CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213182Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY MEMORANDUM

NDA	213182 (semaglutide tablets) 209637/S-003 (semaglutide injection)
Submission Date	March 20, 2019
Brand Name	RYBELSUS (*approved semaglutide tablets*) OZEMPIC (*approved semaglutide injection*)
Generic Name	Semaglutide
Reviewer	Suryanarayana Sista, Ph.D.
Team Leader	Manoj Khurana, Ph.D.
OCP Division	Division of Cardiometabolic and Endocrine Pharmacology
OND Division	Division of Metabolism and Endocrinology Products
Sponsor	Novo Nordisk
Formulation; Strength	Tablets - 3 mg, 7 mg and 14 mg Injection for subcutaneous use – 0.25 mg, 0.5 mg and 1.0 mg
Indication	Semaglutide (RYBELSUS and OZEMPIC) is a glucagon-like peptide 1 (GLP-1) receptor agonist indicated: • as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus • to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (b) (4)

Semaglutide developed by Novo Nordisk, belongs to the glucagon-like peptide 1 (GLP-1) receptor agonist class of antidiabetic agents. Semaglutide injection for subcutaneous use (tradename; OZEMPIC) was approved for marketing on December 05, 2017. Semaglutide oral tablets (tradename: RYBELSUS) was approved for marketing on September 20, 2019.

The sponsor submitted New Drug Applications (NDA) to add the findings from two CVOT trials to an existing NDA under evaluation at the time of submission (now approved) for RYBELSUS® (Semaglutide, NDA 213051), and to an approved NDA for OZEMPIC (Semaglutide, NDA 209637). These two NDAs propose to support inclusion of a new indication in the United States Package Insert (USPI). NDA 213051 was approved with an indication of RYBELSUS as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). NDA 209637 was approved with an indication of OZEMPIC as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

The new indication that the Sponsor is seeking with NDA 213182 and NDA 209637/S-003 adds the following claim: "to reduce the risk of major adverse cardiovascular events (cardiovascular

death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (b) (4)

The Sponsor conducted two cardiovascular outcomes trials: (a) Study NN9535-3744, entitled "*A long-term, randomised, double-blind, placebo-controlled, multinational, multi-centre trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes (SUSTAIN 6)*", and (b) Study NN9924-4221, entitled, "*A trial investigating the cardiovascular safety of oral semaglutide in subjects with type 2 diabetes(PIONEER 6)*". There were a total of 6480 subjects randomized in these 2 studies.

There is no new information relevant to biopharmaceutics of Semaglutide in this supplement. Additionally, pharmacokinetic evaluations were not conducted in the 2 studies.

The acceptability of the data towards the intended indication is deferred to reviews by Clinical and Statistical disciplines.

Glycemic Efficacy - Changes in HbA1c:

SUSTAIN-6

An examination of the changes in HbA1c over time from the SUSTAIN-6 trial indicated that at baseline, observed HbA1c levels were similar across the four treatment groups with a mean value of 8.70%. For all four treatment groups, decreases in HbA1c were seen at week 104 with semaglutide demonstrating a larger decrease in HbA1c compared with placebo (Figure 1). With semaglutide, the nadir in HbA1c occurred around week 16, with placebo HbA1c also reached a plateau after approximately 16 weeks. With semaglutide, a small drift upwards in HbA1c was seen from week 16 and until week 104, while the decrease in HbA1c with placebo remained constant until week 104. HbA1c levels had decreased from a mean baseline level of 8.70%, by 1.09 %-points and 1.41 %-points at week 104 with semaglutide 0.5 mg and 1.0 mg, respectively, and by 0.44 %-point and 0.36 %-point, with placebo 0.5 mg and 1.0 mg, respectively.

For additional details on the discussion of efficacy of Semaglutide in the SUSTAIN-6 program, refer to the review by Dr. Andreea Lungu.

PIONEER-6

An examination of the changes in HbA1c over time from the PIONEER-6 trial indicated that mean HbA1c levels decreased during the initial 14 weeks in both treatment groups and remained relatively constant thereafter (Figure 2). Mean HbA1c had decreased to 7.2% with oral semaglutide at end-of-treatment, corresponding to a mean change from baseline of approximately -1.0%-point, whereas mean HbA1c had decreased to 7.8% with placebo, corresponding to a mean change from baseline of approximately -0.3%-point.

For additional details on the discussion of efficacy of oral semaglutide in the PIONEER-6 program, refer to the review by Dr. Andreea Lungu.

Cardiovascular Outcomes:

SUSTAIN 6

Study NN9535-3744 evaluated the comparison of the risk of experiencing a major adverse cardiovascular event (MACE) defined as the composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, between Semaglutide and placebo on a background of standard of care treatments for diabetes and atherosclerotic cardiovascular disease. The primary endpoint was time from randomization to first occurrence of MACE, defined as CV death, non-fatal MI, or non-fatal stroke

The trial demonstrated that semaglutide was non-inferior to placebo with respect to CV safety. The upper limit of the 95% CI for the HR was below the pre-specified non-inferiority limit of 1.8, with the upper bound of the CI being below 1 showing that treatment with semaglutide was associated with a statistically significant reduction (HR: 0.74; 95%CI (0.58; 0.95); p=0.0167). This corresponded to an estimated 26% risk reduction for first MACE relative to placebo when added to standard-of-care therapy.

For additional details on acceptability of the claims and discussion of cardiovascular safety of Semaglutide in the SUSTAIN-6 program, refer to the Clinical and Statistical reviews.

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For additional details on acceptability of the claims and discussion of cardiovascular safety of Semaglutide in the SUSTAIN-6 program, refer to the refer to Clinical and Statistical reviews.

Figure 1: **Adjusted Mean HbA1c Over Time - Semaglutide 0.5 mg and 1.0 mg Compared to Matching Placebos in Study NN9535-3744 (SUSTAIN 6) – top, and Trial Design - bottom**

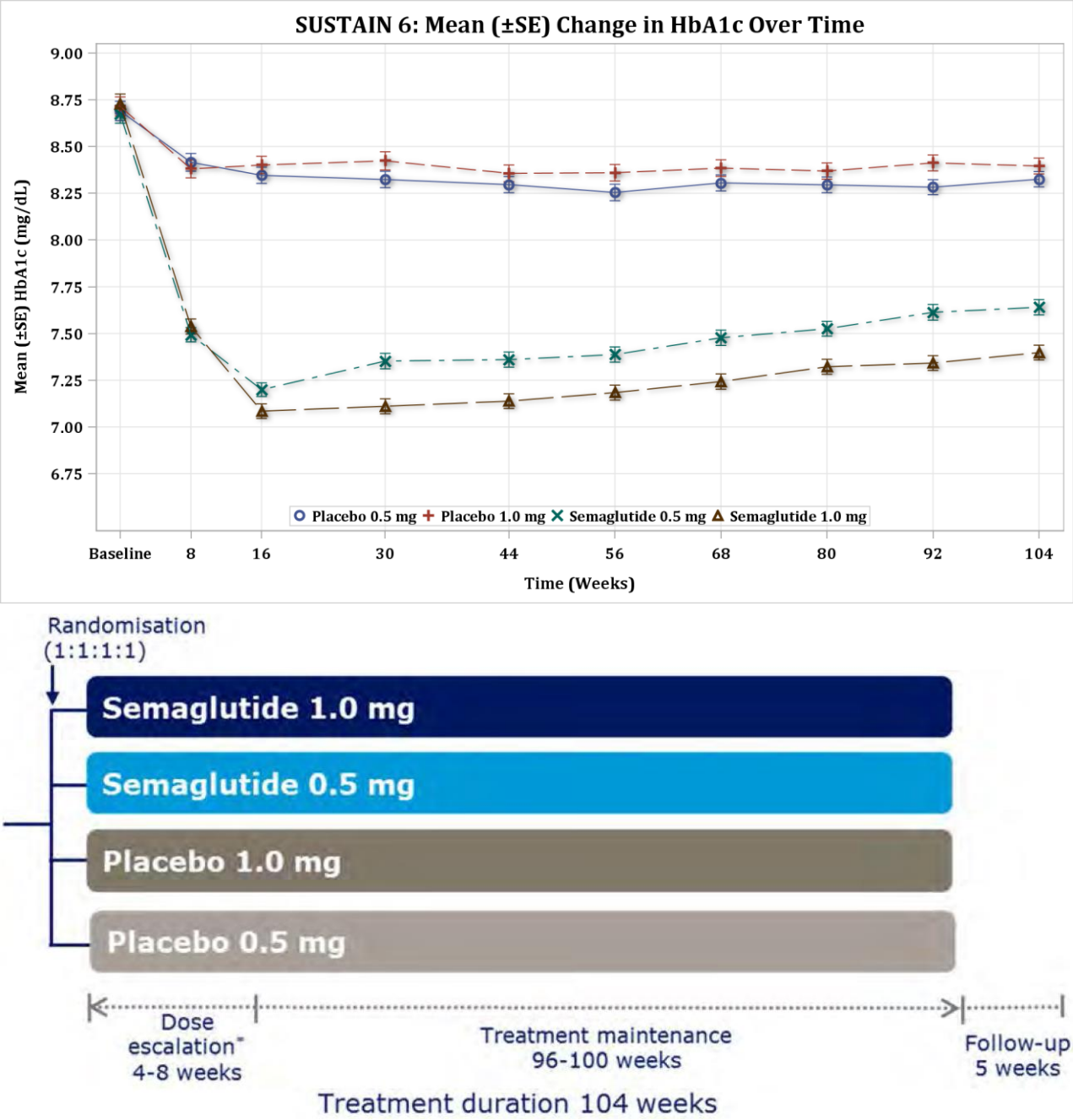
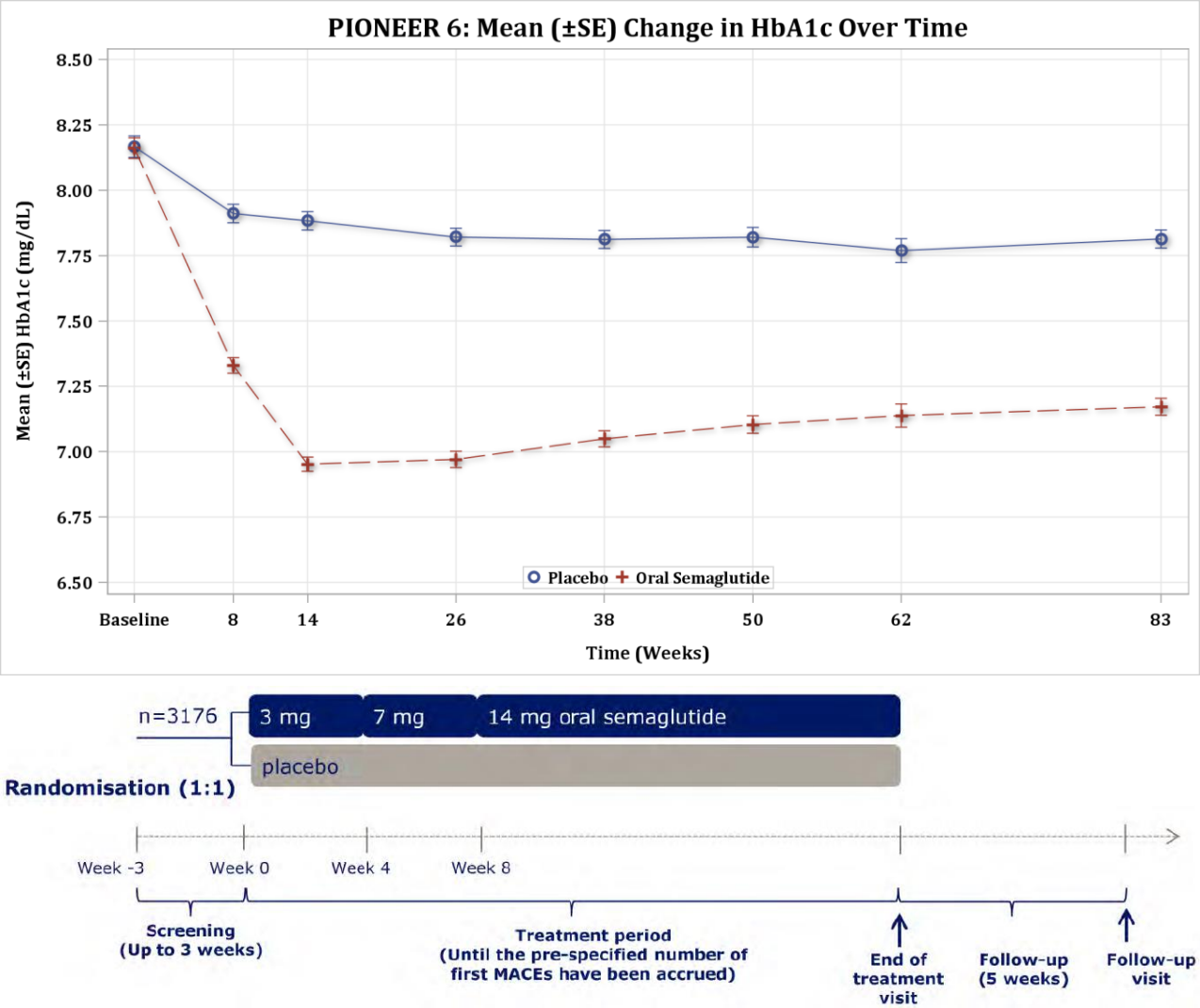


Figure 2: **Adjusted Mean HbA1c Over Time - Semaglutide Compared to Placebo in Study NN9924-4221 (PIONEER 6) – top, and Trial Design - bottom**



Reviewer Comments:

The HbA1c values observed in SUSTAIN-6, specifically Week 30, compare well with reported values for Semaglutide from the original NDA for OZEMPIC (semaglutide SC) as shown in the table below:

Table 7. Results at Week 30 in a Trial of OZEMPIC in Adult Patients with Type 2 Diabetes Mellitus In Combination with Basal Insulin With or Without Metformin

	Placebo	OZEMPIC 0.5 mg	OZEMPIC 1 mg
Intent-to-Treat (ITT) Population (N)[a]	133	132	131
HbA_{1c} (%)			
Baseline (mean)	8.4	8.4	8.3
Change at week 30[b]	-0.2	-1.3	-1.7
Difference from placebo[b] [95% CI]		-1.1 [-1.4, -0.8][c]	-1.6 [-1.8, -1.3][c]
Patients (%) achieving HbA_{1c} <7%	13	56	73
FPG (mg/dL)			
Baseline (mean)	154	161	153
Change at week 30[b]	-8	-28	-39

[a]The intent-to-treat population includes all randomized and exposed patients. At week 30 the primary HbA_{1c} endpoint was missing for 7%, 5% and 5% of patients and during the trial rescue medication was initiated by 14%, 2% and 1% of patients randomized to placebo, OZEMPIC 0.5 mg and OZEMPIC 1 mg, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.

[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value, country and stratification factors.

[c]$p<0.0001$ (2-sided) for superiority, adjusted for multiplicity.

(Source https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209637s001lbl.pdf)

Similarly, the HbA1c values observed in PIONEER-6, specifically Week 26, compare well with reported values for Semaglutide from the original NDA for RYBELSUS (oral semaglutide) as shown in the table below:

Table 3. Results at Week 26 in a Trial of RYBELSUS as Monotherapy in Adult Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise

	Placebo	**RYBELSUS 7 mg**	**RYBELSUS 14 mg**
Intent-to-Treat (ITT) Population (N)[a]	178	175	175
HbA_{1c} (%)			
Baseline (mean)	7.9	8.0	8.0
Change at week 26[b]	-0.3	-1.2	-1.4
Difference from placebo[b] [95% CI]		−0.9 [−1.1; −0.6][c]	−1.1 [−1.3; −0.9][c]
Patients (%) achieving HbA_{1c} <7%	31	69	77
FPG (mg/dL)			
Baseline (mean)	160	162	158
Change at week 26[b]	-3	-28	-33

[a]The intent-to-treat population includes all randomized patients. At week 26, the primary HbA_{1c} endpoint was missing for 5.6%, 8.6% and 8.6% of patients randomized to placebo, RYBELSUS 7 mg and RYBELSUS 14 mg, respectively. Missing data were imputed by a pattern mixture model using multiple imputation (MI). Pattern was defined by randomized treatment and treatment status at week 26. During the trial, additional anti-diabetic medication was initiated as an add on to randomized treatment by 15%, 2% and 1% of patients randomized to placebo, RYBELSUS 7 mg and RYBELSUS 14 mg, respectively.

[b]Estimated using an ANCOVA model based on data irrespectively of discontinuation of trial product or initiation of rescue medication adjusted for baseline value and region.

[c]$p<0.001$ (unadjusted 2-sided) for superiority, controlled for multiplicity.

(Source: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf)

Labeling Recommendations:

Deferred to acceptability of claims by the Clinical discipline.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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