CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213182Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	January 10, 2020
From	Mitra Rauschecker, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	213182
Applicant	Novo Nordisk
Date of Submission	March 20, 2019
PDUFA Goal Date	January 20, 2020
Proprietary Name	Rybelsus
Established or Proper Name	Semaglutide tablets
Dosage Form(s)	Oral tablets
Applicant Proposed Indication(s)/Population(s)	To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (b) (4)
Recommendation on Regulatory Action	Approval (with no change in indication)
Recommended Indication(s)/Population(s) (if applicable)	Not applicable

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. Due to chronic hyperglycemia, patients with T2DM are at increased risk for microvascular (e.g. retinopathy, nephropathy) and macrovascular (e.g. myocardial infarction) complications. There are currently 12 classes of medications approved to treat T2DM, and several anti-diabetic medications are also approved to reduce the risk of major adverse cardiovascular events (MACE) in patients with T2DM and established cardiovascular (CV) disease. 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, and the oral formulation was approved in 2019.

The clinical development program for oral semaglutide included a pre-market CVOT (entitled PIONEER 6) 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 estimated hazard ratio for MACE with semaglutide compared to placebo was 0.79 with a 95% confidence interval of 0.57 to 1.11 (p-value=0.18 for superiority). The data from this study support that semaglutide does not increase the risk of MACE events in adults with T2DM and established CV disease; (b) (4)

With respect to MACE components, there were no statistically significant differences for all MI and all stroke between semaglutide and placebo. Although there was a numeric trend in favor of semaglutide for all-cause death and MACE-free survival, these endpoints were not controlled for type I error, and this finding was not replicated in the CVOT for Ozempic, and should therefore be viewed with caution. The applicant also conducted a Bayesian shrinkage analysis, in which the results of PIONEER 6 were combined with the results from the subcutaneous semaglutide CVOT; however, the upper limit of the confidence interval for the MACE hazard ratio for PIONEER 6 exceeded 1.

In summary, the results from PIONEER-6 demonstrated that oral semaglutide does not increase the risk of MACE in adults with T2DM and established CV disease. (b) (4) I recommend inclusion of a description of the trial results for the purposes of relaying safety information, and for this reason, I recommend approval of the NDA.

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 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. • Three of these medications (liraglutide, canagliflozin, and empagliflozin) also have an indication to reduce the risk of MACE in patients with T2DM and established CV disease.	There are multiple different classes of medication for patients with T2DM, some of which also are approved to reduce the risk of MACE in patients who also have CV disease.
Benefit	• Semaglutide demonstrated a numeric trend reducing the risk of MACE compared to placebo, which was not statistically significant. • The estimated hazard ratio for MACE was 0.79, with a 95% CI of 0.57 to 1.11 (p-value=0.18 for superiority). • Semaglutide also resulted in a numeric trend for all-cause death and MACE-free survival, these endpoints were not controlled for type I error, and these findings were not replicated in the sq semaglutide CVOT. • The results of a Bayesian shrinkage analysis, which included data from both oral and sq semaglutide, also failed to demonstrate superiority for oral semaglutide in the reduction of MACE events.	Semaglutide failed to demonstrate superiority in reducing the risk of MACE compared to placebo in patients with T2DM and CV disease.
Risk and Risk Management	• The safety of semaglutide, including the safety data from SUSTAIN 6, was previously reviewed in the original NDA review • The applicant has not submitted any additional safety data for this supplement.	The safety profile for semaglutide was previously reviewed and no new safety data was submitted.

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 (sq) 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, and the oral formulation was approved in 2019. Novo Nordisk, hereafter referred to as the applicant, has submitted a new drug application (NDA) to confirm that treatment with semaglutide does not result in an unacceptable increase in risk in cardiovascular disease per the December 2008 draft guidance for industry. The applicant conducted the cardiovascular outcomes trial (CVOT) PIONEER 6, which enrolled patients with T2DM and established cardiovascular disease, with the primary outcome of time to randomization to first occurrence of major adverse cardiovascular event (MACE). The applicant has proposed a new indication and labelling changes based on the results of this study. The proposed indication is to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (b) (4)

The applicant has also submitted a separate supplemental application requesting an indication for the reduction in cardiovascular risk for sq semaglutide under NDA 209637, which is discussed in a separate review.

3. Product Quality

Not applicable. No new manufacturing information is included with this application.

4. Nonclinical Pharmacology/Toxicology

Not applicable. No new nonclinical information is included with this application.

5. Clinical Pharmacology

Not applicable. No new clinical pharmacology information is included with this application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The efficacy discussion will focus on PIONEER 6, which was conducted to evaluate cardiovascular safety. 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. Semaglutide was dose-escalated every 4 weeks to reach a goal maintenance dose of 14 mg. The primary endpoint was the occurrence of MACE, which consisted of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The trial was to be terminated after the occurrence of 122 MACE events. The testing hierarchy included two null hypotheses; superiority of semaglutide to placebo was to be tested only if non-inferiority was established. Secondary endpoints were not controlled for multiplicity. Subjects with T2DM, and established or high risk for CV disease, or moderate renal impairment were eligible for enrollment.

The primary endpoint analyses were performed by the applicant for the treatment policy estimand using a stratified Cox proportional hazards model with treatment group as a fixed factor. Pre-specified sensitivity analyses included the inclusion of additional covariates, different ascertainment windows, and a tipping point analysis.

Subject disposition is displayed in Table 1. Overall, a total of 3,183 subjects were randomized to either semaglutide or placebo, and the trial completion rate for both groups exceeded 99%. The impact of missing data on the primary and secondary endpoints was minimal. There was a greater number of subjects who discontinued treatment due to adverse events in the semaglutide group compared to placebo.

Table 1: Subject Disposition for PIONEER 6 (4221)

Patient Category	Treatment	
	S14	Pbo
Randomized (FAS)	1591 (100)	1592 (100)
Completed Trial	1586 (99.7)	1586 (99.6)
Discontinued Treatment	244 (15.3)	156 (9.8)
Total Adverse Events	185 (11.6)	104 (6.5)
Deaths Among Completers	23 (1.4)	45 (2.8)
Deaths Among Non-Completers	1 (0.1)	1 (0.1)
Unknown Mortality Status	0 (0)	0 (0)

Source: Table 2 from Statistical Review

Study Results:
For the time to first occurrence of MACE, treatment with semaglutide was found to be non-inferior to placebo, as the upper bound of the two-sided 95% condifence interval for the hazard ratio was less than 1.3. Superiority of semaglutide was not established, as the upper bound was greater than 1. See Table 2.

Table 2: Time to First Occurrence of MACE

	S14 N=1591 n (%)	Pbo N=1592 n (%)	S14 vs Pbo Hazard Ratio (95% CI)	P value°
MACE *	61 (3.8)	76 (4.8)	0.79 (0.57, 1.11)	.18
CV and undetermined death	15 (0.9)	30 (1.9)	0.49 (0.27, 0.92)	.02
Non-Fatal MI	37 (2.3)	31 (1.9)	1.18 (0.73, 1.90)	.5
Non-Fatal Stroke	12 (0.7)	16 (1.0)	0.74 (0.35, 1.57)	.4
All MI	37 (2.3)	35 (1.9)	1.04 (0.66, 1.66)	.9
All stroke	13 (0.8)	17 (1.1)	0.76 (0.37, 1.56)	.4
All-cause death	23 (1.4)	45 (2.8)	0.51 (0.31, 0.84)	.008
MACE-free survival§	69 (4.3)	89 (5.6)	0.77 (0.56, 1.05)	.10

Source: bayshrinkx.sas, CSR Table 11-3, statistical reviewer's analysis
*MACE: Time to first event among CV-death, non-fatal MI (myocardial infarction), or non-fatal stroke
§ MACE-free survival: Time to first event among all death (CV, non-CV), non-fatal MI, or non-fatal stroke.
°P value (two-sided) is based on the Wald statistic for superiority of Hazard Ratio.

Source: Table 4 from FDA Statistical Review

With respect to MACE components, there were no statistically significant differences for all MI and all stroke between semaglutide and placebo. Although there was a numeric trend in favor of semaglutide for all-cause death and MACE-free survival, these endpoints were not controlled for type I error, and this finding was not replicated in the CVOT for Ozempic, and should therefore be viewed with caution.

The applicant also conducted a Bayesian shrinkage analysis to in order to provide greater clarity regarding the MACE endpoint. The results of this study were combined with the results from the subcutaneous semaglutide CVOT, which is the subjects of a separare review filed under NDA 209637. For details on the Bayesian shrinkage analysis, please see the Office of Biostatistics Review by Dr. Robert Abugov.

The results of the Bayesian shrinkage analysis were supportive of the primary analysis, as the upper limit of the confidence interval for the hazard ratio for PIONEER 6 (4221) exceeded 1, while those for SUSTAIN-6 (Trial 3744) were less than 1. See Table 3.

Table 3: Bayesian Shrinkage Analysis- MACE Hazard Ratios

Trial	Number of Events (%)		Hazard Ratio	
	Sema	Pbo	Estimate	95% Credible Interval
3744	108 (6.6)	146 (8.9)	0.74	(0.59, 0.94)
4221	61 (3.8)	76 (4.8)	0.78	(0.58, 1.06)

source: bayshrinkx.sas
1. Analysis conducted post-hoc

Source: Table 6 from Statistical Review

The results from PIONEER 6 demonstrated that semaglutide does not increase the risk of MACE in adults with T2DM and established CV disease, and I recommend inclusion of a description of trial results for the purposes of relaying safety information, and approval of this sNDA.

(b) (4)

The statistical reviewer, therefore, felt the evidence for superiority for oral semaglutide for reduction in MACE was not robust (b) (4) I agree with his assessment.

8. Safety

The assessment of overall safety, including safety data from PIONEER 6, was previously discussed in the CDTL review for NDA 213051, dated September 19, 2019. Please refer the prior review for a detailed discussion of safety findings.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The applicant requested a waiver for studies in pediatric subjects below the age of 18 with T2DM and high CV risk, due to the low prevalence of disease in this age group, and studies would be impossible or highly impractical. The applicant's request for a waiver was discussed with the Pediatric Review Committee on December 3, 2019, and the PeRC agrees the applicant's proposed waiver is acceptable.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

Prescribing Information

(b) (4)

The data from PIONEER 6 are supportive that use of semaglutide does not increase the risk for MACE, and I recommend inclusion of a description of trial results for the purposes of relaying safety information. The hazard ratios for MACE should be described in text with 95% confidence intervals.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No REMS is recommended for this application.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

No PMRs or PMCs are recommended for this application.

14. Recommended Comments to the Applicant

None.

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MITRA RAUSCHECKER
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LISA B YANOFF
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