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RESEARCH**

APPLICATION NUMBER:

213051Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	September 19, 2019
From	Mitra Rauschecker, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	213051
Applicant	Novo Nordisk
Date of Submission	March 20, 2019
PDUFA Goal Date	September 20, 2019
Proprietary Name	Rybelsus
Established or Proper Name	Semaglutide tablets
Dosage Form(s)	Oral tablets
Applicant Proposed Indication(s)/Population(s)	as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant Proposed Dosing Regimen(s)	Start at 3 mg once daily for 30 days then increase the dose to 7 mg once daily. Dose may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on 7 mg
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommended Dosing Regimen(s) (if applicable)	Start at 3 mg once daily for 30 days then increase the dose to 7 mg once daily. Dose may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on 7 mg

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Type 2 diabetes mellitus (T2DM) is a serious, chronic medical condition, which has been increasing in prevalence in the US. It is characterized by insulin resistance with insufficient insulin production, and resulting hyperglycemia. Current approved therapies for T2DM include glucagon-like peptide 1 (GLP-1) receptor agonists, which acts to improve glucose dependent insulin secretion, slows gastric emptying, and reduces fasting and postprandial glucagon levels. Semaglutide is a GLP-1 receptor agonist, and the subcutaneous (sq) injectable formulation is currently approved as an adjunct to diet and exercise for the treatment of adults with T2DM. The applicant has developed an oral formulation of semaglutide, which would be the first oral GLP-1 receptor agonist, with the same proposed indication as the sq semaglutide formulation.

The clinical development program for semaglutide consisted of 33 studies, which included 7 multi-national, phase 3 controlled clinical studies in adults with T2DM, along with 2 studies conducted in Japan, and a pre-market CVOT to evaluate cardiovascular safety. Semaglutide demonstrated a dose-dependent reduction in HbA1c, and the maintenance doses (7 and 14 mg) were superior to placebo, and active controls (excluding liraglutide). While the reduction in HbA1c compared to placebo was somewhat less for oral semaglutide as compared to sq semaglutide based on historical data, oral semaglutide demonstrated substantial evidence of effectiveness for glycemic control from adequate and well controlled trials, and the oral formulation offers a therapeutic alternative from injectable therapies.

The safety findings for semaglutide were generally consistent with the known safety profile of sq semaglutide. There was a higher incidence of gastrointestinal adverse events versus placebo, specifically nausea and vomiting, which is expected with GLP-1 receptor agonists. In order to enhance oral absorption of semaglutide, the applicant used a novel excipient, salcaprozate sodium (SNAC). The nonclinical data demonstrated an increase in mortality with high dose administration of SNAC, attributed to inhibition of cellular respiration, associated with increased lactate levels. In the phase 3 clinical studies, there were few events of lactic acidosis overall, with no evidence of an imbalance between treatment groups. Similarly, serum lactate levels were evaluated in several of the trials, and there was no evidence of increased lactate levels. Overall, the data do not suggest an increased risk of lactic acidosis related to semaglutide/SNAC.

Nonclinical studies to evaluate the safety of the SNAC demonstrated that SNAC concentrated in the milk of lactating animals. Given there are alternative treatment options, including sq semaglutide, breastfeeding is not recommended for oral semaglutide. In addition, a post-marketing requirement (PMR) for a milk-only lactation study to assess concentration of semaglutide and SNAC in breast milk is recommended.

Diabetic retinopathy was identified as a safety concern during the development program for sq semaglutide, with an increased risk of diabetic retinopathy complications seen in subjects treated with sq semaglutide during the cardiovascular outcomes trial (CVOT). The imbalance in diabetic retinopathy complications was attributed to the glucose lowering effect of sq semaglutide, with an early progression in diabetic retinopathy with improved glycemic control. For oral semaglutide, diabetic retinopathy events were collected by the applicant, and subjects also underwent baseline and end of treatment eye exams, including funduscopy with dilation. Overall, the data do not suggest an imbalance in diabetic

retinopathy events for oral semaglutide, although the trials were not designed to adequately assess the retinopathy risk, given the short duration of the trials, and the low risk population. For this reason, I recommend the risk of diabetic retinopathy is included in labeling for consistency with sq semaglutide.

The applicant also completed a CVOT to assess the cardiovascular safety of semaglutide designed to satisfy the 2008 guidance for industry on assessing cardiovascular safety for new therapies intended to treat type 2 diabetes. The trial was event-driven, and accrued a total of 137 first major adverse cardiovascular events (MACE). The data from this study ruled out a 1.3 risk margin and support that no additional post-marketing study should be required to assess the CV safety of semaglutide.

In summary, the clinical development program demonstrated semaglutide has a favorable benefit-risk profile. Semaglutide demonstrated the ability to improve glycemic control, and the safety profile is generally consistent with sq semaglutide and with other members of the GLP-1 analog class. I recommend approval of semaglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Type 2 diabetes mellitus (T2DM) is a disease characterized by hyperglycemia, insulin resistance, and relative impairment of insulin secretion. • It is a relatively common disease that is estimated to affect approximately 30 million people in the United States as of the 2015 Center for Disease Control report. • T2DM is often associated with other metabolic derangements, such as dyslipidemia, hypertension, and obesity. • Chronic complications of T2DM include cardiovascular disease, retinopathy, nephropathy, and neuropathy.	T2DM is a serious, life-threatening condition that can lead to serious morbidity and mortality if left untreated.
Current Treatment Options	• Treatment options for T2DM includes lifestyle modifications, usually followed by the addition of one or multiple different medications. • There are currently multiple classes of pharmacologic treatments for T2DM, including biguanides, sulfonylureas, insulin and insulin analogs, glucagon-like peptide-1 (GLP-1) analogs, dipeptidyl peptidase-4 (DPP4) inhibitors, and sodium-glucose linked transporter (SGLT)-2 inhibitors.	There are multiple different classes of medication for patients with T2DM.

Cross Discipline Team Leader Review

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Semaglutide is currently approved as a sq formulation. • There are no approved oral GLP-1 receptor agonists.	
Benefit	• Semaglutide demonstrated efficacy in reducing HbA1c in a dose-dependent manner, with an approximate reduction in HbA1c of 0.8-1.1% compared to placebo. • Semaglutide also resulted in weight loss of approximately -1 to -4 kg compared to placebo. • Semaglutide is an oral formulation, which would allow use in patients who cannot or prefer not to use injectable semaglutide.	Semaglutide was effective in improving glycemic control, and also resulted in reduction in body weight.
Risk and Risk Management	• The most common adverse events were gastrointestinal events. • Safety concerns common to all GLP-1 receptor agonists include pancreatitis, medullary thyroid tumors, and acute kidney injury. The development program for semaglutide did not change these concerns, or raise any new safety concerns. • There was no evidence of increased cardiovascular risk. • There was no evidence for increase in lactic acidosis events related to SNAC. Nonclinical studies demonstrated SNAC concentrated in the milk of lactating animals. • There was no evidence of increase in diabetic retinopathy complications.	The safety profile for oral semaglutide was generally consistent with sq semaglutide, and other GLP-1 receptor agonists. The risks associated with semaglutide can be adequately communicated with labeling. A lactation study is recommended to assess whether semaglutide/SNAC concentrates in milk.

2. Background

Type 2 diabetes mellitus (T2DM) is a serious, chronic medical condition, which has been increasing in prevalence in the US. It is characterized by insulin resistance with insufficient insulin production, and resulting hyperglycemia. Patients with T2DM are at risk for secondary complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease, which are the result of chronic hyperglycemia. Current approved therapies for T2DM include glucagon-like peptide 1 (GLP-1) receptor agonists, which acts to improve glucose dependent insulin secretion, slows gastric emptying, and reduces fasting and postprandial glucagon levels.

Semaglutide is a GLP-1 receptor agonist, and the subcutaneous injectable formulation was first approved in the United States in 2017 as an adjunct to diet and exercise for the treatment of adults with T2DM. Novo Nordisk, hereafter referred to as the applicant, has submitted a new drug application (NDA) for an oral formulation of semaglutide. The proposed indication is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. While there are multiple different approved injectable GLP-1 receptor agonists, semaglutide would be the first oral formulation.

The applicant has proposed two therapeutic doses for semaglutide, 7 mg and 14 mg, along with a titration dose of 3 mg, which is to be administered for the first four weeks, followed by an increase to the 7 mg dose. The dose can be increased to 14 mg if additional glycemic control is required.

In support of this NDA, the applicant conducted a total of 7 multi-national efficacy trials, along with 2 efficacy trials conducted in Japan, and a cardiovascular outcomes trial (CVOT) to rule out excess cardiovascular risk. The applicant has also submitted a separate application requesting an indication for the reduction in cardiovascular risk for both oral and sq semaglutide under NDA 213182, which is currently under review. For this reason, the data from the CVOT will only be discussed with respect to safety.

3. Product Quality

Drug Substance:

Semaglutide is a modified analog of the human GLP-1 peptide, which contains two amino acid substitutions, and a modification at the lysine 26 side chain. It binds to and acts at the native GLP-1 receptor. These amino acid substitutions and modifications protects semaglutide from degradation by the dipeptidyl peptidase 4 enzyme, and reduce renal clearance, thus prolonging its half-life. The structure of oral semaglutide drug substance is identical to that of sq semaglutide drug substance.

The molecular formula of semaglutide is shown below:

Table 1: Composition of Semaglutide Drug Product

Component	Quantity per tablet (mg/tablet)			Function	Reference to standards
	Semaglutide 3 mg tablet	Semaglutide 7 mg tablet	Semaglutide 14 mg tablet		
Active pharmaceutical ingredient					
Semaglutide	3	7	14	Active ingredient	Novo Nordisk A/S
Excipients					
Salcaprozate sodium	300	300	300	Absorption enhancer	Novo Nordisk A/S
Cellulose, microcrystalline	(b) (4)				Ph. Eur., USP, JP
Povidone (b) (4)					Ph. Eur., USP, JP
Magnesium stearate					Ph. Eur., USP, JP
Gross weight*	400.7	404.7	411.7	-	-

(b) (4)

Source: Table 1 from Applicant's eCTD 2.3.P.1

SNAC is manufactured by the applicant, (b) (4). The excipients used in the manufacture of the drug product, including the manufacturing process for SNAC, were reviewed by Dr. Galliford, and found to be adequate.

The drug substance is manufactured using (b) (4). The drug product composition, process for manufacturing the drug product, and packaging system used for the phase 3 clinical studies is the same process proposed for commercial use. Dr. Galliford has found the manufacturing process and in-process controls to be adequate.

The drug product is light sensitive, and is stored in blister packaging. The applicant conducted testing to evaluate long-term storage conditions, which included testing at 25°C/60% RH, and at the accelerated storage condition 40°C/75% RH. Based on the provided stability data, Dr. Galliford recommends an expiration period of 24 months when stored at 20-25°C in blister packaging. For detailed discussion of the drug product manufacturing process, see the OPQ review.

Facilities:

The applicant's manufacturing facility has an adequate inspection history for both manufacture of drug substance and drug product, and based on previous experience with the manufacture of other drug products that are considered equivalent to the proposed manufacturing operation in this application, no pre-approval inspections were recommended.

4. Nonclinical Pharmacology/Toxicology

The nonclinical program was designed to assess the novel excipient, SNAC, as sq semaglutide is an approved product. While SNAC is present in a marketed "medical food", at a maximum

dose of 200 mg in a vitamin B12 formulation, SNAC has not been used in an approved product, and it is present at a lower dose in the vitamin B12 formulation than that proposed for oral semaglutide (300 mg).

Nonclinical pharmacology studies were conducted with SNAC in *in vitro* studies, in rats, and in monkeys. After a single oral dose of SNAC, signs of CNS depression were exhibited, including decreased touch response, decreased respiration, and piloerection (which occurred at ≥ 16 -fold higher than clinical exposure based on BSA). Decreased respiration rates and mortality also occurred (which occurred at ≥ 32 -fold higher than clinical exposure based on BSA) which were attributed to the inhibition of cellular respiration.

Following oral administration, the absorption of semaglutide co-formulated with SNAC demonstrated high inter-animal variability in rats, dogs, and monkeys, and was influenced by the fasting state of the animals. SNAC is highly bound to plasma proteins, with albumin being predominant. Pregnant rats treated orally with ^{14}C -SNAC demonstrated SNAC-related radioactivity that crossed the placenta. SNAC was present in fetal tissues, and was also present in the milk of lactating rats when administered to rats 10 days post-partum. It was noted that SNAC and/or its metabolites appeared to accumulate the milk of lactating rats. The metabolism of SNAC is through β -oxidation and glucuronidation, mainly by UGT2B7 with additional contributions by UGT1A8 and UGT1A7. Metabolites resulting from β -oxidation also inhibit ATP synthesis in the mitochondria, but were noted to be 10-times less potent. SNAC is primarily excreted through the kidney, although metabolism is responsible for the majority of the clearance of SNAC.

Repeat dose toxicology studies were conducted in mice (up to 3 months), rats (up to 12 months), and monkeys (up to 9 months). All species tested demonstrated adverse clinical signs, including sedation, ruffled fur, abnormal respiration, and increased salivation, and mortality at low multiples to the clinical exposure. However, there was considerable inter-individual variability for SNAC plasma concentrations with overlap of exposure between dosing groups, making it difficult to make correlations between SNAC exposure levels and clinical signs. For this reason, additional mechanistic studies were conducted to further evaluate SNAC-associated mortality in animals.

In the *in vitro* studies, SNAC demonstrated a concentration-dependent inhibition of ATP synthesis in the mitochondria, and human albumin increased the concentration of SNAC needed to inhibit cellular respiration. The *in vivo* studies conducted in rats demonstrated increases in plasma and CSF lactate levels, which generally occurred at $\geq 42\text{X}$ clinical C_{max} , with a few animals showing increased lactate levels at lower exposures (3-30X clinical C_{max}). The increases in lactate levels generally correlated with clinical signs and mortality.

The applicant conducted a 2-year carcinogenicity study in rats, and SNAC was not found to be carcinogenic. Developmental and reproductive toxicology studies were conducted in rats and rabbits. SNAC was not found to affect fertility in rats, and was not teratogenic in rats or rabbits. Prolonged gestation and increased incidence of stillbirths and early pup mortality was seen at 32X clinical exposure in pre- and post-natal development studies in rats.

Pediatric patients may be at risk for higher SNAC exposures given that UGT2B7, one of the enzymes responsible for the metabolism of SNAC, operates only at 3-10% of its maximal activity in adults. However, β -oxidation is the primary mechanism of metabolism, which is present in pediatric patients. Given the findings of SNAC which was concentrated in the milk of lactating animals, and due to alternative treatment options, including sq semaglutide, breastfeeding is not recommended for oral semaglutide. In addition, a post-marketing requirement (PMR) for a milk-only lactation study to assess concentration of semaglutide and SNAC in breast milk is recommended.

The nonclinical data for semaglutide co-formulated with SNAC support approval of semaglutide. Based on the data reviewed, Dr. Elena Braithwaite recommends approval.

5. Clinical Pharmacology

Semaglutide is a long-acting recombinant analog of human GLP-1, an incretin hormone which acts to stimulate glucose-dependent insulin secretion and inhibit glucagon secretion. In order to enhance oral absorption, semaglutide has been co-formulated with SNAC for the tablet formulation. SNAC works to transiently increase transcellular permeability of the gastric epithelium to facilitate absorption, by increasing the pH in the localized environment in the stomach directly beneath the tablet, to prevent degradation of the semaglutide tablet by gastric enzymes. Following absorption, oral semaglutide is distributed, metabolized, and eliminated in the same way as sq semaglutide.

The clinical pharmacology data was reviewed by the Office of Clinical Pharmacology (OCP) reviewers, Dr. Suryanarayana Sista, Dr. Mohammad Absar, Dr. Justin Penzenstadler, Dr. Justin Earp, and Dr. Manoj Khurana. The clinical pharmacokinetics of oral semaglutide are summarized in Figure 2 below.

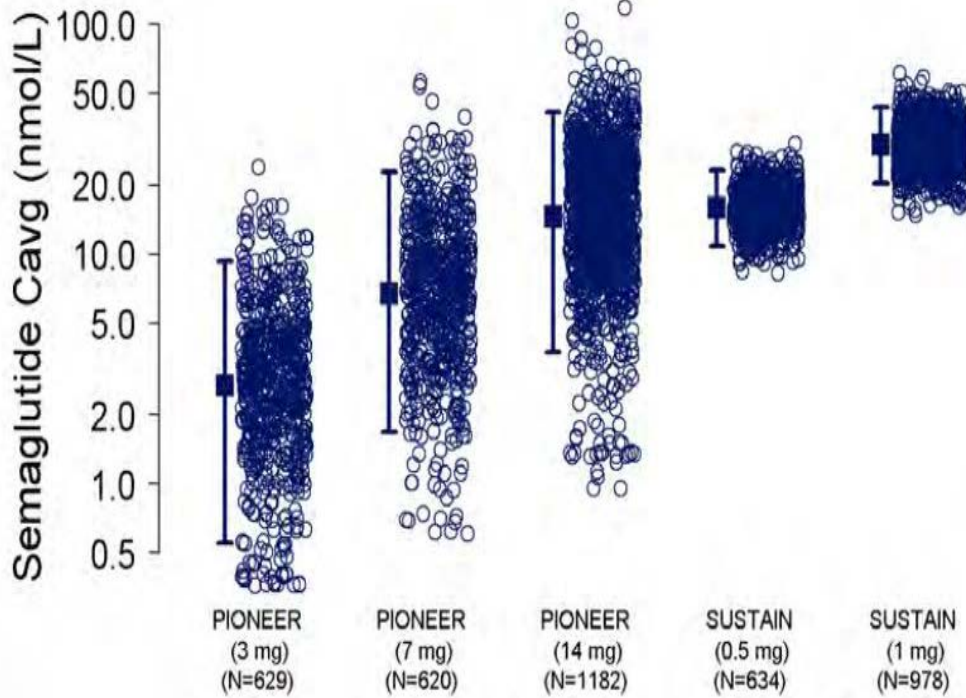
Figure 2: Clinical Pharmacokinetics of Oral Semaglutide

<i>Absorption:</i>	Following oral administration, maximum concentration of semaglutide is reached 1-hour post-dose. Steady-state exposure is achieved following 4-5 weeks administration. In patients with type 2 diabetes, the mean population-PK estimated steady-state concentrations following once daily oral administration of 7 and 14 mg semaglutide were approximately 6.7 nmol/L and 14.6 nmol/L, respectively. Based on population pharmacokinetics (PK) estimates, semaglutide exposure increases in a dose-proportional manner. The Population-PK estimated absolute bioavailability of semaglutide to be approximately 0.4 - 1%, following oral administration.
<i>Distribution:</i>	Semaglutide is extensively bound to plasma albumin (>99%). The estimated volume of distribution of semaglutide following oral administration in healthy subjects is approximately 8 L.
<i>Elimination:</i>	- The elimination half-life of semaglutide is approximately 1-week. The clearance of semaglutide following oral administration in healthy subjects is approximately 0.04 L/h. - The primary excretion routes of semaglutide-related material are via the urine and feces, with approximately 3% of the absorbed dose excreted in the urine as intact semaglutide.
<i>Metabolism:</i>	The primary route of elimination for semaglutide is metabolism following proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side chain.

Source: Clinical Pharmacology Review

The clinical development program for oral semaglutide consisted of 33 trials, which included 10 Phase 3 studies, of which 2 studies were conducted in Japan, and one study was a CVOT. See Appendix 1 for further details. The Applicant conducted a modeling-based comparison of exposure-response data in the Phase 3 trials comparing sq semaglutide (SUSTAIN) with oral semaglutide (PIONEER). The comparative exposures demonstrated that the exposure after administration of oral semaglutide were comparable to exposures following sq semaglutide administration.

Figure 3: Semaglutide Exposures- oral (PIONEER) and sq (SUSTAIN)



Source: Figure 3-2 from Applicant's Clinical Overview

In order to evaluate oral semaglutide dose selection, the Applicant conducted a randomized, dose escalation, dose ranging study with 9 treatment arms, which included 7 oral semaglutide groups, 1 oral placebo group, and 1 sq semaglutide group (Study 3790). Mean steady-state exposures after administration of 2.5-40 mg of oral semaglutide were in the range of 2-50 mmol/L, while sq semaglutide dosed once weekly had a mean steady-state exposure of 30 mmol/L. A dose-response relationship for change in HbA1c for oral semaglutide and body weight was supportive of the selected doses for oral semaglutide of 3 mg, 7 mg, and 14 mg, which demonstrated similar exposure and efficacy parameters in comparison to approved doses of sq semaglutide.

The Applicant has formulated all three strengths of oral semaglutide (3 mg, 7 mg, and 14 mg) with a fixed amount of SNAC (300 mg). The dose of SNAC was selected based on the results of Study 3691, which demonstrated plasma semaglutide concentration increased with increasing SNAC concentration (150 mg to 300 mg), however, increasing SNAC content further (from 300 mg to 600 mg) did not increase semaglutide exposure. The exposure of semaglutide appeared to be lower with 600 mg of SNAC in comparison to 300 mg of SNAC, although the data was highly variable and there was missing data. As a result, it is not clear if increasing SNAC concentrations to 600 mg would result in similar systemic exposure in comparison to 300 mg of SNAC. The clinical pharmacology reviewers conclude that product labeling should clearly state patients should not take two 7 mg tablets in place of one 14 mg tablet, as this may result in different semaglutide exposures, and I agree with their assessment.

The Applicant has proposed that oral semaglutide be administered on an empty stomach, and should be swallowed with 120 mL of water, following which patients should wait at least 30 minutes before the first meal or drink, and before taking other medications. These proposed dosing administration instructions were based on two clinical pharmacology studies in which the exposure of semaglutide (C_{max} and AUC_{0-24h}) was decreased following dosing with 240 mL of water, in comparison to either 50 mL or 120 mL of water. Additional clinical pharmacology studies evaluated the effect of the absorption of semaglutide after post-dose food intake. These studies demonstrated that post-dose food intake and stomach contents, along with the volume of water, affected the absorption of oral semaglutide. As a result, the dosing conditions were stipulated in the Phase 3 trials.

In the drug-drug interactions studies, semaglutide and SNAC did not affect the absorption of orally administered medications to any clinically relevant degree, although when a single dose of levothyroxine was administered concurrently with semaglutide, the total exposure (AUC) was increased for levothyroxine. This can be communicated in labeling.

A thorough QT study did not identify any significant prolongation of QT interval. Studies in patients with renal impairment did not demonstrate any relationship between creatinine clearance and exposure across the range of renal function studies. Exposure of SNAC metabolites increased with increasing degree of renal impairment, but the level remained well below the safety margin established from non-clinical studies, and is therefore not considered to pose a safety concern.

Immunogenicity data was collected in three Phase 1 trials, along with 1 Phase 2 trial, and six of the Phase 3 trials (PIONEER 1-5, and 9). There were only 14 of 2924 subjects (0.5%) who tested positive for anti-semaglutide antibodies at any time point post-baseline. However, anti-semaglutide in vitro neutralizing antibodies, or anti-semaglutide antibodies with an in vitro neutralizing effect on endogenous GLP-1 were not found in any subject. Additionally, all antibody responses were transient, and none of the subjects had positive antibody titers at follow-up. The formation of anti-semaglutide antibodies did not affect either plasma semaglutide levels or the efficacy of semaglutide as measured by reduction in HbA1c levels.

The OCP reviewers, Dr. Suryanarayana Sista, Dr. Mohammad Absar, Justin Penzenstadler, Justin Earp, and Manoj Khurana recommend approval of oral semaglutide based on the reviewed clinical pharmacology data. The Office of Study Integrity and Surveillance (OSIS) determined that an inspection was not warranted.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The efficacy discussion will focus on six randomized controlled efficacy trials conducted by the Applicant in support of this NDA, and include PIONEER 1-5, and PIONEER 8. Due to

differences in trial design and study population, PIONEER 9-10 (studies conducted in Japan), PIONEER 7 in which a flexible dosing design was utilized, and PIONEER 6, which was a CVOT, will not be discussed further in the efficacy review. PIONEER 6 was conducted to evaluate cardiovascular safety, and efficacy data for this trial will be discussed in the review for NDA 213182. See Table 2 for a list of the key efficacy trials.

Table 2: Clinical Efficacy Trials

Trial	Background	Inclusion HbA1c	Blinding	Treatments	N	Duration (Weeks)
P1 (4233)		7.0-9.5%	DB	S3 S7 S14 Pbo	175 175 175 178	26
P2 (4223)	Met	7.0-10.5%	OL	S14 SGLT2i (E)	411 410	52
P3 (4222)	Met SU±Met	7.0-10.5%	DB	S3 S7 S14 DPP-4i (Si)	466 465 465 467	78
P4 (4224)	Met±SGLT2i	7.0-9.5%	DB DD	S14 GLP1 RA (L1.8) Pbo	284 283 142	52
P5 (4234)	Met±SU SU±Met BasIns BasIns±Met	7.0-9.5% renal imp	DB	S14 Pbo	163 161	26
P8 (4280)	Ins±Met Japan: Met w/BasIns only	7.0-9.5%	DB	S3 S7 S14 Pbo	184 182 181 184	52

Met metformin, SU sulfonylurea, SGLT2i sodium-glucose co-transporter 2 inhibitor, BasIns basal insulin, Ins basal with or without bolus, or premixed insulin, OAD oral anti-diabetic drug using any of the above therapies, plus thiazolidinedione with or without metformin, renal imp moderate renal impairment, DB double-blind, OL open-label, DD double-dummy, S3 S7 S14 semaglutide maintenance doses 3 mg, 7 mg, or 14 mg qd po, Pbo placebo, DPP-4i dipeptidyl peptidase-4 inhibitor, Si sitagliptin 100 mg qd po, E empagliflozin 25 mg qd po, L1.8 liraglutide injection qd escalated to 1.8 mg, DPP-4i (Si)

Source: Table 1 from Statistical Review

The primary efficacy endpoint in all the trials was the change from baseline in HbA1c at week 26. Four of the trials were placebo-controlled trials (PIONEER 1,4,5, and 8), with one trial (PIONEER 4) including both a placebo and an active-control arm (liraglutide 1.8 mg), and two other trials which were active-comparator trials (PIONEER 2, vs. empagliflozin, and PIONEER 3, vs. sitagliptin). The dose of semaglutide was escalated every four weeks from 3 mg to 7 mg to 14 mg. Multiple doses of semaglutide were evaluated in PIONEER 1, 3, and 8,

while only the highest dose of semaglutide was evaluated in PIONEER 2, 4, and 5. All the trials were double-blinded, except for PIONEER 2, due to the infeasibility of producing a placebo tablet to match empagliflozin.

The primary and secondary endpoints (continuous variables) were analyzed by the Applicant using a pattern mixture model with ANCOVA-based multiple imputation to impute missing data. Missing data was imputed using a regression based on data collected from other subjects in the same group. Following imputation, an ANCOVA model was used with categorical fixed effects of treatment, stratification, and region, and baseline value as a covariate. Binary endpoints were evaluated using logistic regression after accounting for missing data using the same approach as for continuous variables. A pre-defined, weighted Bonferroni closed testing strategy was used for hypothesis testing, in which non-inferiority in the active-controlled trials, and superiority in the placebo-controlled trials for HbA1c was first demonstrated, followed by testing for secondary endpoints. For non-inferiority, a margin of 0.4% was used to compare the upper bound of the 95% confidence interval (CI). For trials with multiple doses, testing occurred first for 14 mg, followed by 7 mg, and then 3 mg doses.

Subject disposition is displayed in Table 3, Table 4, and Table 5. Overall, the number and percent of patients with missing HbA1c was less than 10% for all studies. In the placebo-controlled studies, there was a dose-dependent trend in the semaglutide groups for increase in treatment discontinuation due to adverse events. The use of rescue medication was lower in the semaglutide groups vs. placebo, and was comparable to the liraglutide group in PIONEER 4. See Table 3 and Table 4.

Table 3: Subject Disposition for Placebo-Controlled Efficacy Trials PIONEER 1 (4223) and 4 (4224)

Trial	4233				4224		
	S14	S7	S3	Pbo	S14	Lira	Pbo
Randomized (FAS)	175 (100)	175 (100)	175 (100)	178 (100)	285 (100)	284 (100)	142 (100)
Discontinued Treatment	24 (13.7)	18 (10.3)	12 (6.9)	19 (10.7)	38 (13.3)	28 (9.9)	14 (9.9)
Adverse Event	13 (7.4)	7 (4)	4 (2.3)	4 (2.2)	30 (10.5)	21 (7.4)	6 (4.2)
Protocol Violation	0 (0)	1 (0.6)	2 (1.1)	0 (0)	1 (0.4)	0 (0)	0 (0)
Study Withdrawal	5 (2.9)	5 (2.9)	0 (0)	3 (1.7)	2 (0.7)	3 (1.1)	2 (1.4)
Other	6 (3.4)	5 (2.9)	6 (3.4)	12 (6.7)	5 (1.8)	4 (1.4)	6 (4.2)
Rescue Medication	2 (1.1)	4 (2.3)	13 (7.4)	27 (15.2)	10 (3.5)	9 (3.2)	11 (7.7)
Death	1 (0.6)	0 (0)	0 (0)	0 (0)	2 (0.7)	2 (0.7)	1 (0.7)
HbA1c Measured	160 (91.4)	160 (91.4)	167 (95.4)	168 (94.4)	278 (97.5)	272 (95.8)	134 (94.4)
HbA1c Not Measured	15 (8.6)	15 (8.6)	8 (4.6)	10 (5.6)	7 (2.5)	12 (4.2)	8 (5.6)
Retrieved Data	11 (6.3)	8 (4.6)	16 (9.1)	34 (19.1)	41 (14.4)	26 (9.2)	17 (12)

Source: Table 5 from Statistical Review

Table 4: Subject Disposition for Placebo-Controlled Efficacy Trials PIONEER 5 (4234) and 8 (4280)

Trial	4234		4280			
	S14	Pbo	S14	S7	S3	Pbo
Randomized (FAS)	163 (100)	161 (100)	181 (100)	182 (100)	184 (100)	184 (100)
Discontinued Treatment	29 (17.8)	20 (12.4)	31 (17.1)	24 (13.2)	15 (8.2)	13 (7.1)
Adverse Event	24 (14.7)	10 (6.2)	22 (12.2)	12 (6.6)	9 (4.9)	3 (1.6)
Protocol Violation	0 (0)	0 (0)	2 (1.1)	5 (2.7)	2 (1.1)	2 (1.1)
Pregnancy	1 (0.6)	3 (1.9)	0 (0)	1 (0.5)	0 (0)	0 (0)
Study Withdrawal	0 (0)	2 (1.2)	2 (1.1)	2 (1.1)	0 (0)	2 (1.1)
Other	4 (2.5)	5 (3.1)	5 (2.8)	4 (2.2)	4 (2.2)	6 (3.3)
Rescue Medication	7 (4.3)	16 (9.9)	4 (2.2)	2 (1.1)	5 (2.7)	9 (4.9)
Death	1 (0.6)	2 (1.2)	2 (1.1)	0 (0)	0 (0)	0 (0)
HbA1c Measured	154 (94.5)	155 (96.3)	173 (95.6)	174 (95.6)	176 (95.7)	176 (95.7)
HbA1c Not Measured	9 (5.5)	6 (3.7)	8 (4.4)	8 (4.4)	8 (4.3)	8 (4.3)
Retrieved Data	28 (17.2)	28 (17.4)	27 (14.9)	18 (9.9)	14 (7.6)	13 (7.1)

Source: Table 5 from Statistical Review

In the active-controlled trials, there was also a dose-dependent trend for increase in treatment discontinuation for the semaglutide groups in comparison to active comparator, and treatment discontinuation occurred at a higher rate in all semaglutide groups vs. comparators. The use of rescue medication was lower in the 7 mg and 14 mg semaglutide groups vs. sitagliptin, and was comparable between the 14 mg semaglutide group and empagliflozin group. See Table 5.

Table 5: Subject Disposition for Active-Controlled Efficacy Trials PIONEER 2 (4223) and 3 (4222)

Trial	4222				4223	
	S14	S7	S3	Sita	S14	Empa
Randomized (FAS)	465 (100)	465 (100)	466 (100)	467 (100)	411 (100)	410 (100)
Discontinued Treatment	58 (12.5)	44 (9.5)	48 (10.3)	32 (6.9)	53 (12.9)	28 (6.8)
Adverse Event	39 (8.4)	20 (4.3)	15 (3.2)	13 (2.8)	36 (8.8)	10 (2.4)
Protocol Violation	3 (0.6)	5 (1.1)	4 (0.9)	4 (0.9)	0 (0)	3 (0.7)
Pregnancy	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)
Study Withdrawal	4 (0.9)	3 (0.6)	11 (2.4)	1 (0.2)	5 (1.2)	6 (1.5)
Other	12 (2.6)	16 (3.4)	17 (3.6)	14 (3)	12 (2.9)	9 (2.2)
Rescue Medication	5 (1.1)	11 (2.4)	25 (5.4)	13 (2.8)	8 (1.9)	5 (1.2)
Death	0 (0)	2 (0.4)	1 (0.2)	0 (0)	0 (0)	0 (0)
HbA1c Measured	436 (93.8)	438 (94.2)	435 (93.3)	446 (95.5)	392 (95.4)	395 (96.3)
HbA1c Not Measured	29 (6.2)	27 (5.8)	31 (6.7)	21 (4.5)	19 (4.6)	15 (3.7)
Retrieved Data	38 (8.2)	31 (6.7)	43 (9.2)	25 (5.4)	44 (10.7)	18 (4.4)

Source: Table 6 from Statistical Reviewe

Study Results:

In all of the placebo-controlled trials, treatment with semaglutide was found to result in a statistically significant greater reduction in HbA1c compared to placebo, and superiority versus placebo was established. See Table 6.

Table 6: Change from Baseline in HbA1c Compared to Placebo- Week 26

Trial	Trt	N	Baseline	Δ Baseline	Difference from Placebo		
					LSMean	95% CI	P-value
4233	S3	175	7.9	-0.89	-0.59	(-0.82, -0.36)	<.0001
	S7	175	8.0	-1.16	-0.86	(-1.11, -0.62)	<.0001
	S14	175	8.0	-1.40	-1.10	(-1.34, -0.87)	<.0001
	Pbo	178	7.9	-0.30			
4224	S14	285	8.0	-1.23	-1.06	(-1.23, -0.89)	<.0001
	Pbo	142	7.9	-0.17			
4234	S14	163	8.0	-1.02	-0.84	(-1.05, -0.63)	<.0001
	Pbo	161	7.9	-0.18			
4280	S3	184	8.2	-0.57	-0.50	(-0.72, -0.29)	<.0001
	S7	182	8.2	-0.94	-0.88	(-1.10, -0.66)	<.0001
	S14	181	8.2	-1.25	-1.19	(-1.40, -0.97)	<.0001
	Pbo	184	8.2	-0.06			

source: hba1c 4222pa.sas, hba1c 4223pa.sas, hba1c 4224pa.sas, hba1c 4233pa.sas, hba1c 4234pa.sas, hba1c 4280pa.sas, compile primary.sas

Source: Table 11 from Statistical Review

For the active-controlled trials, semaglutide (14 mg, 7 mg) was statistically superior to sitagliptin; semaglutide (14 mg) was statistically superior to empagliflozin; but semaglutide (14 mg) was not statistically superior to liraglutide. Since the upper bound of the 95% CI was less than 0.4%, semaglutide (14 mg) was non-inferior to liraglutide. See Table 7. Tipping point analyses to evaluate the impact of missing data support the conclusions for the primary analysis for change in HbA1c.

Table 7: Change from Baseline in HbA1c Compared to Active Controls- Week 26

Trial	Trt	N	Baseline	Δ Baseline	Difference from Active Control		
					LSMean	95% CI	P-value
4224	S14	285	8.0	-1.23	-0.13	(-0.27, 0.01)	.065
	Lira 1.8	284	8.0	-1.10			
4222	S3	466	8.3	-0.60	0.17	(0.04, 0.29)	0.008
	S7	465	8.4	-1.04	-0.27	(-0.39, -0.14)	<.0001
	S14	465	8.3	-1.29	-0.52	(-0.64, -0.39)	<.0001
	Sita 100	467	8.3	-0.77			
4223	S14	411	8.1	-1.31	-0.44	(-0.57, -0.31)	<.0001
	Empa 25	410	8.1	-0.86			

source: hba1c 4222pa.sas, hba1c 4223pa.sas, hba1c 4224pa.sas, compile primary.sas

Source: Table 12 from Statistical Review

Change in body weight from baseline to week 26 was a confirmatory secondary endpoint in all trials, and was included in the pre-specified testing hierarchy. In the placebo-controlled trials, semaglutide 14 mg was statistically superior to placebo in all trials. In PIONEER 1, semaglutide 3 mg and 7 mg were not statistically significant, but in PIONEER 8, both doses of semaglutide demonstrated a statistically significant change in body weight at week 26. See Table 8.

Table 8: Change from Baseline in Body Weight (kg) Compared to Placebo-Week 26

Trial	Trt	N	Baseline	Δ Baseline	Difference from Placebo		
					LSMean	95% CI	P-value
4233	S3	175	86.9	-1.46	-0.07	(-0.90, 0.76)	.9
	S7	175	89.0	-2.27	-0.88	(-1.89, 0.13)	.086
	S14	175	88.1	-3.68	-2.29	(-3.14, -1.45)	<.0001
	Pbo	178	88.6	-1.39			
4224	S14	285	92.9	-4.36	-3.84	(-4.66, -3.03)	<.0001
	Pbo	142	93.2	-0.52			
4234	S14	163	91.3	-3.43	-2.50	(-3.24, -1.76)	<.0001
	Pbo	161	90.4	-0.93			
4280	S3	184	85.9	-1.37	-0.95	(-1.84, -0.05)	.04
	S7	182	87.1	-2.42	-1.99	(-3.00, -0.97)	.0001
	S14	181	84.6	-3.68	-3.26	(-4.17, -2.35)	<.0001
	Pbo	184	86.0	-0.43			

source: bw 4222pa.sas, bw 4223pa.sas, bw 4224pa.sas, bw 4233pa.sas, bw 4234pa.sas, bw 4280pa.sas, compile primary.sas

Source: Table 13 from Statistical Review

In the active-controlled trials, semaglutide demonstrated a statistically significant effect on body weight in comparison to sitagliptin (all doses, although p-value for 3 mg was nominally significant), and liraglutide, but not empagliflozin. See Table 9. Tipping point analyses to evaluate the impact of missing data support the conclusions for the analysis for body weight.

Table 9: Change from Baseline in Body Weight (kg) Compared to Active Control-Week 26

Trial	Trt	N	Baseline	Δ Baseline	Difference from Active Control		
					LSMean	95% CI	P-value
4224	S14	285	92.9	-4.36	-1.22	(-1.88, -0.56)	.0003
	Lira 1.8	284	95.5	-3.15			
4222	S3	466	91.6	-1.17	-0.57	(-1.05, -0.10)	.02
	S7	465	91.3	-2.16	-1.57	(-2.05, -1.10)	<.0001
	S14	465	91.2	-3.09	-2.50	(-2.98, -2.03)	<.0001
	Sita 100	467	90.9	-0.59			
4223	S14	411	92.0	-3.83	-0.09	(-0.66, 0.48)	.76
	Empa 25	410	91.3	-3.74			

source: bw 4222pa.sas, bw 4223pa.sas, bw 4224pa.sas, compile secondary.sas

Source: Table 14 from Statistical Review

The Applicant evaluated additional secondary endpoints, including the proportion of subjects with HbA1c<7% at week 26, and change from baseline in fasting blood glucose, which were not included in the testing hierarchy. Overall, semaglutide (7 mg and 14 mg) demonstrated nominally significant differences in the proportion of subjects with HbA1c<7% at week 26 compared to placebo and active controls, and nominally significant differences compared to placebo and sitagliptin in fasting plasma glucose, although not compared to empagliflozin and liraglutide.

The Office of Scientific Investigations conducted inspections in support of this application, which consisted of five domestic clinical sites as well as five foreign clinical sites. The inspection of the ten clinical sites revealed no regulatory violations. The inspectional findings support the validity of the data, and the data is considered reliable. For further details, please see the OSI review by Dr. Cynthia Kleppinger.

Semaglutide demonstrated a dose-dependent reduction in HbA1c, which was superior to placebo and all active controls (except liraglutide). Although semaglutide did not demonstrate superiority to liraglutide, this is not unreasonable since semaglutide and liraglutide are both members of the same drug class. Overall, the data support that the intended maintenance doses of semaglutide (7 mg and 14 mg) were effective in reducing HbA1c, and Dr. Abugov, the statistical reviewer, recommends approval.

8. Safety

The assessment of overall safety was conducted by Dr. Andreea Lungu. In my CDTL review, I will briefly review the overall safety findings and discuss selected safety findings unique to this product, namely diabetic retinopathy, cardiovascular safety, and lactic acidosis related to SNAC. Please refer to Dr. Lungu's review for a detailed discussion of safety findings.

The Applicant defined three trial pools for the assessment of safety:

- **Phase 3a pool-** included all phase 3a trials, except PIONEER 6
- **Placebo pool-** included all multinational placebo-controlled phase 3a trials (PIONEER 1,4,5, and 8)
- **Placebo-dose pool-** two multinational placebo-controlled phase 3a trials which evaluated all three doses of semaglutide (PIONEER 1 and 8)

See Appendix 2 for a table of the phase 3 studies. The CVOT, PIONEER 6, was not included in the safety pool due to differences in trial design, and will be discussed separately. Briefly, PIONEER 6 was an event-driven, randomized, double-blind, placebo-controlled CVOT, in which subjects with established cardiovascular disease (CV) or at high CV risk were randomized to semaglutide versus placebo. The semaglutide was dose-escalated every 4 weeks to reach a goal maintenance dose of 14 mg. The primary endpoint was the occurrence of MACE, and safety assessments were limited to the collection of SAEs, AEs leading to treatment discontinuation, and a selection of AEs of special interest.

For all trials, the Applicant defined the on-treatment observation window as the time period when a subject was on treatment with a trial product, including after initiation of rescue medication and until stop of trial product. In the phase 3a pool, the total exposure to semaglutide in the on-treatment observation period was 4379 patient-years of exposure (PYE). In the placebo pool, the total exposure to semaglutide was 1197 PYE. In PIONEER 6, the total exposure to semaglutide was 1932 PYE. The safety database for semaglutide is considered to be acceptable.

Safety Summary:

The safety profile of semaglutide was consistent with the known safety profile of other GLP-1 agonists, with an increase in AEs related to gastrointestinal disorders. There did not appear to be an increased risk for CV events based on the dedicated CVOT. There was no imbalance in diabetic retinopathy or events of lactic acidosis.

Deaths:

In the phase 3a pool there were 31 deaths, which included one death in a subject who was randomized but not treated. The remaining 30 deaths occurred during the in-trial period, in subjects who were exposed to study drug. The proportion of subjects were similar between the pooled semaglutide group (0.4%) and comparators (0.5%). In the placebo pool, there were 11 deaths, and as with the phase 3a pool, the proportion of patients was similar (0.6% with semaglutide, 0.4% with placebo). In PIONEER 6, there were 71 deaths, of which a greater proportion occurred in the placebo group (2.9%) versus semaglutide (1.6%).

Serious Adverse Events:

In both the phase 3a pool, and the placebo pool, the incidence of serious adverse events (SAEs) were similar between semaglutide and comparator (8.6% vs. 9.0%, respectively), and semaglutide and placebo (7.9% vs. 8.3%, respectively). In PIONEER 6, there was a lower incidence of SAEs reported with semaglutide versus placebo (18.9% vs. 22.5%, respectively).

Table 10: Serious Adverse Events- Phase 3a pool, Placebo Pool, and PIONEER 6

	Oral sema N (Adj.%)	E	Adj.R	Comparator or Placebo N (Adj.%)	E	Adj.R
Phase 3a pool						
Number of subjects	4116			2236		
Exposure time (years)	4379			2335		
SAEs	345 (8.6)	518	12.8	202 (9.0)	282	12.2
Placebo pool						
Number of subjects	1519			665		
Exposure time (years)	1197			523		
SAEs	114 (7.9)	184	16.3	57 (8.3)	78	14.5
	N (%)	E	R	N (%)	E	R
PIONEER 6						
Number of subjects	1591			1592		
Observation time (years)	1932			1987		
SAEs	301 (18.9)	545	28	358 (22.5)	618	31

Phase 3a pool: PIONEER 1-5 and 7-10. Placebo pool: PIONEER 1, 4, 5 and 8. 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). 'Comparator' for the phase 3a pool: sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo. 'Comparator' for the placebo pool and PIONEER 6: placebo. N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of exposure; E: number of events; R: event rate/100 patient-years of observation.

Source: Table 2-11 from Applicant's ISS

The SAEs reported in the phase 3a pool were most commonly from the cardiac disorders, neoplasms, and infections and infestations SOC, with a similar incidence reported between treatment groups.

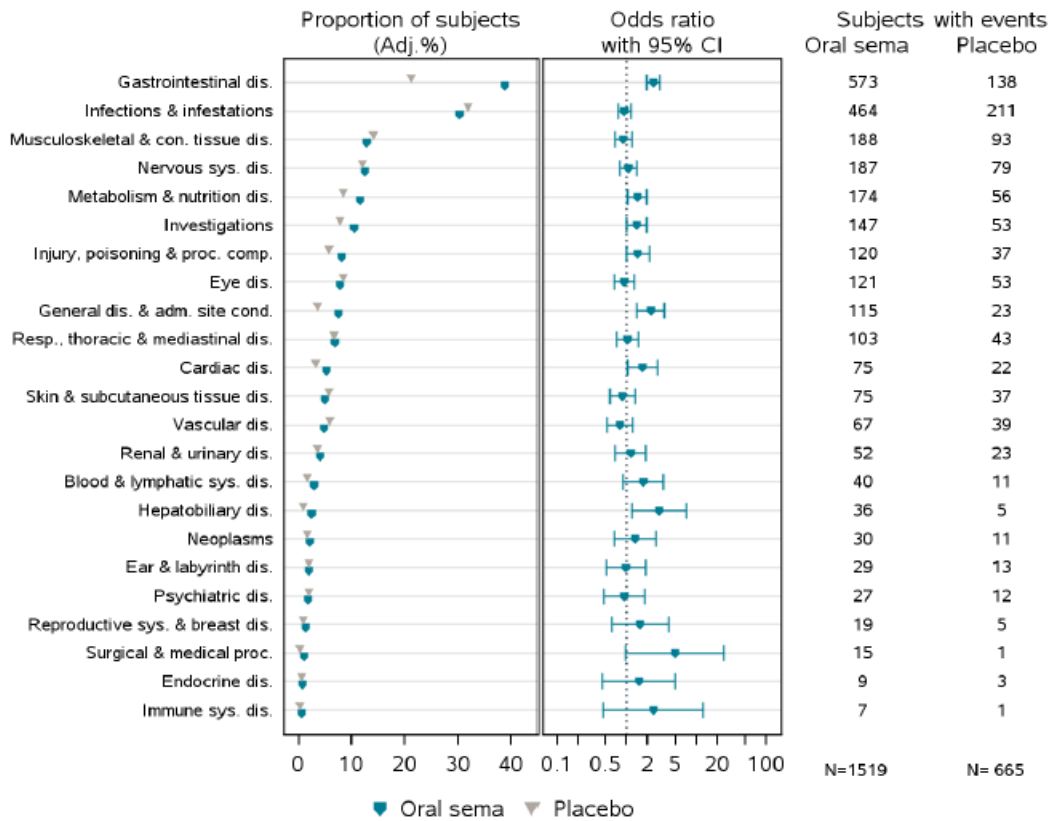
Similarly, in the placebo pool, the SAEs were most commonly from the cardiac disorders SOC. Other SOCs included nervous system disorders, infections and infestations, and neoplasms. There was a similar incidence reported between treatment groups.

In PIONEER 6, the most common SOC for reported SAEs was also cardiac disorders, with a lower incidence for semaglutide vs. placebo. Infections and infestations, and nervous system disorders were the next most common reported SOC, with a similar incidence reported between treatment groups.

Treatment-Emergent Adverse Events:

The discussion of common treatment-emergent adverse events (TEAEs) will focus on the placebo pool, to avoid confounding effects of active comparator drugs. In the placebo pool, the most common SOC was Gastrointestinal Disorders, which occurred more frequently in the semaglutide group compared to placebo. The next most common SOCs were Infections and Infestations, and Musculoskeletal Disorders. See Figure 4, for more details.

Figure 4: Adverse Events $\geq 5\%$ by System Organ Class-Placebo Pool

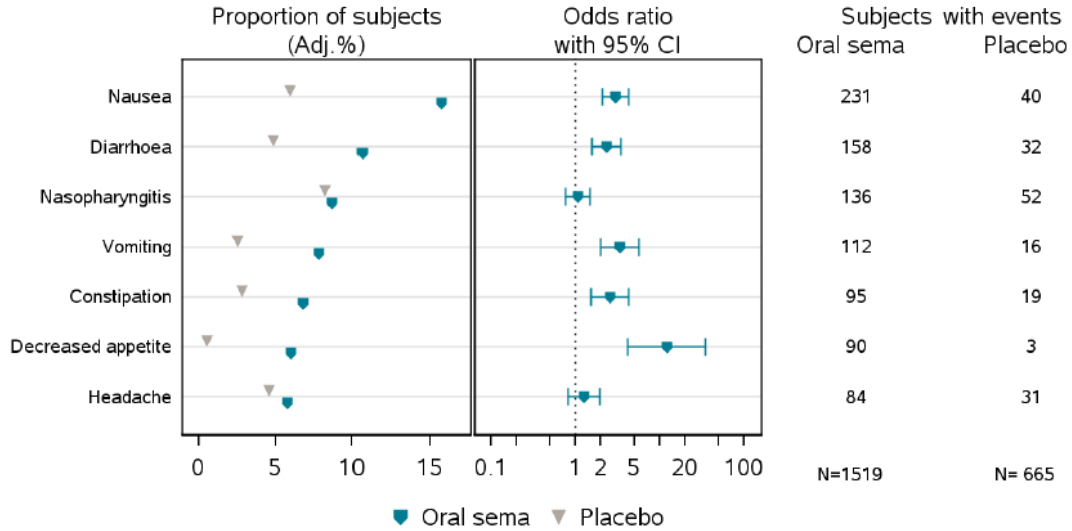


Placebo pool: PIONEER 1, 4, 5 and 8.
 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg).
 System organ classes with more than 5 events in total are presented.
 Sorted in descending order by system organ class based on the proportion of subjects with at least one event in the oral semaglutide group.
 Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%); CI: confidence interval; dis.: disorders; con.: connective; sys.: system; proc.: procedural/procedures; resp.: respiratory; adm.: administration; cond.: conditions; cong.: congenital; N: number of subjects.

Source: Figure 2-10 from Applicant's ISS

By PT, the most common TEAE with a treatment imbalance not favoring semaglutide was nausea, followed by diarrhea, vomiting, constipation, and decreased appetite. These are known AEs associated with GLP-1 receptor agonists. See Figure 5, for further details.

Figure 5: Adverse Events ≥5% by Preferred Term-Placebo Pool



Placebo pool: PIONEER 1, 4, 5 and 8.
 Oral sema: data from all three oral semaglutide doses (3, 7 and 14 mg).
 Sorted in descending order by preferred term based on the proportion of subjects with at least one event in the oral semaglutide group.
 Adj.: The % is the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%): CI: confidence interval; N: number of subjects.

Source: Figure 7.2.27, Applicant’s ISS, Appendix 7.2 (p. 605).

Cardiovascular Safety:

The assessment of cardiovascular safety for semaglutide was based on PIONEER 6, which was a dedicated event-driven CVOT in patients with T2DM and high risk of CV events, or established CV disease, as well as a pre-defined MedDRA search for CV events for the phase 3 studies, along with adjudication of CV events. Since the majority of CV events came from PIONEER 6, it is the focus of this discussion.

There were a total of 137 first MACE events which occurred during the trial, with 61 subjects (3.8%) in the semaglutide group versus 76 subjects (4.8%) in the placebo group. Based on these events, the estimated HR for MACE with semaglutide relative to placebo was 0.79 with a 95% CI [0.57; 1.11]. Since the upper bound of the 95% CI was less than 1.3, the results from this study excluded excess cardiovascular risk for semaglutide. The data from PIONEER 6 support that no additional post-marketing study should be required to assess the CV safety of semaglutide. For a detailed discussion, see Dr. Lungu’s review.

Table 11: First EAC-Confirmed MACE-PIONEER 6

	Oral semaglutide N (%)	Placebo N (%)
Number of subjects	1591	1592
Observation time (years)	2101	2081
First EAC-confirmed MACE	61 (3.8)	76 (4.8)
Myocardial infarction, non-fatal	37 (2.3)	31 (1.9)
Acute myocardial infarction	32 (2.0)	31 (1.9)
Silent myocardial infarction	5 (0.3)	0
Stroke, non-fatal	11 (0.7)	16 (1.0)
Cardiovascular and undetermined cause of death	13 (0.8)	29 (1.8)
Cardiovascular death	8 (0.5)	22 (1.4)
Undetermined cause of death	5 (0.3)	7 (0.4)

EAC: event adjudication committee; MACE: major adverse cardiovascular event, N: number of subjects; PYO: patient-years of observation; R: event rate per 100 PYO; %: percentage of subjects.

Source: Table 2-38 from Applicant's ISS

Retinopathy:

Diabetic retinopathy was identified as a safety concern during the development program for sq semaglutide, with an increased risk of diabetic retinopathy complications seen in subjects treated with sq semaglutide during the CVOT.

The Division of Transplant and Ophthalmology Products was consulted for an opinion on the finding of increased risk for diabetic retinopathy complications, which was also discussed at a public Advisory Committee meeting. It was felt that it was likely due to the glucose lowering effect of sq semaglutide, with an early progression in diabetic retinopathy with improved glycemic control. Although these findings were not seen with other members of the class, the method of identifying diabetic retinopathy events differed in the other CVOTs, and a greater effect in glycemic efficacy was seen with sq semaglutide compared with other members of the class.

For oral semaglutide, diabetic retinopathy events were assessed via MedDRA search, along with collection of events on a diabetic retinopathy form. Subjects underwent baseline and end of treatment eye exams, including funduscopy with dilation.

In the phase 3a pool, there were 269 subjects who reported 294 events of diabetic retinopathy, with 4.2% subjects in the semaglutide arm, vs. 3.8% subjects in the comparator/placebo group. In the placebo pool, there were 3.8% subjects in the semaglutide arm, vs. 2.9% subjects in the placebo group, and in PIONEER 6, there were 7.1% subjects in the semaglutide arm, vs. 6.3% subjects in the placebo group. See Table 12 for further details.

Table 12: Diabetic Retinopathy AEs and Complications Based on MedDRA Search

	Oral sema			Comparator or Placebo		
	N (Adj.%)	E	Adj.R	N (Adj.%)	E	Adj.R
Phase 3a pool						
Number of subjects	4116			2236		
Observation time (years)	4719			2452		
AEs	195 (4.2)	211	4.0	74 (3.8)	83	3.5
SAEs	2 (<0.1)	2	<0.1	3 (0.2)	4	0.1
Placebo pool						
Number of subjects	1519			665		
Observation time (years)	1292			548		
AEs	60 (3.8)	66	4.9	18 (2.9)	19	3.5
SAEs	1 (<0.1)	1	<0.1			
	N (%)	E	R	N (%)	E	R
PIONEER 6						
Number of subjects	1591			1592		
Observation time (years)	2101			2081		
AEs	113 (7.1)	127	6	101 (6.3)	113	5
SAEs	0			1 (0.1)	1	0

Phase 3a pool: PIONEER 1-5 and 7-10, comparator: sitagliptin, empagliflozin, liraglutide, dulaglutide, placebo. Placebo pool and PIONEER 6 comparator: Placebo
 'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg). Placebo pool: PIONEER 1, 4 and 8. N: number of subjects with at least one event; Adj.: The % and R are the Cochran-Mantel-Haenszel adjusted proportion of subjects with at least one event (%) and event rate per 100 patient-years of observation (R); E: number of events.

Source: Table 2-76 from Applicant's ISS

Overall, the data do not suggest an imbalance in diabetic retinopathy events for semaglutide, although the trials were not designed to adequately assess the retinopathy risk, given the short duration of the trials, and the low risk population. I agree with the Applicant's proposal to include the risk of diabetic retinopathy in labeling for consistency with sq semaglutide.

Lactic Acidosis:

The nonclinical data demonstrated an increase in mortality with high dose administration of SNAC, attributed to inhibition of cellular respiration, associated with increased lactate levels. As a result, lactic acidosis events were an adverse event of special interest and were collected based on predefined MedDRA searches, and events were adjudicated.

There were few events of lactic acidosis overall, with only 3 subjects (<0.1%) in the semaglutide group versus 1 subject (<0.1%) in the comparator/placebo group in the phase 3a pool. In PIONEER 6, there were 3 subjects with reported SAEs (0.2%) of lactic acidosis in the semaglutide group, and 2 subjects (0.1%) in the placebo group. There were six events of lactic acidosis in 5 subjects sent for adjudication in the phase 3a pool, with only one event confirmed in a subject with respiratory failure and septic shock which occurred 89 days after receiving last dose of study drug. In PIONEER 6, there were 8 events in 6 subjects sent for adjudication, with 2 events of lactic acidosis in 2 subjects confirmed by the EAC (one in each treatment group).

Lactate levels were also monitored in PIONEER 1 and 2, and were also measured during a clinical pharmacology trial in healthy volunteers (Trial 4247) evaluating the effects of exposure to high dose SNAC (involving doses up to 3.6 grams of SNAC). There was no difference in lactate levels during PIONEER 1 and 2 between treatment groups, and no clinically relevant elevations in lactate levels were seen following exposure to high doses of

SNAC. Overall, the data do not suggest an increased risk of lactic acidosis related to semaglutide.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

There are no data on the use of semaglutide in pediatric subjects with T2DM. The applicant submitted an initial Pediatric Study Plan on January 18, 2017. The applicant's request for a partial waiver for studies in pediatric subjects less than 10, and a deferral in patients aged 10 to less than 18 years of age was discussed with the Pediatric Review Committee on August 14, 2019, and is acceptable. A PREA postmarketing requirement will be issued for the sponsor to study oral semaglutide in pediatric patients with type 2 diabetes ages 10 to less than 18.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

Prescribing Information

The applicant has proposed the following indication for semaglutide: as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. I agree that the submitted data supports the use of semaglutide for the proposed indication.

The applicant has proposed two therapeutic dosage strengths, 7 mg and 14 mg. The proposed dosage and administration includes a starting dose of 3 mg, and after 30 days, patients will be uptitrated to 7 mg. Additional up-titration of dose to 14 mg should occur after 30 days on the 7 mg dose if additional glycemic control is needed. The applicant has provided sufficient data to support that both doses are effective in reducing HbA1c, and there was a dose-dependent trend for greater efficacy with the 14 mg dose. The applicant has also proposed to include instructions related to the optimal timing of the dose with respect to intake of food, water, or other medications. I agree with the inclusion of these instructions to ensure optimal absorption of semaglutide.

The labeling includes a Boxed Warning describing the risk of medullary thyroid cancer, which is also included as a Contraindication. This is consistent with labeling for other GLP-1 receptor agonists, and I agree with its inclusion in the semaglutide label. The applicant has also proposed a contraindication for patients with a known hypersensitivity to semaglutide. Warnings and Precautions include pancreatitis, diabetic retinopathy complications which includes the pooled data from oral semaglutide along with the data from sq semaglutide CVOT, hypoglycemia, acute kidney injury, and hypersensitivity reactions. I agree with the

applicant's proposed contraindication and warnings and precautions, as they are consistent with labeling for approved sq semaglutide.

The safety data proposed by the applicant focuses on placebo-controlled data, which I think is most appropriate since it eliminates potential confounding from active comparators. In the Use in Special Populations section, under lactation, due to concerns for serious adverse reactions in the breastfed infant due to SNAC, and given there are alternative formulations, including sq semaglutide, which do not contain SNAC, I recommend the addition of language that breastfeeding is not recommended during treatment with semaglutide.

In the description of clinical studies, the applicant's analysis excludes subjects who were on treatment but took rescue medication. As discussed in Dr. Abugov's review, these subjects should be included in the analysis in order to reflect actual clinical practice, and I agree with his recommendation.

Other Labeling:

The applicant has proposed the proprietary name RYBELSUS. This name was reviewed by Dr. Ariane Conrad of DMEPA, who has found the name to be acceptable.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No REMS is recommended for semaglutide.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Under the Pediatric Research Equity Act (PREA), I recommend a PMR for a study to evaluate the safety and efficacy of semaglutide in pediatric patients with T2DM ages 10 years to 17 years (inclusive). A medullary thyroid carcinoma registry-based case series is also recommended, as it is for all GLP-1 receptor agonists. In addition, based on the nonclinical data which demonstrated concentration of SNAC in the milk of lactating rats, and due to concerns regarding inhibition of cellular respiration related to high dose SNAC exposure in nonclinical studies, a milk-only lactation Post-marketing required study is recommended to assess the concentration of semaglutide and SNAC in breast milk.

The Office of Biotechnology Products (OBP) has proposed two PMCs; developing an assay to assess neutralizing activity of anti-semaglutide antibodies, and to assess the incidence of these antibodies in patients exposed to semaglutide.

14. Recommended Comments to the Applicant

None.

Appendix 1: Table of Clinical Studies

Phase 3a trials – PIONEER 1-10

P1 4233 – monotherapy vs placebo	P6 4221 – CVOT vs placebo and standard-of-care
P2 4223 – vs empagliflozin	P7 4257 ^a – flexible dose vs sitagliptin
P3 4222 – long-term vs sitagliptin	P8 4280 – add-on to insulin vs placebo
P4 4224 – vs liraglutide and placebo	P9 4281 ^b – monotherapy vs liraglutide and placebo, Japan
P5 4234 – renal impairment vs placebo	P10 4282 – add-on to OADs vs dulaglutide, Japan

Phase 2 trial

3790 – dose finding

Phase 1/clinical pharmacology trials

Pharmacokinetics	Pharmacodynamics	4141 – omeprazole
3691 – single ascending dose (FHD)	NN9535-3685 – energy intake ^c	4394 – probenecid and cyclosporine
3692 – multiple ascending dose 1	NN9535-3635 – beta-cell function ^c	
3991 – multiple ascending dose 2	NN9535-3684 – hypoglycaemia ^c	Special populations
4140 – Caucasian/Japanese		4079 – renal impairment
3794 – dosing conditions	Drug-drug interaction	4082 – hepatic impairment
4154 – food effect	4065 – lisinopril and warfarin	4267 – upper gastrointestinal disease
3957 – pharmacoscintigraphy	4145 – metformin and digoxin	
NN9535-3789 – AME semaglutide ^c	4249 – oral contraception	Special studies
ERP23 – AME SNAC ^d	4250 – furosemide and rosuvastatin	NN9535-3652 – QTc semaglutide ^c
	4279 – levothyroxine and placebo	4247 – QTc SNAC

Appendix 2: Phase 3 Studies

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
<i>Controlled Studies to Support Efficacy and Safety</i>						
PIONEER 1- 4233	Semaglutide vs placebo monotherapy DB	1) Semaglutide (3, 7, and 14 mg) 2) Placebo	Change from baseline in HbA1c	26 weeks	703	Multinational (incl. US); T2DM; diet and exercise only HbA1c 7-9.5%
PIONEER 2 - 4223	Semaglutide vs SGLT2 inhibitor OL	1) Semaglutide 14 mg 2) Empagliflozin 25 mg	Change from baseline in HbA1c	52 weeks	821	Multinational (incl. US); T2DM; inadequately controlled on metformin HbA1c 7-10.5%
PIONEER 3 - 4222	Semaglutide vs DPP-4 inhibitor DB	1) Semaglutide (3, 7, and 14 mg) 2) Sitagliptin 100 mg	Change from baseline in HbA1c	78 weeks	1862	Multinational (incl. US); T2DM; Inadequately controlled on metformin +/-SU
PIONEER 4 - 4224	Semaglutide vs GLP-1 RA DB	1) Semaglutide 14 mg 2) Liraglutide 1.8 mg 3) Placebo	Change from baseline in HbA1c	52 weeks	711	Multinational (incl. US); T2DM; Inadequately controlled on metformin +/-SGLT2i
PIONEER 5 - 4234	Semaglutide vs placebo DB	1) Semaglutide 14 mg 2) Placebo	Change from baseline in HbA1c	26 weeks	324	Multinational (incl. US); T2DM; with moderate renal impairment inadequately controlled on metformin +/-SU, basal insulin alone, or metformin in combination with basal insulin
PIONEER 7 - 4257	Flexible dose vs sitagliptin OL	1) Semaglutide flexible dose	Change from baseline in HbA1c	52 weeks	504	Multinational (incl. US); T2DM;

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
		2) Sitagliptin 100 mg				inadequately controlled on 1-2 OADs
PIONEER 8 - 4280	Insulin add-on vs placebo DB for the first 26 weeks	1) Semaglutide (3, 7, and 14 mg) 2) Placebo	Change from baseline in HbA1c	52 weeks	731	Multinational (incl. US); T2DM; background of insulin
<i>Studies to Support Safety</i>						
PIONEER 6 - 4221	Semaglutide vs placebo cardiovascular outcomes study DB	1) Semaglutide 14 mg 2) Placebo	Time from randomisation to first occurrence of a MACE, defined as cardiovascular death, nonfatal myocardial infarction, or non-fatal stroke	Event-driven	3183	Multinational (incl. US); T2DM; high risk of CV events
<i>Other studies pertinent to the review of efficacy or safety – Studies in Japanese population</i>						
PIONEER 9 - 4281	Monotherapy vs placebo and liraglutide DB	1) Semaglutide (3, 7, and 14 mg) 2) Placebo 3) Liraglutide 0.9 mg daily		52 weeks	243	Japan; T2DM;
PIONEER 10 - 4282	Semaglutide vs dulaglutide OL	1) Semaglutide (3, 7, 14 mg) 2) Dulaglutide 0.75 mg weekly		52 weeks	308	1) Japan; T2DM; inadequately controlled on one OAD

Source: generated by Dr. Lungu using the tabular listing of clinical trials provided by the applicant

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