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RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/BLA: NDA 213182

Sequence #: 0001

Drug Name: Rybelsus (semaglutide oral tablets)

Indication(s): To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (b) (4)

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1 EXECUTIVE SUMMARY

The applicant submitted this new drug application (NDA) to confirm that treatment with oral semaglutide (RYBELSUS), a GLP-1 receptor agonist, does not result in unacceptable increase in cardiovascular risk (CV) compared to placebo in adults who have type 2 diabetes mellitus with concurrent cardiovascular disease (b) (4)

To evaluate the effect of oral semaglutide on CV risk, the applicant conducted Study 4221 (PIONEER-6), a parallel-arm, double-blind cardiovascular outcome trial (CVOT) which enrolled 3183 adults who had type 2 diabetes mellitus with established cardiovascular disease and/or chronic kidney disease. Enrolled patients were randomized in a 1:1 ratio to daily doses of placebo or semaglutide oral tablet (po) 14 mg as add-ons to other treatments for type 2 diabetes. The primary endpoint is time from randomization to first occurrence of major adverse cardiovascular event (MACE), consisting of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The trial was terminated after the occurrence of 122 MACE events. Compared to placebo, the upper two-sided 95% confidence limit on the hazard ratio for MACE was less than the prespecified non-inferiority margin of 1.8 (hazard ratio of 0.79, two-sided 95% confidence interval [0.57, 1.11]). Additionally, that the upper bound was less than 1.3 suggesting no need for post-marketing demonstration of adequate CV safety for oral semaglutide .

(b) (4)
[REDACTED] compared to placebo, semaglutide po 14 mg did not significantly reduce the risk of MACE (two-sided p-value of 0.18 for superiority test). Even after a Bayesian shrinkage analysis, which included information from PIONEER-6 and SUSTAIN-6, the upper two-sided 95% credible interval for MACE hazard ratio remained above one. Further, nominally significant superiorities for endpoints which were not included in the analysis hierarchy in PIONEER-6, e.g. cardiovascular death and all-cause death, were not corroborated by results from SUSTAIN-6.

This submission confirms RYBELSUS does not increase CV risk in adults who have type 2 diabetes mellitus with concurrent cardiovascular disease (b) (4)
[REDACTED]

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). It is a GLP-1 analogue modified for resistance to metabolic degradation through albumin binding and additionally modified for resistance to enzymatic degradation by dipeptidyl peptidase-4. Tablets for oral administration are co-formulated with the absorption enhancer salcaprozate sodium, also known as sodium N-8-[(2-hydroxybenzoyl) amino] caprylate.

RYBELSUS is currently approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The present submission proposes an additional indication, to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (b) (4)

2.1.2 History of Drug Development

The injectable version of semaglutide, OZEMPIC, was originally approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) on December 6, 2017 under NDA 209637, and the orally administered version, RYBELSUS, was approved for the same indication on September 20, 2019 under NDA 213051.

A two-year cardiovascular outcome trial, documented in NDA 209637 sequence 0001, demonstrated non-inferiority of OZEMPIC to placebo for major adverse cardiovascular events (MACE). In addition, the upper two-sided 95% confidence limit on the MACE hazard ratio comparing OZEMPIC to placebo was less than 1 (b) (4)

Potential superiority of OZEMPIC for reduction of MACE risk was briefly revisited during an Endocrinologic and Metabolic Drugs Advisory Committee hearing held on October 18, 2017 to consider approval of OZEMPIC for T2DM. In that hearing, the committee did not achieve consensus on whether type 1 error would be unacceptably increased by inclusion on the label of an indication for reduction of MACE risk.

Superiority of OZEMPIC for reduction of MACE risk is currently under review under NDA 209637 sequence 0076. The present submission focuses on safety for MACE of RYBELSUS, semaglutide for oral administration.

2.1.3 Data Sources

Data sources for the current review are located at

<\\cdsesub1\evsprod\NDA213182\0001\m5\datasets\cv\analysis\adam\datasets> .

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and analysis programs provided by the applicant were consistently well organized. Adequacy of trial design and analyses are further discussed in this review.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

To evaluate the effect of oral semaglutide on CV risk, the applicant conducted Study 4221 (PIONEER-6), a randomized, placebo-controlled, parallel-group cardiovascular outcome trial , which enrolled 3183 adults who had type 2 diabetes mellitus with established cardiovascular disease and/or chronic kidney disease (Table 1). The enrolled patients were randomized in a 1:1 ratio to daily doses of placebo (Pbo) or semaglutide po 14 mg (S14) as add-ons to other treatments for type 2 diabetes mellitus. The primary endpoint is time from randomization to first occurrence of MACE, consisting of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The trial was terminated after the occurrence after 122 MACE events.

Prohibited medications included GLP-1 receptor agonists other than semaglutide, DPP4 inhibitors, and pramlintide.

Prespecified analyses for study 4221 included both superiority and non-inferiority for time to first occurrence of MACE .

Table 1. Randomized Cardiovascular Outcome Trial 4221

Design	Population	Endpoints
S14 Pbo + OL SOC - GLP-1 RA - DPP4 inhib - pramlintide DB, PC, PG 122 event min	T2D ≥ 50 years + clinical CVD/CKD ≥ 60 years + subclinical CVD N = 1591:1592 max 650 w/ subclinical CVD Strat: subclinical vs clinical CVD	<i>Primary:</i> Time to First MACE

source: reviewer

S14 semaglutide 14 mg po oral qd maintenance dose with 3 or 7 mg acceptable if tolerability at issue, Pbo placebo, OL open label, SOC standard of care, DPP4 inhib dipeptidyl peptidase 4 inhibitor, DB double blind, PC placebo-controlled, PG parallel-group, min minimum, CVD cardiovascular disease, CKD chronic kidney disease, Strat stratification factors, MACE major adverse cardiovascular events

3.2.2 Statistical Methodologies

Time to first occurrence of MACE was analyzed using a proportional hazards model with independent variable treatment. Analyses were stratified by the same factors used in the randomization, summarized in Table 1.

The planned non-inferiority safety analysis for time to first occurrence of MACE evaluated the null hypothesis that the one-sided 97.5% upper confidence interval of the hazard ratio for treatment compared to placebo is greater than or equal to 1.8.

The treatment policy estimand was used to evaluate efficacy.

Planned sensitivity analyses included a tipping point analysis as well as other exploratory models which included different covariates, inclusion of events which occurred only during the on-treatment period, and extension of right-hand censoring beyond the on-treatment and planned study end dates.

To control type 1 error, the confirmatory analysis hierarchy included two null hypotheses; both evaluated time to first MACE, with superiority of S14 to placebo to be tested only if S14 was non-inferior to placebo.

Where useful, results from descriptive analyses of this product will be evaluated for corroboration with results from analyses of the subcutaneously administered version of semaglutide, OZEMPIC.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Trial completion rates exceeded 95% (Table 2)¹. Patients administered semaglutide discontinued treatment due to adverse events more often than patients administered placebo. Median follow-up time was 16.1 months (range 0.8 to 19.9 months) for S14 and 15.8 months (range 0.4 to 19.9 months) for Pbo.

Table 2. Patient Disposition – Study 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: Adapted from CSR Table 10-1

¹ Disposition given as number of patients and, in parentheses, percent of full analysis set

There were no obvious differences between treatments for baseline characteristics (Table 3).

Table 3. Patient Demographics, Full Analysis Set – Study 4221

Patient Category			Treatment	
			S14	Pbo
Randomized (FAS)			1591 (100)	1592 (100)
Sex	Female	n (%)	507 (31.9)	500 (31.4)
Age	mean	(sd)	66 (7)	66 (7)
	range		50-86	29-83
	50-64	n (%)	700 (44.0)	634 (39.8)
	65-74		691 (43.4)	747 (46.9)
	75-84		196 (12.3)	201 (12.6)
	≥ 85		4 (.3)	10 (.6)
Race	White	n (%)	1148 (72.2)	1152 (72.4)
	Asian		324 (20.4)	306 (19.2)
	African American		89 (5.6)	103 (6.5)
	Native American		14 (0.9)	15 (0.9)
	Pacific Islander		5 (0.3)	1 (<0.1)
	Other		11 (0.7)	15 (0.9)
Ethnicity	Hispanic	n (%)	253 (15.9)	261 (16.4)
	Not Hispanic		1338 (84.1)	1331 (83.6)
BMI	mean	(sd)	32.3 (6.6)	32.4 (6.4)
Country	USA	n (%)	75 (26.3)	28 (19.7)

source: Adapted from CSR Tables 10-2 and 10-3

FAS: Full analysis Set; sd: standard deviation

3.2.4 Results and Conclusions

3.2.4.1 Results for Primary Endpoint and Its Components

Semaglutide is non-inferior to placebo for time to first occurrence of MACE, with the upper two-sided 95% confidence limit for hazard ratio less than 1.3 (Table 4). However, since the upper two-sided 95% confidence limit for hazard ratio is greater than 1, superiority of semaglutide 14 mg for time to first occurrence of MACE is not established (Table 4). Similarly, differences between S14 and placebo were not statistically significant for all MI and all strokes (Table 4).

Table 4. Results for Time to First Occurrence of Relevant Events – Study 4221

	S14 N=1591 n (%)	Pbo N=1592 n (%)	S14 vs Pbo Hazard Ratio (95% CI)	P value^o
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.

^o P value (two-sided) is based on the Wald statistic for superiority of Hazard Ratio.

Compared to placebo, treatment with RYBELSUS was associated with favorable numerical trends for all-cause death and MACE-free survival, i.e. survival without MI or stroke (Table 4). However, nominal statistical significance for reduction of all-cause death in study 4221 should not be over interpreted given that type 1 error was not controlled for that endpoint, and because the reduction in risk of all-cause death seen in trial 4221 for RYBELSUS was not mirrored in trial 3744 for OZEMPIC (Table 5).

Table 5. Results for Time to First Occurrence of Adverse Events of Special Interest– Studies 4221 and 3744

Event	Trial	Number of Events (%)		Hazard Ratio		
		Sema	Pbo	Estimate	95% CI ¹	P-Value ¹
CV and undetermined death	3744	44 (2.6)	46 (2.8)	0.98	(0.65, 1.50)	.9
	4221	15 (0.9)	30 (1.9)	0.49	(0.27, 0.92)	.02
Non-fatal MI	3744	47 (2.9)	64 (3.9)	0.74	(0.51, 1.09)	.12
	4221	37 (2.3)	31 (1.9)	1.18	(0.73, 1.90)	.5
Non-fatal stroke	3744	27 (1.6)	44 (2.7)	0.61	(0.38, 0.99)	.044
	4221	12 (0.7)	16 (1.0)	0.74	(0.35, 1.57)	.44
All cause death	3744	62 (3.8)	60 (3.6)	1.05	(0.74, 1.50)	.8
	4221	23 (1.4)	45 (2.8)	0.51	(0.31, 0.84)	.008

source: macecomp.sas

1. For test of superiority, p-values and confidence intervals are nominal and incorrectly biased toward statistical significance

CV cardiovascular, MI myocardial infarction

(b) (4)

3.2.4.2 *Shrinkage Analyses Combining Results from Study 4221 and Study 3744*

In an attempt to gain further precision regarding risk of MACE, the applicant provided a Bayesian shrinkage analysis combining results from this study with those from a study of semaglutide for subcutaneous injection, trial 3744 (SUSTAIN-6), whose design is detailed in the Appendix.

Assuming that observations from oral and injectable of the drug are exchangeable (roughly, that, prior to examining the data, the review team did not have any opinion as to whether one dosage form is more effective than the other), a Bayesian shrinkage analysis was conducted to establish credible intervals for MACE hazard ratios.

In the applicant's Bayesian shrinkage analysis, for $i = 1, 2$ where Y_i represents the observed sample estimate of log-hazard ratio for study i , the applicant assumed $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variances for sample estimates
- $\mu \sim N(0, 1000)$,
- $\gamma_i \sim N(0, \omega_i^2)$, $\omega_i \sim \text{Normal}(0, 1)$,
- $\mu_i = \mu + \gamma_i$

Results from the applicant's Bayesian shrinkage analyses (Table 6) did not contradict those seen from the frequentist analyses (Table 4), that is, the upper credible limit for the hazard ratio exceeded 1 for study 4221 and was less than 1 for study 3744. Similar results were seen when a supplemental Bayesian shrinkage analysis was conducted with $\mu \sim N(0, 16)$, $\mu_i \sim N(\mu, \tau^2)$, and $1/\tau^2 \sim \text{Gamma}(0.001, 0.001)$.

Table 6. Bayesian Shrinkage Analysis, MACE Hazard Ratios¹

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

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Whether safety depends on subgroups, such as race, gender, age class, or region, was evaluated by adding to the primary analysis model terms for the particular subgroup under examination as well as the interactions of that subgroup with each dependent factor (blue lines in Figure 1 and Figure 2).

In the traditional subgroup analyses, there were random highs and random lows in sample estimates of subgroup treatment effects due to small sample size and large variability for some subgroups. Therefore, we also derived shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates (red lines in Figure 1 and Figure 2). The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a “weighted” average of the sample estimate and the overall estimate. The weights are based on the ratio of the between-subgroup variability to the within-subgroup variability. The greater the ratio is, the smaller the weight on the overall estimate (the less the shrinkage). We used the same flat prior distribution to derive shrinkage estimates for all subgroups. The Bayesian hierarchical model assumptions are:

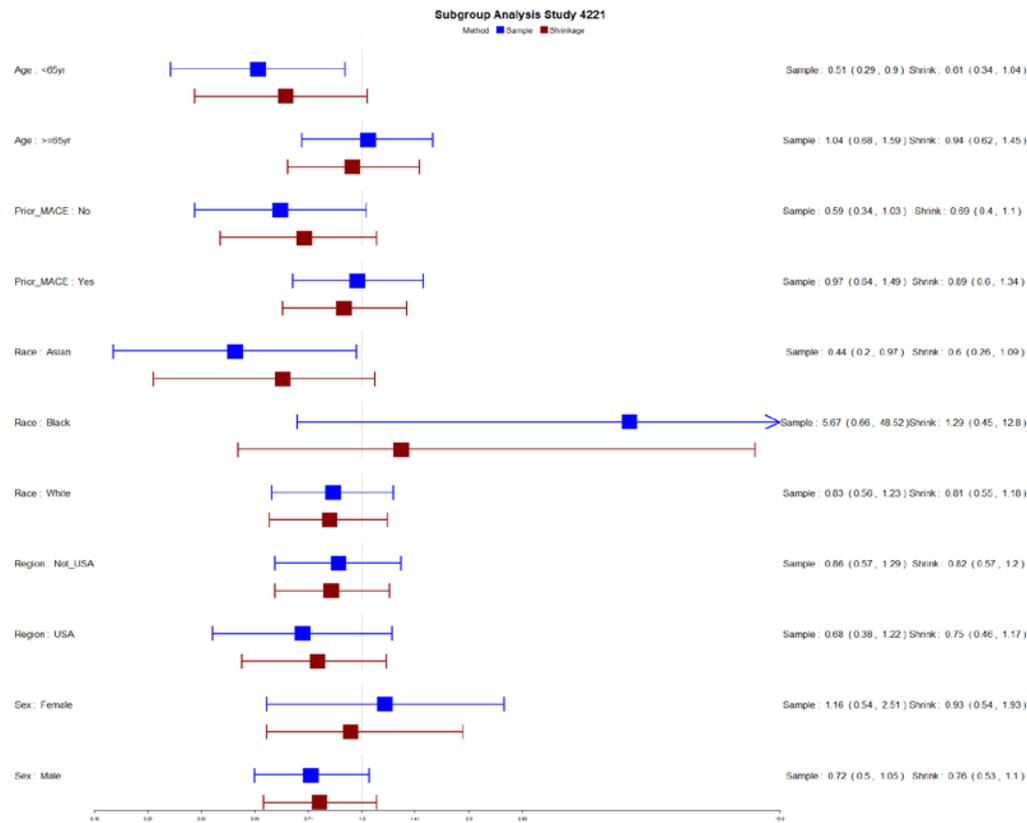
For $i = 1, 2, \dots$, where Y_i represents the observed sample estimate of treatment effect in a subgroup level i , assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 16)$, $1/\tau^2 \sim \text{Gamma}(0.001, 0.001)$

In general, the treatment effect of semaglutide was consistent across the different subgroups. For MACE hazard ratio, gender, age class (<65, ≥65), and region (USA vs not USA) had no qualitative impact on the effect of semaglutide compared to control (Figure 1 and Figure 2, sample sizes on Table 7).

Study 4221 suggested that semaglutide may be less effective in Blacks and African Americans than in other racial subgroups, with the point estimate indicating potential harm (Figure 1). However, the estimate for this racial subgroup was extremely imprecise because of low enrollment numbers: there were only 6 MACE events among Blacks and African Americans in study 4221 and 12 in study 3744 (Table 7). Indeed, the confidence intervals included potential benefits for this racial subgroup because, for studies 4221 and 3744, the lower confidence and credibility limits for hazard ratios were less than 1 (Figure 1 and Figure 2) and also because, for study 3744, the point estimate for the hazard ratio is in the direction of benefit (Figure 2).

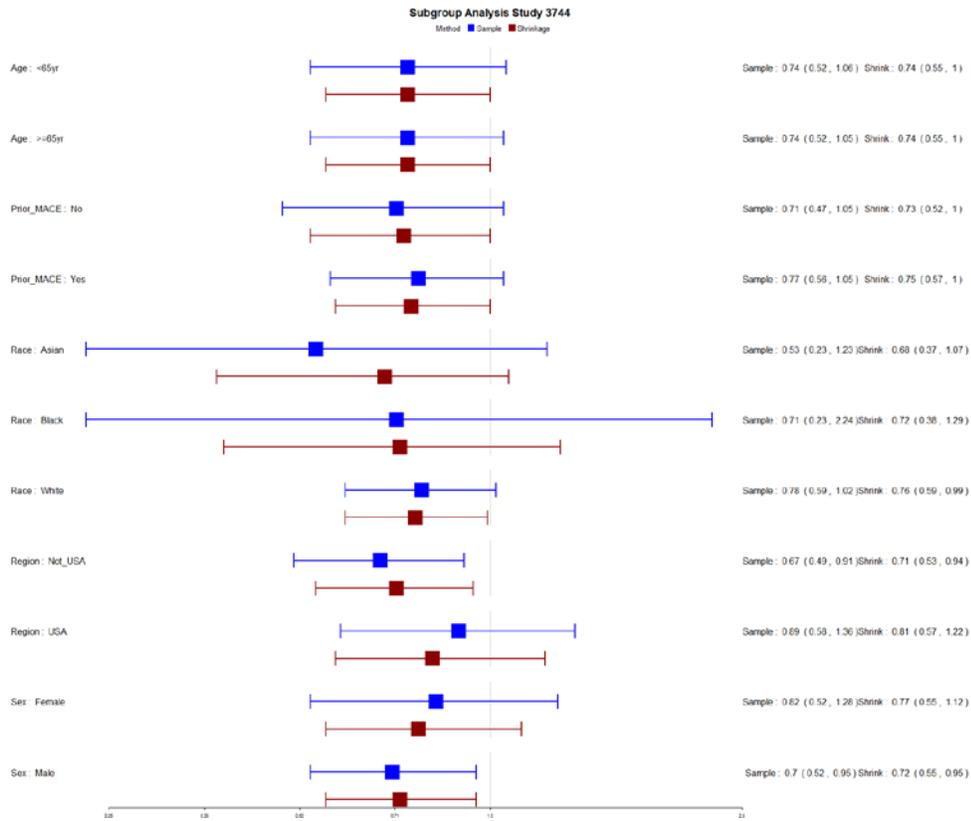
Figure 1. Subgroup Analyses, Semaglutide PO 14 mg vs Placebo, Study 4221



source: S4221 Subgroup Forest Plot.R, subgr bayshrinkx.sas

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Figure 2. Subgroup Analyses, Semaglutide SC vs Placebo, Study 3744



source: S3744 Subgroup Forest Plot 2019 09 03.R, subgr bayshrinkx.sas

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Table 7. Number of MACE Events, Subgroup Analyses

Study	Group	Subgroup	Pbo	Semaglutide	
4221	Age	< 65 yr	33	19	
		≥ 65 yr	43	42	
	Prior Mace	No Prior	32	20	
		Prior	44	41	
	Race	Asian	19	9	
		Black	1	5	
		White	55	46	
	Region	Not USA	49	42	
		USA	27	19	
	Sex	Female	12	14	
		Male	64	47	
	3744	Age	<65 yr	70	53
			≥ 65 yr	76	55
Prior Mace		No Prior	58	42	
		Prior	88	66	
Race		Asian	17	8	
		Black	7	5	
		White	118	93	
Region		Not USA	101	68	
		USA	45	40	
Sex		Female	43	35	
	Male	103	73		

source: subgr bayshrinkx.sas

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no unresolved statistical issues in this submission.

5.2 Collective Evidence

Compared to placebo, the hazard ratio for MACE was less than the prespecified non-inferiority margin of 1.8 (hazard ratio 0.79, two-sided 95% confidence interval [0.57, 1.11]). Additionally, the upper bound of the two-sided 95% confidence interval was less than 1.3, suggesting no need for further post-marketing requirement to evaluate the adequacy of safety for MACE.

(b) (4)
the trial failed to demonstrate superiority at the two-sided .05 level of significance. In particular, as detailed above, the upper confidence limit for the MACE hazard ratio exceeded 1, with a p-value for superiority equal to .18. Further, nominally significant superiorities for cardiovascular death and for death due to any cause were not corroborated by results from study 3744 conducted for a subcutaneously administered version of the same study drug. Similarly, even after a Bayesian shrinkage analysis on MACE incidence rate, which included information from Study 4221 and Study 3744, the upper credible interval for MACE hazard ratio for Study 4221 exceeded one.

5.3 Conclusions and Recommendations

This submission confirms RYBELSUS does not increase CV risk in adults who have type 2 diabetes mellitus with concurrent cardiovascular disease (b) (4)

[REDACTED]

[REDACTED]

5.4 Labeling Recommendations

The review team may wish to consider the following revisions to proposed labeling:



5. In Section 14 for study 4221, MACE hazard ratio with 95% confidence limits should be reported in text (b) (4).

6. Documentation and results presented for study 4221 in Section 14 should consistently and clearly indicate that the MACE hazard ratio was calculated with a 16-month median trial duration.

7. Documentation and results presented for study 4221 in Section 14 should consistently and clearly indicate that only the 14 mg dose was evaluated.



6 APPENDIX: CARDIOVASCULAR OUTCOME TRIAL 3744 FOR OZEMPIC

Trial 3744 (Table 8) was conducted to evaluate time to first occurrence of MACE for injectable semaglutide. As in trial 4221, prohibited drugs included GLP-1 receptor agonists other than semaglutide, DPP4 inhibitors, and pramlintide. At least 122 MACE events were required before study termination.

Study 3744, unlike study 4221, additionally required that all patients remain on randomized treatment for at least 104 weeks, and also required that all enrolled patients have $HbA1c \geq 7\%$. Study 3744 randomized patients to both approved doses, while study 4221 only randomized patients to the highest approved dose. Inclusion criteria for chronic kidney disease also differed between the two studies, both required that patients have $eGFR < 60 \text{ mL/Min/1.73 m}^2$, but study 4221 excluded patients with $eGFR < 30 \text{ mL/Min/1.73 m}^2$.

Like study 4221, the analysis of time to first occurrence of MACE in study 3744 used a proportional hazards model with independent variable treatment. Analyses were stratified by the same factors used in the randomization, summarized in Table 8.

The planned analysis for non-inferiority of MACE evaluated the null hypothesis that the one-sided 97.5% upper confidence interval of the hazard ratio for treatment compared to placebo is greater than or equal to 1.8. For study 3744, the two semaglutide treatments were pooled and compared to the two placebo treatments pooled.

The treatment policy estimand was used to evaluate efficacy, i.e., all study endpoints were assessed in all randomized patients, regardless of adherence to randomized treatment, use of prohibited medications, or adherence to study protocol.

Results from study 3744 suggest superiority of subcutaneously administered semaglutide for time to first occurrence of MACE (Table 9). Further details of this study, including demographics, disposition, and efficacy results from supportive endpoints, will be provided in a separate review.

Table 8. Randomized Cardiovascular Outcome Trial 3744 for OZEMPIC

Trial	Design	Population	Endpoints
3744	S05 S1 Pbo05 Pbo1 + SOC - GLP-1 RA - DPP4 inhib - pramlintide DB, PC, PG 104 week min 122 event min	T2D HbA1c $\geq 7.0\%$ ≥ 50 years + clinical CVD/CDK ≥ 60 years + subclinical CVD N= 826:822:824:825 Strat: subclin vs clin CVD insulin (none, basal, premix) severe renal impairment eGFR $<30, \geq 30$ mL/min/1.73 m ²)	<i>Primary:</i> Time to first MACE <i>Secondary:</i> Δ weight week 104 Δ HbA1c week 30 insulin premix SU monotherapy

source: reviewer

S05 S1 semaglutide sc 0.5 1 mg maintenance doses administered once weekly, Pbo 05 01 placebo sc in volumes corresponding to S05 and S1, SOC standard of care, DPP4 inhib dipeptidyl peptidase 4 inhibitor, DB double blind, PC placebo-controlled, PG parallel-group, T2DM type 2 diabetes mellitus, CVD cardiovascular disease, CKD chronic kidney disease, Strat stratification factors, eGFR estimated glomerular filtration rate, NI non-inferiority, SU sulfonylurea

Table 9. Relative Risk of MACE, Study 3744, Median Trial Duration 25.2 Months

Trial	Number of Events		Hazard Ratio		
	Semaglutide	Pbo	Estimate	95% CI	P-Value for Superiority
3744	108	146	0.74	(0.58, 0.95)	.017

source: bayshrinkx.sas, CSR Study 3744 Table 11-4, CSR Study 4221 Table 11-3

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