistent with prescribing information for other GLP-1 RAs.

The safety data presented should be limited to the placebo-controlled data. None of the studies was designed to support comparative safety claims, and it may be misleading to present data comparing adverse reactions to active-comparators.

The description of clinical studies should present the estimand and results based on Dr. He's analysis. (b) (4) findings for body weight (b) (4) . Ideally this data would not be included as it is not relevant to the indication and could be interpreted as an implied claim for weight loss, however I acknowledge that this information is currently presented in the prescribing information for other GLP-1 RAs. I recommend (b) (4) describing the results in text separate from the discussion of HbA1c and glycemic control.

As discussed above, I have concerns with presenting SUSTAIN 4. (b) (4) and I would favor removing it completely. Alternatively, the presentation should include language to provide contextual information with regards to the insulin titration achieved during the study.

In presenting SUSTAIN-6, I recommend that the presentation be limited and that language conclude no increased cardiovascular risk. The presentation of this study should not imply indications or uses other that have not been approved (b) (4) The applicant has also proposed (b) (4) . These should be deleted. Discussion of (b) (4) should be deleted as well as (b) (4) This has not been adequately demonstrated.

Other items in the proposed presentation for SUSTAIN 6 (b) (4) These should be removed (b) (4)

Other Labeling

The applicant has proposed the proprietary name OZEMPIC. This name was reviewed by Dr. Susan Rimmel [6] of the Division of Medication Error Prevention and Analysis who has found the name to be acceptable.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No REMS is recommended for semaglutide.

In the NDA submission, the applicant has proposed a communication plan REMS to mitigate the risk of thyroid C-cell tumors and pancreatitis. This proposal is consistent with what has been required with other long-acting GLP-1 RAs and has a goal of communicating the potential risk of MTC and pancreatitis.

[6] See Dr. Rimmel's February 22, 2017 Proprietary Name Review for NDA 209637

In considering whether a REMS is necessary for semaglutide, the DRISK reviewer has considered the benefits, risks, and previous experience with other approved long-acting GLP-1 RAs. While the nonclinical signal for MTC and the findings for pancreatitis in the semaglutide development program are similar to that of other long-acting GLP-1 RAs, REMS assessment data for other long-acting GLP-1 RA products indicate that the risk for these two concerns has been acceptably communicated to the relevant prescriber groups. Given the REMS assessment data from other GLP-1 RA products, the DRISK and DMEP review teams believe that the risks of MTC and pancreatitis can be adequately communicated with appropriate labeling and, thus, do not recommend a REMS for semaglutide.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Under the Pediatric Research Equity Act, I recommend a PMR for an efficacy and safety trial in pediatric patients age 10 to < 18 years with type 2 diabetes mellitus.

The Office of Biotechnology Products has proposed two PMCs. The first is for the development of a sensitive assay to assess neutralizing activity of anti-semaglutide antibodies and potential for cross-neutralizing activity with native GLP-1. The second is to conduct an assessment of the incidence of these neutralizing antibodies in patients exposed to semaglutide.

14. Recommended Comments to the Applicant

I do not have any additional comments to convey to the applicant.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H CHONG
12/01/2017

JAMES P SMITH
12/02/2017
Concur with regulatory recommendation.

MARY T THANH HAI
12/02/2017