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<td>2016-2764; 2016-2766</td>
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<tr>
<td>Reviewer Name(s)</td>
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<tr>
<td>Review Completion Date</td>
<td>November 06, 2017</td>
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<tr>
<td>Subject</td>
<td>Review to determine if a REMS is necessary</td>
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<tr>
<td>Established Name</td>
<td>Semaglutide</td>
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<tr>
<td>Trade Name</td>
<td>Ozempic</td>
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<tr>
<td>Name of Applicant</td>
<td>Novo Nordisk Inc.</td>
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<td>Therapeutic Class</td>
<td>Antidiabetic drug, glucagon-like peptide 1 receptor agonist.</td>
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<td>1.34 mg/mL in 1.5 mL pre-filled, disposable, single-patient-use pen injector that delivers 0.25 mg, 0.5 mg, or 1 mg per injection and 1.34 mg/mL in 1.5 mL pre-filled, disposable, single-patient-use pen injector that delivers 1 mg per injection.</td>
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<tr>
<td>Dosing Regimen</td>
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity semaglutide (Ozempic) is necessary to ensure the benefits outweigh its risks. Novo Nordisk Inc. submitted a New Drug Application (NDA) 209637 for semaglutide with the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Semaglutide is a selective dipeptidyl peptidase-4 (DPP-4)-resistant glucagon-like peptide 1 receptor agonist (GLP-1 RA). The serious risks associated with the use of semaglutide are thyroid C-cell tumor, pancreatitis, diabetic retinopathy complications, hypoglycemia (with concomitant use of sulfonylurea or basal insulin), renal impairment, and hypersensitivity reactions. The applicant’s proposed REMS (b)(4). The applicant also proposed Prescribing Information that includes Boxed Warning, Warnings and Precautions, and a Medication Guide as part of labeling to inform patients of the potential risks of thyroid C-cell tumor, pancreatitis, diabetic retinopathy complications, and hypoglycemia.

DRISK and DMEP have determined that if approved, a REMS is not necessary to ensure the benefits of semaglutide outweigh its risks. Semaglutide would join the class of GLP-1 RAs as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. In the clinical trial, semaglutide appeared efficacious in both its primary and secondary outcomes. The most concerning adverse reactions associated with the use of semaglutide are thyroid C-cell tumor, pancreatitis, and diabetic retinopathy. The Medication Guide, Boxed Warning, and Warnings and Precautions, which will be maintained as part of approved labeling, will be used to communicate the risks. Available REMS assessment data of the other approved GLP-1 RA (Bydureon, Tanzeum, Trulicity and Victoza) indicate acceptable knowledge of these risks suggesting that these risk messages of potential risk of MTC and pancreatitis have been communicated to the relevant prescriber groups. In addition, there are no new post-marketing safety signals for the drug class warranting continuation of the communication activities. DMEP and DRISK have determined that additional measures beyond labeling are not necessary to ensure the benefits outweigh the risks of semaglutide.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) semaglutide (Ozempic) is necessary to ensure the benefits outweigh its risks. Novo Nordisk Inc. submitted a New Drug Application (NDA) 209637 for semaglutide with the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. This application is under review in the Division of Metabolism and Endocrinology Products (DMEP). The applicant’s proposed REMS (b)(4). The applicant also proposed Prescribing Information that includes Boxed Warning, Warnings and Precautions and a Medication Guide as part of labeling to inform patients regarding the potential risks of thyroid C-cell tumor, pancreatitis, diabetic retinopathy complications and hypoglycemia.

Reference ID: 4177175
2 Background

2.1 PRODUCT INFORMATION

Semaglutide is a NME NDA type 505(b)(1) pathway application. It is a glucagon-like peptide 1 receptor agonist (GLP-1 RA), proposed for indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Glucagon-like peptide 1 (GLP-1), an incretin hormone secreted from cells in the gastrointestinal tract after ingestion of a meal, has three main effects on glucose metabolism: (1) stimulation of insulin release from the pancreatic islets through a glucose-dependent activation of the GLP-1 receptor, (2) suppression of glucagon release, and (3) delay in gastric emptying mediated through post-prandial GLP-1 receptor activation. These effects on glucose metabolism result in lowering of fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) and weight loss. GLP-1 RAs are designed to mimic the effect of endogenous GLP-1. Due to the very short half-life of less than 1.5 minutes after intravenous administration, native GLP-1 is not suitable for therapeutic use. The pharmacokinetic and hence the pharmacodynamic effect needs to be protracted to achieve the full therapeutic potential of GLP-1. The principal mechanism of protraction resulting in the long half-life is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilized against degradation by the DPP-4 enzyme. Semaglutide is supplied as 1.34 mg of semaglutide per mL solution in a 1.5 mL pre-filled, disposable, single-patient-use pen injector that delivers 0.25 mg, 0.5 mg, or 1 mg per subcutaneous injection and second pen as 1.34 mg of semaglutide per mL solution in a 1.5 mL pre-filled, disposable, single-patient-use pen injector that delivers 1 mg per subcutaneous injection. The proposed starting dose of semaglutide is 0.25 mg subcutaneously once weekly, titrating to 0.5 mg once weekly after 4 weeks. After an additional 4 weeks, the dosage may be increased to 1 mg once weekly to further improve glycemic control, if needed. Semaglutide, like other members of the GLP-1 RAs, has a Boxed Warning to inform healthcare providers (HCPs) about the potential risk of medullary thyroid cancer (MTC). Semaglutide is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for semaglutide (NDA 209637) relevant to this review:

- 09/19/2008: Investigation New Drug (IND) 079754 submission was received.
- 12/17/2013: FDA grants SUSAR waiver for NN9535-3744, SUSTAIN™ 6 trials.
- 08/16/2014: Type C meeting written responses on NN9535-3744 and potential postmarketing trial.
- 08/18/2014: FDA agreed with the applicant’s initial pediatric study plan and acknowledged the request for a partial waiver from PREA requirements from conducting pediatric studies in the pediatric population with T2DM less than 10 years of age.

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a Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

b Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.
• 08/02/2016: Applicant’s background package for pre-NDA meeting stated that a REMS addressing the risk of MTC would be submitted and it would be aligned with the REMS for other currently approved GLP-1 agonist products.

• 12/05/2016: NDA 209637 submission for semaglutide with the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, received. The applicant also proposed a REMS.

• 06/01/2017: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The applicant proposed submitting a revised REMS that would be updated from the original REMS that was included with the application, to include diabetic retinopathy information. Since diabetic retinopathy is still being assessed and going to the original REMS that was included with the application, to include diabetic retinopathy of this indication received currently approved GLP-1 products addressing the risk of MTC.

• 10/18/2017: Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) was convened to discuss risk-benefit profile of semaglutide with long-term use for glycemic control. The AC voted 16/0/1 in favor/against/abstain approval. A REMS proposal was not discussed.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Diabetes is a group of diseases (e.g., Type I diabetes, Type II diabetes, gestational diabetes, maturity-onset diabetes of youth or latent autoimmune diabetes in adults) characterized by high levels of blood glucose due to problems with the production and/or function of insulin. Complications of diabetes include vision loss, kidney injury, lower extremity amputation, heart attacks, and strokes. In addition, people with poorly controlled diabetes may experience decreased sense of well-being, impaired quality of life, cognitive impairment, depression, and periodontal disease among many other adverse effects. Per the Centers of Disease Control and Prevention (CDC), diabetes affects over 30.3 million Americans (9.4% of the US population). In 2015, there were 1.5 million new cases of diabetes (6.7 per 1,000 persons) were diagnosed among U.S. adults aged 18 years or older. Diabetes is the 7th leading cause of death in the US in 2015. The estimated cost of diabetes in the US in 2012 was $245 billion.

Type 2 diabetes often begins with insulin resistance and as the need for insulin rises, pancreatic beta cells gradually lose the ability to produce sufficient quantities of the hormone. However, the role of insulin resistance versus beta cell dysfunction differs among individuals. Glucose control tends to be more challenging over time. Risk factors for the development of Type 2 diabetes include older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity.

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c Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.
3.2 Description of Current Treatment Options

The treatment of type 2 diabetes usually begins with lifestyle modifications (e.g., exercise, balanced nutrition, weigh management) and treatment with metformin. Diabetes is a complex, chronic illness requiring continuous individualized medical care and treatment strategies with multifactorial risk reduction targets beyond glycemic control. Standard of care guidelines for treatment of diabetes and associated cardiovascular disease recommend lifestyle interventions such as cessation of smoking, diet and exercise, as well as treatment with antiglycemic, antihypertensive, and lipid lowering drugs with the aim of achieving recommended goals for body weight, blood glucose, blood pressure, cholesterol, and triglycerides.\textsuperscript{6, 7} When adequate control is not achieved with the life modification measures, other therapies are prescribed. About 45% of adult patients with incident diabetes had anti-hyperglycemic therapy intensified within 1 year of starting anti-hyperglycemic medication; usually, intensification occurred within 6 months. The first intensification was most often accomplished by increasing dosage of initial medication (78%) and least often by adding or switching to insulin (<1%).\textsuperscript{8} Other types of drugs used in the treatment of type 2 diabetes include drugs in the following classes: sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, GLP-1 receptor agonists, and insulin. Although these agents can substantially reduce diabetes-related morbidity and mortality, the extent of treatment benefits may be limited by a lack of treatment adherence. Inflexible treatment regimens restrict the patients’ lifestyle and can contribute to lack of adherence and failure to achieve the desired glycemic control.\textsuperscript{9} Therefore, there is a medical need for the development of safe and effective anti-hyperglycemic therapies formulated in ways that may increase compliance with therapy.

In a 2016 consensus statement on the management of type 2 diabetes, recommendations by the American Association of Clinical Endocrinologists and the American College of Endocrinology suggest that GLP-1 receptor agonists are at the top of the list of second-line treatment of type 2 diabetes.\textsuperscript{10} GLP-1 receptor agonists currently approved in the US include exenatide (twice-daily injection), liraglutide (once-daily injection), exenatide extended release (once-weekly injection), albiglutide (once-weekly injection), dulaglutide and (once-weekly injection), lixisenatide (once-daily injection) and combination products of insulin degludec & liraglutide (once-daily injection) and insulin glargine & lixisenatide (once-daily injection).

Exenatide (Byetta\textsuperscript{11}) had a communication plan REMS to mitigate the risk of pancreatitis and renal failure but the REMS was eliminated upon completion of all communication activities. The following GLP-1 RA Victoza\textsuperscript{12} (liraglutide), Bydureon\textsuperscript{13} (exenatide), Trulicity\textsuperscript{14}, Xultophy (insulin degludec & liraglutide)\textsuperscript{15}, and Tanzeum (albiglutide)\textsuperscript{16} were required to have a REMS with a communication plan to address the increased risks of medullary thyroid cancer (MTC) and acute pancreatitis. The REMS for Bydureon and Victoza, were released after DMEP and DRISK determined that the communication activities have been completed. Most recently DRISK completed reviews for both Trulicity\textsuperscript{17} and Tanzeum\textsuperscript{18} that support releasing these REMS as they were meetings the goals of the REMS, all communication plan activities have been completed, there was no new safety information that warranted the need for the REMS to be extended.

4 Benefit Assessment

The efficacy of semaglutide for the indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus was evaluated was demonstrated in five key efficacy
phase 3 trials (3623-SUSTAIN 1, 3626- SUSTAIN 2, 3624- SUSTAIN 3, 3625-SUSTAIN 4, 3627- SUSTAIN 5) and a cardiovascular outcome trial (CVOT) (3744- SUSTAIN 6). Semaglutide has been studied as monotherapy and in combination with metformin, metformin and sulfonylureas, metformin and/or thiazolidinedione, and basal insulin. The efficacy of semaglutide was compared with placebo, sitagliptin, exenatide ER, and insulin glargine. Trials 3623, 3627 and the CVOT were placebo-controlled, and Trials 3626, 3624, and 3625 were active-controlled. SUSTAIN 1 was a 30-week double-blind trial where a total of 388 patients inadequately controlled with diet and exercise, were randomized to semaglutide 0.5 mg or 1 mg once-weekly (OW) or placebo. SUSTAIN 2 was a 56-week, double-blind trial where a total of 1231 patients were randomized to semaglutide 0.5 mg or 1 mg once-weekly or sitagliptin 100 mg once-daily, all in combination with metformin (94%) and/or thiazolidinediones (6%). SUSTAIN 3 was a 56-week open-label trial where a total of 813 patients on metformin alone (49%), metformin with sulfonylurea (45%) or other (6%) were randomized to semaglutide 1 mg once-weekly or exenatide 2 mg once-weekly. SUSTAIN 4 was a 30-week open-label trial where a total of 1089 patients were randomised to semaglutide 0.5 mg or 1 mg once-weekly, or insulin glargine once-daily on a background of metformin (48%) or metformin and sulfonylurea (51%). SUSTAIN 5 was a 30-week double-blind where a total of 397 patients inadequately controlled with basal insulin with or without metformin were randomized to semaglutide 0.5 or 1 mg once-weekly or placebo. SUSTAIN 6 was a 104-week double-blind trial where 3,297 patients with type 2 diabetes and high risk of cardiovascular events were randomized to semaglutide 0.5 mg or 1 mg once-weekly or placebo in addition to standard-of-care. The placebo-controlled trials were double-blinded within dose groups (0.5 mg and 1.0 mg). No blinding of dose was performed. Double-blinding was also attained for the sitagliptin-controlled trial 3626 via a double dummy design. The insulin-controlled trial 3625 and the exenatide-controlled trial 3624 were both open-label. The applicant stated the open-label design was necessary due to the complexity of blinding insulin and the complexity of preparing a placebo version of exenatide ER.

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information for semaglutide. The primary efficacy endpoint in the 5 key efficacy trials was change in HbA1c from baseline to the end of the planned treatment period. The key secondary endpoint in the 5 key efficacy trials was change in body weight from baseline to the end of the planned treatment period. The primary objective in the placebo-controlled trials 3623 and 3627 was to demonstrate superiority of OW dosing of 2 dose levels of semaglutide vs placebo on glycemic control after 30 weeks of treatment. The primary objective in the active-controlled trials 3626, 3624 and 3625 was to compare the effect of OW dosing of semaglutide vs active comparator on glycemic control. The secondary objectives in all the trials were to compare the effects of semaglutide on inducing and maintaining weight loss as well as other parameters of efficacy, safety and tolerability. The CVOT had a primary objective of studying the safety of semaglutide.

Both doses of semaglutide (0.5 mg and 1.0 mg) demonstrated superiority to placebo in terms of change in HbA1c from baseline, in a monotherapy Trial 3623 as well as Trial 3627 with basal insulin background therapy. Both doses of semaglutide also demonstrated superiority to active comparators sitagliptin and insulin glargine for the HbA1c primary endpoint. Semaglutide 1.0 mg also demonstrated superiority to exenatide ER.\(^e\) In all the key efficacy trials, both doses of semaglutide also demonstrated superiority to placebo and the active comparators in terms of change in body weight from baseline. In the CVOT, both doses of semaglutide demonstrated superiority to placebo in terms of change in HbA1c and body weight.

\(^e\) Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.
at Week 104 as well as change in HbA1c at Week 30 for subjects on premix insulin at baseline and for subjects on sulfonylurea (SU) monotherapy at baseline, although change in HbA1c at Week 104 was not a pre-specified secondary endpoint. The efficacy results are summarized in Table 1 and 2 in the Appendix.

5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant safety information to date for semaglutide. The safety analysis of semaglutide is primarily based on seven phase 3 studies (3623-SUSTAIN 1, 3626-SUSTAIN 2, 3624-SUSTAIN 3, 3625-SUSTAIN 4, 3627-SUSTAIN 5, 4091, and 4092), which enrolled 4807 subjects (3150 patients in the semaglutide arm, and 1657 in the comparator arm), as well as a two year cardiovascular outcomes trial (CVOT) (3744-SUSTAIN 6). Two of those seven studies were placebo-controlled trials (3623-SUSTAIN 1 and 3627-SUSTAIN 5), with the remaining five comparing semaglutide to an active comparator [i.e., sitagliptin (3626- SUSTAIN 2 and 4092), exenatide extended-release (3624- SUSTAIN 3), insulin glargine (3625-SUSTAIN 4), and oral anti-diabetic drugs (4091)]. In considering the safety data from the phase 3 studies (excluding the CVOT), the safety profile of semaglutide appears to be consistent with what has been seen with other GLP-1 receptor agonists.

The SUSTAIN 6 trial was a multi-national, randomized, double-blind, and placebo-controlled cardiovascular outcome trial designed to assess cardiovascular safety of semaglutide. The pre-specified primary CV endpoint was time from randomization to first major adverse cardiovascular events (MACE). In addition to the primary MACE endpoint, some secondary CV-related endpoints including expanded MACE, all-cause death, and primary MACE (on-treatment +42 days) were also investigated using time to event analysis methods. SUSTAIN 6 was designed to rule out a hazard ratio of 1.8 for major adverse cardiovascular events. A total of 3297 subjects were included in the intent to treat (ITT) population, with 1648 randomized to semaglutide and 1649 randomized to placebo (both administered in addition to their standard-of-care treatment). The median treatment exposure time was 104 weeks for both treatment arms.

Deaths and serious adverse events were generally balanced in both safety pools. The proportion of patients with events is shown on the Table 3 in the Appendix. Semaglutide treated patients were approximately twice more likely to discontinue due to an adverse event. This was primarily due to gastrointestinal (GI) adverse events, and it appears to be dose-dependent.

Deaths

No deaths were reported in any of the two placebo-controlled trials (3623, and 3627).

There were 16 deaths in the phase 3 pool (excluding the CVOT). All cases were sent to the EAC for adjudication to identify all potential causes of death. A total of 10 patients (0.3%) randomized to semaglutide died, and 6 patients (0.4%) randomized to comparator products died.

A total of 62 deaths (3.8%) were observed in the semaglutide arm and 60 deaths (3.6%) were observed in the placebo arm in the SUSTAIN 6. All-cause mortality was not different between semaglutide and
placebo groups. There were 123 reported deaths during the treatment period (3.8% of patients on
semaglutide, and 3.7% of patients on placebo arm). Approximately half of the events in each treatment
arm belonged to the cardiac disorders system organ class.\textsuperscript{20}

**Serious Adverse Events (SAE)**

A higher proportion of patients were 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 in placebo pool.\textsuperscript{20}

The proportion of patients with SAEs was higher with semaglutide (0.5 mg and 1.0 mg) than with
comparator products in phase 3 pool. SAEs within the system organ class (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%). The proportion of patients who discontinued
treatment prematurely due to AEs was higher with semaglutide than with comparator products. This
difference was mostly due to GI AEs (nausea, vomiting, and diarrhea) leading to discontinuation in the
semaglutide groups, and this appeared to be dose-related. Other AEs more frequently leading to
premature treatment discontinuation with semaglutide than with placebo included decreased appetite,
decreased weight, and increased lipase.\textsuperscript{20}

The proportion of patients reporting SAEs during the trial SUSTAIN 6 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. The proportions of patients with AEs leading to
premature discontinuation and the corresponding rates were higher with semaglutide than with
placebo. AEs in the SOC GI disorders and the PT decreased appetite (within the SOC metabolism and
nutrition disorders) were the most frequent AEs leading to premature discontinuation. In general, the
proportions of patients with AEs leading to premature discontinuation in SOC GI disorders were lower
with placebo than with either dose of semaglutide.\textsuperscript{20}

Adverse events of special interest for the GLP-1 RA class include thyroid C-cell cancer and pancreatitis.\textsuperscript{f}

**Thyroid Neoplasms**

Thyroid neoplasms were analyzed separately because of the theoretical concern of C-cell hyperplasia
with long-acting GLP-1 RAs. Additionally, the non-clinical data showed an association between
semaglutide and c-cell adenomas and carcinomas in rats and mice. It is unknown whether semaglutide
causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human
relevance could not be determined. Thyroid C-cell tumors in rodents are a known class effect for
glucagon-like peptide (GLP-1) receptor agonists.

There were only 4 adjudicated events of malignant thyroid neoplasm in the phase 3 pool and 3
adjudicated events of malignant thyroid neoplasm in SUSTAIN 6.\textsuperscript{20} No meaningful conclusions can be

\textsuperscript{f} Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events
that may be related to the drug and the background incidence of such events in the population likely to use the
drug.
made based on these events, however it was noted that there was one semaglutide treated patient with histopathologic evidence of thyroid C-cell hyperplasia. The patient with histopathologic evidence of C-cell hyperplasia had thyroid abnormalities at baseline that make it unlikely that the case was a result of exposure to semaglutide.

Serum calcitonin was also measured centrally during the phase 3 trials; a value >20 ng/L was considered to be a value of special interest. No notable change in mean serum calcitonin was seen in any treatment arm in any safety pool. In the phase 3 pool, the incidence of marked outliers was similar between comparator and semaglutide. In SUSTAIN 6, a slight increase in the incidence of serum calcitonin greater than 50 or greater than 100 was seen with semaglutide, however, the number of outliers was very small.

If approved, labeling will be consistent with other GLP-1 RAs and risk of MTC will be included as Boxed Warnings.

**Pancreatitis**

Pancreatitis was identified as a medical event of special interest (MESI), as the use of incretin-based drugs has been associated with development of pancreatitis. The potential for an increased risk of pancreatitis was evaluated through review of the MedDRA coded adverse events. There were few cases of ‘confirmed’ pancreatitis seen in the phase 3 pool and in SUSTAIN 6.\(^\text{20}\)

No significant difference was seen between treatment groups, but it is notable that all the events from the comparator arm in the Phase 3 pool came from patients treated with exenatide extended-release. A total of 42 events were referred for adjudication with 12 events of pancreatitis confirmed by the EAC in the phase 3 pool. Of the 12 confirmed events, 11 occurred during the on-treatment observation period (5 [0.4%] with semaglutide 0.5 mg, 3 [0.2%] with semaglutide 1 mg, and 3 [0.2%] with comparator). All of the comparator events occurred with exenatide ER. An additional event of chronic pancreatitis with semaglutide 0.5 mg was confirmed during the in-trial period. The 29 non-confirmed events were mainly reported as elevated pancreatic enzymes or suspicion of pancreatitis. In the non-incretin subset of the phase 3 pool, only 2 events were confirmed, both with semaglutide 0.5 mg.

The review of the MedDRA coded events yielded similar findings. A total of 20 AEs in 18 patients were captured in the phase 3 pool (5 patients [0.4%] treated with semaglutide 0.5 mg, 6 patients [0.3%] treated with semaglutide 1 mg, 7 patients [0.4%] treated with comparator). Of the 7 patients from the comparator pool, 5 were treated with exenatide ER and 2 were treated with sitagliptin. Only 3 events were identified in the non-incretin subset, 2 with semaglutide 0.5 mg, and one with semaglutide 1 mg.

A total of 61 events were referred for adjudication and 22 of these events were confirmed by the EAC in SUSTAIN 6. Of the 22 confirmed events, 18 occurred during the on-treatment observation period, and additional 3 events during the in-trial observation period. The remaining event occurred after the in-trial observation period. The EAC was unable to adjudicate 2 investigator-reported events due to insufficient information, 1 with semaglutide 0.5 mg and 1 with placebo. Of the 18 patients with on-treatment EAC-confirmed pancreatitis, 8 were on semaglutide (5 [0.6%] in semaglutide 0.5 mg and 3 [0.4%] in semaglutide 1 mg), and 10 (0.6%) on placebo. The overall incidence was balanced between treatment arms. All 18 events were categorized by the applicant as mild acute pancreatitis.
The MedDRA search identified 22 AEs in 21 patients (8 [1%] in semaglutide 0.5 mg, 3 [0.4%] in semaglutide 1 mg, and 11 [0.7%] in placebo). All the events were sent for adjudication, and 13 were confirmed by the EAC (4 [0.5%] patients in semaglutide 0.5 mg, 1 [0.1%] patient in semaglutide 1 mg, and 8 [0.5%] patients in placebo).

In addition to the events identified during the trial, 1 non-CV death was adjudicated by the EAC as a pancreatic death and severe acute pancreatitis. After having received semaglutide 1 mg, the patient discontinued treatment on treatment day 21 because of gastrointestinal side effects, but completed the trial. On day 854, the patient developed severe acute pancreatitis, sepsis, and multi-organ failure, and died 2 days after event onset.

In addition to pancreatitis AEs, the relevant laboratory data was also reviewed. The non-incretin subset of the phase 3 pool was used in exploring the data for serum amylase and lipase. Mean serum amylase increased in semaglutide treated patients while remaining relatively unchanged in the comparator arm. Similar findings were seen in SUSTAIN 6. The mean serum amylase did not exceed the upper limit of the reference range. A similar trend was observed for lipase, both in the phase 3 non-incretin subset, and SUSTAIN 6. Mean lipase levels increased over the course of the trials with both semaglutide doses, while remaining relatively unchanged with comparator. Although the levels increased, the mean lipase levels remained below the ULN for all treatment groups.

If semaglutide is approved, the risk of pancreatitis will be communicated in the Warnings and Precautions section of the label in consistent with other GLP-1 RAs.

**Diabetic Retinopathy**

The results of SUSTAIN 6 suggest that semaglutide is not associated with increased cardiovascular risk relative to placebo, both added to standard-of-care. In SUSTAIN 6, based on the reported adverse events, an increased risk for diabetic retinopathy (DR) events was seen with semaglutide compared to placebo.\(^{20}\) The most commonly reported term was diabetic retinopathy, though the terms retinopathy and vitreous hemorrhage were also more commonly reported with semaglutide than placebo.

In the phase 3 pool, review of AEs did not identify any overall imbalance: 2% of patients on semaglutide, and 1.9% of patients on comparator reported DR AEs. However, there are some limitations of the data from this pool. The population enrolled in the trials was lower risk, as known proliferative retinopathy or maculopathy was an exclusion criterion. Additionally, there was no standardized follow-up retinal exam for most of the phase 3 trials.

A total of 79 subjects experienced diabetic retinopathy complications during the course of the trial; 50 in the semaglutide arm (1.5 per 100 patient-years), and 29 in the placebo arm (0.9 per 100 patient-years). An increase in diabetic retinopathy complications were associated with semaglutide treatment, with a HR of 1.76, and a 95% CI 1.11 to 2.78. Subgroup analyses did not show any significant interactions between various subgroups and treatment. A post-hoc mediator analysis controlling for the direct effect of treatment (in this case A1C lowering in the first 16 weeks of treatment) was conducted by applicant, yielded a lower hazard ratio of 1.22, with a 95% CI 0.71, 2.09. The DMEP clinical reviewer noted at EMDAC\(^{21}\) that there are limitations to this analysis; even if the model is correct, the estimate of the total effect is unchanged. Additionally, the modifier “change in HbA1c at week 16” was chosen post-hoc, rather than being pre-specified.
Subjects with a baseline history of retinopathy were more likely to experience retinopathy complications during the trial (8.2% of subjects on semaglutide, 5.2% on placebo) than subjects without a baseline history of retinopathy (0.7% on semaglutide, 0.4% on placebo). The exploratory analysis shows that the group of subjects with baseline retinopathy and more than 1.5% HbA1c reduction from baseline to week 16 was found to have the highest observed risk of developing diabetic retinopathy complications.

The Division of Transplant and Ophthalmology Products (DTOP) was consulted by DMEP semaglutide for an additional perspective on the findings from the ‘retinopathy’ composite, DTOP’s review stated that even though the procedures in place to capture events, the FDA ophthalmologist did not believe them to be adequate. There was no standardized approach to evaluating the fundus. Exams could be dilated or undilated, and could be performed by the investigator or by a local ophthalmologist or optometrist. Additionally, no formal grading or scoring system was used. Use of formal grading allows for better capture of retinal changes and captures multiple levels of progression. The FDA consultant also had concerns with the components of the endpoint. One of the components was termed ‘need for photocoagulation or intravitreal agent’. However, there is no uniform agreement on what characteristics indicate a need for treatment. Further, while it was termed ‘need for treatment’, positive adjudication of an event required that treatment had actually been administered, and many factors can influence whether or not photocoagulation or intravitreal injection is administered. While vitreous hemorrhage may be a reasonable endpoint, the duration and severity was not captured limiting assessments of clinically significant events. The component termed ‘diabetes-related blindness’ was also felt to be inadequate for purposes of evaluating diabetic retinopathy as it could include events of loss of visual acuity not related to diabetic retinopathy, even including reversible events such as cataracts. And lastly, while the definition of blindness was appropriate in identifying legal blindness of any cause, it was not always followed in identifying patients with blindness.

Even with the concerns with respect to the process and endpoints, the FDA Ophthalmologist agreed that there was a signal for risk but concluded that the findings are consistent with what would be expected given the decrease in HbA1c. The FDA Ophthalmologist did not raise any ophthalmic concerns or believe that there was a need to restrict the patient population or alter the approach to dose titration. There is also no reason to require any more or less ophthalmic follow-up. This was based on the understanding that it is better to improve glycemic control quickly regardless of an initial increase in retinopathy progression because this leads to long-term benefit.

Similar findings of a reduced risk for retinopathy have been reported in other large trials of patients with T2DM. The UKPDS and the ACCORD Eye study both reported a reduced risk for microvascular complications such as retinopathy. An early increased risk was not reported in either of these, though that maybe due to not performing repeat funduscopy in the early period. The United Kingdom Prospective Diabetes Study (UKPDS) first evaluated retinopathy at 3 years, and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study did so at 4 years.

The DMEP clinical reviewer noted at EMDAC that the data from semaglutide falls somewhere between these trials. The data comes from patients with type 2 diabetes and show an early increased risk. However, the data are limited to 2 years and the long-term outcome is unknown. It is unclear whether the observed risk will go away, and whether we will see a long-term benefit from improved glucose control with semaglutide as we would expect base on previous trials.

If semaglutide is approved, the risk of DR will be communicated in the Warnings and Precautions section of the label.
Hypoglycemia

Hypoglycemia is a concern for all antidiabetic therapies. Assessment of the risk of hypoglycemia was done using a definition which included events of severe hypoglycemia and events of hypoglycemic symptoms with a glucose < 56 mg/dL. Based on data from the phase 3 pool and SUSTAIN 6, semaglutide appears to have a low inherent risk for hypoglycemia.20

If semaglutide is approved, the risk of hypoglycemia will be communicated in the Warnings and Precautions section of the label in consistent with other GLP-1 RAs.

Renal Impairment

A risk for acute kidney injury exists for GLP-1 RAs. The renal safety of semaglutide was evaluated by a search of the MedDRA coded events for events of acute renal failure and nephropathy, an adjudicated nephropathy composite, and review of renal laboratory tests. Review of the MedDRA coded events did not suggest a risk for either acute renal failure or nephropathy with semaglutide. Treatment with semaglutide did not appear to result in meaningful differences in eGFR vs comparator.20

If semaglutide is approved, the risk of renal impairment will be communicated in the Warnings and Precautions section of the label in consistent with other GLP-1 RAs.

Immunogenicity and Hypersensitivity Reactions

Immunogenicity and hypersensitivity reactions were considered a safety area of interest because semaglutide is a protein-based product, and therefore has potential to cause immunogenicity-related AEs such as allergic reactions, immune complex reactions, and injection site reactions. Additionally, hypersensitivity reactions have been reported with other GLP-1 RAs. Anti-semaglutide antibodies were reported in approximately 2% of patients. The proportion of patients with an allergic event was similar between the treatment groups in Phase 3 pool.20 No AEs of anaphylactic reaction or anaphylactic shock were reported, and no AE was fatal. There was no difference between the proportion of patients on semaglutide vs placebo who experienced an allergic event (5.5% of patients in each semaglutide arm and 6% in placebo) in SUSTATIN-6.20 None of the patients that tested positive for semaglutide antibodies post-baseline was reported to have any allergic-related adverse event.

Twenty-six injection site reaction events were reported in 17 (0.6%) patients in phase 3 pool on semaglutide (8 [0.6%] on semaglutide 0.5 mg and 9 [0.5%] on semaglutide 1 mg) vs 138 events in 99 (5.8%) patients on comparator. No SAEs were reported. None of the patients reported with injection site reactions tested positive for anti-semaglutide antibodies. Overall, injection site reactions captured by the MedDRA search were reported in approximately 1% of the patients in SUSTATIN-6. The proportion of patients with events and corresponding rate of events in the on-treatment observation period were similar across the semaglutide 0.5 mg, semaglutide 1 mg, and placebo treatment groups. No SAEs or AEs leading to discontinuation were reported.

If semaglutide is approved, the risk of hypersensitivity reactions will be communicated in the Warnings and Precautions section of the label in consistent with other GLP-1 RAs.
Gastrointestinal Adverse Events

Gastrointestinal adverse events are the most common adverse events with GLP-1 receptor agonists. Findings from non-GLP-1RA subset of phase 3 pool and SUSTAIN 6 shows that the treatment with semaglutide resulted in a greater incidence of gastrointestinal adverse events. Higher incidences of serious gastrointestinal adverse events were observed with semaglutide arm than with comparator and placebo arms.20

Similar to other drugs in this class, the risk of gastrointestinal adverse reactions will be communicated in labeling in the Adverse Reactions section of the label.

6 Expected Postmarket Use

Semaglutide is expected to be prescribed by the same healthcare providers currently prescribing other GLP-1 RAs in the market (e.g., endocrinologists, internists, and primary care providers). As described in Table 1 above, the relevant GLP-1 RA prescriber population seems to be knowledgeable of the risk of thyroid C-cell tumor and the risk of pancreatitis associated with these products. Semaglutide will be administered as a subcutaneous injection by patients themselves, their caretakers or healthcare providers in all clinical settings in which patients with type 2 diabetes receive treatment.

7 Risk Management Activities Proposed by the Applicant

The applicant submitted a REMS similar to the other GLP-1 RAs in the market, (b) (4)

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for semaglutide, DRISK considered patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

Semaglutide is a GLP-1 RA, proposed for indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Based on the efficacy and safety information currently available, the clinical reviewers stated that application provided statistical evidence that both doses of semaglutide (0.5 mg and 1.0 mg) demonstrated superiority to placebo and active comparators in terms of change in HbA1c from baseline as well as in terms of change in body weight from baseline.

DRISK and DMEP have determined that if approved, a REMS is not necessary to ensure the benefits of semaglutide outweigh its risks. The non-clinical data showed an association between semaglutide and C-cell adenomas and carcinomas in rats and mice, however it is unknown whether semaglutide causes
thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. Thyroid C-cell tumors in rodents are a known class effect for glucagon-like peptide (GLP-1) receptor agonists.

The risk of pancreatitis identified with exposure to semaglutide is consistent with that observed with other GLP-1 RAs.

Available REMS assessment data of Bydureon\textsuperscript{23}, Tanzeum\textsuperscript{18}, Trulicity\textsuperscript{17} and Victoza\textsuperscript{24} indicate acceptable knowledge of the risks of pancreatitis and MTC suggesting that these risk messages have been communicated to the relevant prescriber groups. In addition, there are no new post-marketing safety signals for the drug class warranting continuation of the communication activities. The Medication Guide, Boxed Warning, and Warnings and Precautions in labeling will be used to communicate the risks. DMEP and DRISK believe that, based on the current information, communicating the risks of MTC via a Boxed Warning and acute pancreatitis via a Warning and Precaution. DRISK and DMEP have determined that a REMS is no longer necessary to communicate these risks.

The FDA ophthalmology consultant, while acknowledging the diabetic retinopathy signal with semaglutide, felt that the findings were consistent with expectation given observed decrease in HbA1c, and that there is no need to restrict the patient population, or alter the dosing. Current thinking of agency is that the risk of diabetic retinopathy associated with semaglutide does not require a boxed warning and will be communicated in the Warnings and Precautions section of the label. In general DRISK recommends maximizing labeling (e.g., box warning) before a REMS is considered.

The EMDAC was convened on October 18, 2017 to discuss risk-benefit profile of semaglutide with long-term use for glycemic control. The EMDAC voted 16 yes, 0 no, 1 abstain to the following 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? The AC voted 16/0/1 in [favor/against/abstain] to recommend approval of semaglutide for the indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

9 Conclusion & Recommendations

If approved, DRISK has determined that a REMS is not necessary to ensure the benefits outweigh the risks of semaglutide. The management of the risks associated with semaglutide treatment can be communicated through labeling. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated specifically REMS.
# 10 Appendices

Table 1\(^\text{15}\): Change in HbA1c (%) from baseline to the end of treatment period using multiple imputation based on retrieved dropouts in FAS\(^1\)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Endpoint Visit/Week</th>
<th>Treatment Arms</th>
<th>N</th>
<th>Baseline Change from Baseline(^2)</th>
<th>Treatment Difference (Semaglutide-Comparator)</th>
<th>Achieving HbA1c&lt;7%</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
<td>LS Mean</td>
<td>SE</td>
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<tr>
<td>3623-SUSTAIN 1</td>
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<td>Sema 0.5mg</td>
<td>128</td>
<td>8.09</td>
<td>-1.37</td>
<td>0.11</td>
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<tr>
<td></td>
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<td>3626-SUSTAIN 2</td>
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<td>409</td>
<td>8.01</td>
<td>-1.29</td>
<td>0.06</td>
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<td></td>
<td></td>
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<td>8.04</td>
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<td>0.05</td>
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<td></td>
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<td>Sitagliptin</td>
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<td>8.17</td>
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<td>3624-SUSTAIN 3</td>
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<td>Exenatide</td>
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<td>0.06</td>
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<td>-1.48</td>
<td>0.06</td>
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<td></td>
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<td>Insulin Glargine</td>
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<td>8.36</td>
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<tr>
<td>(overall population)(^3)</td>
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<td>Sema 1.0mg</td>
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<td>8.73</td>
<td>-1.37</td>
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<td>3744-SUSTAIN 6</td>
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<td>Sema 0.5mg</td>
<td>223</td>
<td>8.77</td>
<td>-1.25</td>
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<tr>
<td>(premix insulin subgroup)</td>
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<td>-1.75</td>
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<td>3744-SUSTAIN 6</td>
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<td>8.20</td>
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<td>(SU monotherapy subgroup)</td>
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<td>64</td>
<td>8.39</td>
<td>0.08</td>
<td>0.16</td>
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</table>

\(^2\) FAS (Full Analysis Set): Control arms were pooled in studies 3623, 3626, 3627, 3744 in the analyses. Missing values at the end of trial were imputed based on retrieved dropouts. For the key efficacy trials, an ANCOVA model was fit including treatment, country as fixed factors, and baseline HbA1c as covariate. For trials 3625 and 3627, the model also included the stratification variable as a fixed factor. For the CVOT 3744 overall population, an ANCOVA model was fit containing treatment and the stratification variable as fixed factors, and baseline HbA1c as covariate. For the CVOT 3744 subgroups, the model included treatment by subgroup interaction.

\(^3\) The LS (Least Squares) means were adjusted according to the distribution of baseline covariates.

\(^1\) Change in HbA1c from baseline to Week 104 in the overall population was not a pre-specified confirmatory secondary endpoint in Trial 3744.
Table 2: Change in body weight (kg) from baseline to the end of treatment period using multiple imputations based on retrieved dropouts in FAS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Endpoint Visit/Week</th>
<th>Treatment Arms</th>
<th>N</th>
<th>Baseline Mean</th>
<th>Change from Baseline Mean</th>
<th>Treatment Difference (Semaglutide-Comparator) Mean</th>
<th>LS Mean</th>
<th>SE</th>
<th>95% CI</th>
<th>P-value</th>
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<td>128</td>
<td>89.81</td>
<td>-3.81</td>
<td>-2.64</td>
<td>[-3.82; -1.46]</td>
<td>&lt;.000</td>
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<td></td>
<td></td>
<td>Sema 1.0mg</td>
<td>130</td>
<td>96.87</td>
<td>-4.70</td>
<td>-3.53</td>
<td>[-4.82; -2.24]</td>
<td>&lt;.000</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Placebo</td>
<td>129</td>
<td>89.05</td>
<td>-1.17</td>
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<td>3626-SUSTAIN 2</td>
<td>56</td>
<td>Sema 0.5mg</td>
<td>409</td>
<td>89.93</td>
<td>-4.19</td>
<td>-2.51</td>
<td>[-3.24; -1.79]</td>
<td>&lt;.000</td>
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<td></td>
<td></td>
<td>Sema 1.0mg</td>
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<td>89.21</td>
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<td>[-4.51; -3.09]</td>
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<td>Sitagliptin</td>
<td>407</td>
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<td>-1.67</td>
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<td>56</td>
<td>Sema 1.0mg</td>
<td>404</td>
<td>96.21</td>
<td>-4.82</td>
<td>-2.86</td>
<td>[-3.62; -2.09]</td>
<td>&lt;.000</td>
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<td>Exenatide</td>
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<td>-4.66</td>
<td>-5.60</td>
<td>[-6.36; -4.84]</td>
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<td>-4.72</td>
<td>[-5.82; -3.61]</td>
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<td>3744-SUSTAIN 6</td>
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<td>826</td>
<td>91.80</td>
<td>-3.52</td>
<td>-2.79</td>
<td>[-3.34; -2.25]</td>
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<td>[-4.60; -3.52]</td>
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<td>91.86</td>
<td>-0.72</td>
<td>0.16</td>
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</table>

Control arms were pooled in studies 3623, 3626, 3627, 3744 in the analyses. Missing values at the end of trial were imputed based on retrieved dropouts. An ANCOVA model was fit including treatment, country as fixed factors, and baseline body weight as covariate. For trials 3625 and 3627, the model also included the stratification variable as a fixed factor. For the CVOT 3744, an ANCOVA model was fit containing treatment and the stratification variable as fixed factors, and baseline body weight as covariate.

The LS means were adjusted according to the distribution of baseline covariates.

Table 3: Deaths, SAEs, and Discontinuations due to AEs

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Sema 0.5</th>
<th>Sema 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1657</td>
<td>N=1373</td>
<td>N=1777</td>
</tr>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
</tbody>
</table>

Phase 3 pool

Deaths   | 6 (0.4) | 7 (0.5) | 3 (0.2) |
SAEs     | 95 (5.8) | 92 (6.6) | 118 (6.7) |
Discontinuation due to AE | 51 (3) | 84 (6.1) | 156 (8.7) |

SUSTAIN 6

Deaths   | 61 (3.7) | 31 (3.8) | 31 (3.8) |
SAEs     | 574 (34.9) | 264 (32.1) | 240 (29.3) |
Discontinuation due to AE | 110 (6.7) | 95 (11.5) | 119 (14.5) |

Sema = semaglutide; SAE = serious adverse event; AE = adverse event

Reference ID: 4177175
11 References

1 Proposed Prescribing Information for semaglutide as currently edited by the FDA, last updated June 29, 2017.


21 Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Clinical review presentation, October 18, 2017.


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/s/

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11/06/2017

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