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RESEARCH**

*APPLICATION NUMBER:*

**213182Orig1s000**

**CLINICAL REVIEW(S)**

### CLINICAL REVIEW

<b>Application Type</b>	New Drug Application
<b>Application Number(s)</b>	213182
<b>Priority or Standard</b>	Standard
<b>Submit Date(s)</b>	March 20, 2019
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<b>Division/Office</b>	DMEP
<b>Reviewer Name(s)</b>	Andreea Ondina Lungu
<b>Review Completion Date</b>	January 14, 2020
<b>Established/Proper Name</b>	semaglutide
<b>(Proposed) Trade Name</b>	Rybelsus
<b>Applicant</b>	Novo Nordisk
<b>Dosage Form(s)</b>	Oral tablet
<b>Applicant Proposed Dosing Regimen(s)</b>	14 mg
<b>Applicant Proposed Indication(s)/Population(s)</b>	To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (b) (4)
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	No new indication. Changes to Section 14 of the prescribing information to reflect the results of PIONEER 6

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## Glossary

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AC	advisory committee
ACE	angiotensin converting enzyme
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CV	cardiovascular
CVOT	cardiovascular outcomes trial
DBP	diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DILI	drug-induced liver injury
DMC	data monitoring committee
DPP-4	Dipeptidyl peptidase-4
EAC	Event Adjudication Committee
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GCP	good clinical practice
GLP-1	glucagon-like peptide 1
GLP-1 RA	GLP-1 receptor agonist
HbA1c	Hemoglobin A1c/glycosylated hemoglobin
HDL	High density lipoprotein cholesterol
HLT	Medical Dictionary for Regulatory Activities High Level Term
ICH	International Council for Harmonization

IND	Investigational New Drug Application
ITT	intent to treat
LDL	Low density lipoprotein cholesterol
MACE	Major adverse cardiovascular event
MESI	Medical Event of Special Interest
MDRD	Modification of diet in renal disease
MI	Myocardial infarction
NA	not applicable
mITT	modified intent to treat
NDA	new drug application
NN	Novo Nordisk
OAD	oral antidiabetic drug
OSI	Office of Scientific Investigation
OW	once weekly
PI	prescribing information or package insert
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PRO	patient reported outcome
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SE	standard error
Sema	semaglutide
SGLT2	Sodium-dependent glucose co-transporter-2
SU	sulfonylurea
TEAE	treatment emergent adverse event
T2DM	type 2 diabetes mellitus
TG	triglycerides
TZD	thiazolidinedione

## 1. Executive Summary

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### 1.1. Product Introduction

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA) approved for daily oral administration (trade name Rybelsus) indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2DM). Semaglutide is also approved for the same indication as a weekly subcutaneous injection (trade name Ozempic), which will be discussed in a separate review.

This application consists of the submission of the results of PIONEER 6, the Rybelsus pre-market cardiovascular outcomes trial (CVOT), as well as a summary of supportive CV findings with the subcutaneous semaglutide product (SUSTAIN 6 trial). The applicant is proposing to use data from both studies to support the following indication for Rybelsus:

*Rybelsus is indicated to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease* (b) (4)

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

Rybelsus was approved for glycemic control indication in patients with T2DM in 2019. The evaluation of cardiovascular (CV) risk was assessed via a pre-market CV outcome study, PIONEER 6. This study aimed to demonstrate that oral semaglutide is not associated with an unacceptable increase in CV risk per the FDA guidance, and was event driven aiming to collect 122 Major Adverse Cardiovascular Events (MACE), consisting of CV death, non-fatal myocardial infarction (MI) and non-fatal stroke. The events were adjudicated by an Event Adjudication Committee (EAC). The study enrolled adult patients with T2DM with high risk of CV disease as follows: age 50 and above and clinical evidence of CV disease (including chronic kidney disease with eGFR 30-59 mL/min/1.73m<sup>2</sup> per MDRD), or age 60 and above and subclinical evidence of CV disease.

The primary analysis for PIONEER 6 was non-inferiority, followed by superiority of Rybelsus vs placebo for time to first occurrence of MACE.

In PIONEER 6, 3183 patients were randomized (1:1) to receive semaglutide 14 mg or placebo. Over 99% of patients in either treatment group completed the trial, and more than 85% completed the treatment. Median follow up time was 16.1 months.

There were a total of 137 first MACE with onset during the in-trial observation period. The proportion of patients with first MACE was lower with oral semaglutide than with placebo; a total of 61 patients (3.8%) experienced EAC-confirmed MACE with oral semaglutide versus 76

patients (4.8%) with placebo. The difference did not achieve statistical significance for superiority, the HR was 0.79 [0.57; 1.11] 95% CI for oral semaglutide relative to placebo. The applicant also performed a Bayesian shrinkage analysis using the results of SUSTAIN 6 for support. The shrinkage analysis still did not achieve superiority for PIONEER 6 as the upper credible limit for the hazard ratio exceeded 1 (HR 0.78 with 95% credible interval 0.58, 1.06).

While PIONEER 6 showed a nominally significant difference in CV death and all-cause death favoring semaglutide vs placebo, these data should not be overinterpreted as the event number was small, the endpoints were not controlled for type 1 error, and these data were not supported by the CVOT with subcutaneous semaglutide, SUSTAIN 6, where no difference was seen for CV- or all-cause death.

Taking into consideration all the above information, [REDACTED] (b) (4)

[REDACTED] I do recommend that we approve this supplement with changes to Section 14 of the prescribing information to better reflect the results of PIONEER 6.

### 1.3. Benefit-Risk Assessment

#### **Benefit-Risk Integrated Assessment**

Diabetes mellitus is a serious disease that affects approximately 30 million people in the United States. Diabetes mellitus can lead to macrovascular and microvascular complications that can reduce the quality of life and longevity of afflicted patients. In the US, diabetes is the leading cause of kidney failure, non-traumatic lower limb amputations, and new cases of blindness. Diabetes has been associated with an increase in the risk of cardiovascular disease, cardiovascular death and all-cause mortality, with the majority of people with diabetes dying from cardiovascular causes.

There are currently 12 classes of diabetes medications approved for the treatment of type 2 diabetes mellitus including GLP-1 receptor agonists. Several antidiabetics also have an indication to reduce the risk of CV events in patients with T2DM and history of CV disease. Oral semaglutide (Rybelsus) has an indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

PIONEER 6 has been conducted as a pre marketing cardiovascular outcomes trial, based on the 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. The purpose of the study was to demonstrate that oral semaglutide therapy is not associated with an increased risk for major adverse cardiovascular events (MACE).

PIONEER 6 demonstrated a nominal reduction in the risk of MACE with oral semaglutide 14 mg compared to placebo when added to standard of care therapies for diabetes in patients with history of T2DM and CV disease. This reduction was mainly due to a reduction in CV death and non-fatal stroke. The analysis for superiority of semaglutide vs placebo did not achieve statistical significance for even after a Bayesian shrinkage analysis performed using the results of the subcutaneous semaglutide CVOT, SUSTAIN 6. (b) (4)

However, the PIONEER 6 review justifies addition of new data to Section 14 of the Rybelsus prescribing information. For this, I recommend approval of this supplement.

**Benefit-Risk Dimensions**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> <li>• T2DM is a chronic disease characterized by insulin resistance and inadequate insulin secretion, resulting in hyperglycemia</li> <li>• T2DM affects approximately 30 million people in the United States</li> <li>• Diabetes is associated with multiple complications including macrovascular and microvascular complications which may shorten and affect the quality of life of patients.</li> <li>• Improved glycemic control, measured by HbA1c reduction, improves microvascular outcomes and may improve macrovascular outcomes</li> </ul>	<p>Diabetes is a serious condition associated with chronic morbidity and premature death. Achievement of recommended glycemic targets is an important therapeutic goal in treatment of T2DM, as it reduces the risk of end-organ complications.</p>
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> <li>• Twelve classes of drugs, including GLP1-RAs, are FDA approved in the United States to improve glycemic control in patients type 2 diabetes.</li> <li>• Professional societies recommend initiating treatment with lifestyle interventions and metformin, followed by other drugs if needed for glycemic control, with choice of additional therapies based on factors such as baseline CV risk, patient preference, and cost</li> <li>• In addition to indications for glycemic control, two SGLT2 inhibitors (canagliflozin and empagliflozin) and one GLP-1 agonist (liraglutide) have indications to reduce the risk of CV events</li> <li>• Canagliflozin also has an indication statement to reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death and hospitalization for heart failure in patients with T2DM and diabetic nephropathy with albuminuria</li> <li>• Dapagliflozin has an indication to reduce the risk of new or worsening heart failure as measured by the occurrence of hospitalization for heart failure or CV death</li> </ul>	<p>There are multiple effective treatment options available for the treatment of type 2 diabetes, some of which have indications for reduction in MACE and/or other relevant diabetes complications. Therefore, patient factors such as CV disease are important factors tailoring therapeutic regimens for individual patients.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b><u>Benefit</u></b>	<ul style="list-style-type: none"> <li>• Oral semaglutide CVOT demonstrated a nominal reduction in the risk of MACE with oral semaglutide 14 mg compared to placebo when added to standard of care therapies for diabetes in patients with history of T2DM and CV disease.</li> <li>• This reduction was mainly due to a reduction in CV death.</li> <li>• The results did not achieve statistical significance even after a Bayesian shrinkage analysis was performed using the results of the subcutaneous semaglutide CVOT, SUSTAIN 6.</li> </ul>	<p>PIONEER 6 did not demonstrate substantial evidence of effectiveness for reduction of the incidence of first MACE in patients with T2DM and CV disease.</p>
<b><u>Risk and Risk Management</u></b>	<ul style="list-style-type: none"> <li>• Not applicable.</li> </ul>	<p>No new safety information was reviewed.</p>

#### 1.4. Patient Experience Data

Not applicable.

## 2. Therapeutic Context

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### 2.1. Analysis of Condition

Diabetes mellitus is a disease of impaired glucose homeostasis resulting in chronic hyperglycemia that is associated with significant morbidity and mortality due to microvascular and macrovascular pathologies, and is a major cause of hospitalization, blindness, renal failure, amputations and cardiovascular (CV) disease. With Type 1 diabetes mellitus, patients lose the ability to secrete endogenous insulin and require exogenous insulin replacement. With T2DM, patients have varying degrees of insulin resistance and are unable to maintain euglycemia with endogenous insulin secretion.

There is no cure for T2DM, but therapies aimed at improving glycemic control are available. Currently approved therapies in T2DM aim to improve glycemic control by improving insulin resistance, enhancing insulin secretion, or increasing glucose excretion. One such therapeutic approach is through the incretin pathway, which is the pathway relevant for the semaglutide application.

### 2.2. Analysis of Current Treatment Options

Several classes of drugs are currently approved for the treatment of T2DM, used either alone or in combination. These drug classes include:

- Biguanides (i.e. metformin)
- Sulfonylureas
- Thiazolidinediones (TZDs)
- Meglitinides
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Glucagon-like peptide-1 receptor agonists (GLP-1 RA)
- SGLT2 inhibitors
- Alpha-glucosidase inhibitors
- Amylin-mimetics

- Dopamine agonist (i.e. bromocriptine)
- Insulin and insulin analogues
- Bile acid sequestrant (i.e. colesevelam hydrochloride)

Despite the relatively large number of drugs available for the treatment of T2DM, a substantial proportion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an anti-diabetic drug. Further, some drug classes may be poorly tolerated by some patients or have limited usefulness in certain populations. For example, sulfonylureas and insulin are associated with a high risk for hypoglycemia, thiazolidinedione's (TZDs) may be associated with edema and are not for use in many patients with congestive heart failure, while metformin and SGLT2i are contraindicated in patients with severe renal dysfunction. Additionally, progressive  $\beta$ -cell dysfunction may lead to secondary treatment failure to the anti-diabetic therapy over time requiring the addition of other agents. For these reasons, and because T2DM is a disease that is heterogeneous in both pathogenesis and clinical manifestation, there is an unmet need for new anti-diabetic therapies and concomitant treatment options for T2DM.

### **3. Regulatory Background**

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#### **3.1. U.S. Regulatory Actions and Marketing History**

Semaglutide is already marketed in the US as a daily oral product under the trade name of Rybelsus, and as weekly subcutaneous injection under the trade name Ozempic.

#### **3.2. Summary of Presubmission/Submission Regulatory Activity**

Rybelsus was approved for glycemic indication in the US in September 2019. Prior to Rybelsus submission, the FDA and the applicant discussed the plan for evaluating the CV data with oral and subcutaneous semaglutide as follows.

A Type C meeting was held on March 12, 2018 to discuss post-marketing CVOTs for sc semaglutide. At this meeting, the FDA commented that they would be open to using data from other semaglutide development programs across indications and patient populations, to support a CV risk reduction indication for sc semaglutide.

The FDA asked Novo Nordisk to submit a proposal for their review and on April 23, 2018, the Agency provided their feedback. The Agency agreed that, in principle, data for oral semaglutide could be leveraged as supportive evidence for s.c. semaglutide and vice versa.

Preliminary results from the oral semaglutide clinical development program were presented by the applicant at the pre-NDA meeting for oral semaglutide on November 29, 2018. MACE data

from PIONEER 6 (oral semaglutide pre-market CVOT) were presented to the FDA along with SUSTAIN 6 MACE results at a teleconference on December 20, 2018. In addition, a pre-NDA meeting to discuss the strategy for application of a CV indication was held February 27, 2019. At this meeting the Agency recommended to evaluate data from SUSTAIN 6 and PIONEER 6 using a Bayesian shrinkage analysis.

### **3.3. Foreign Regulatory Actions and Marketing History**

Not applicable.

## **4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

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### **4.1. Office of Scientific Investigations (OSI)**

Not applicable. Please see OSI review for Rybelsus for details.

### **4.2. Product Quality**

Not applicable.

### **4.3. Clinical Microbiology**

Not applicable.

### **4.4. Nonclinical Pharmacology/Toxicology**

Not applicable.

### **4.5. Clinical Pharmacology**

Not applicable.

### **4.6. Devices and Companion Diagnostic Issues**

Not applicable.

#### 4.7. Consumer Study Reviews

Not applicable.

### 5. Sources of Clinical Data and Review Strategy

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#### 5.1. Table of Clinical Studies

Only one study is included for this review. The study is the pre-market CVOT for Rybelsus, PIONEER 6.

#### 5.2. Review Strategy

The applicant re-submitted the pre-market CVOT for Ozempic, SUSTAIN 6. Additional data from PIONEER 6 (oral semaglutide) will be reviewed separately under NDA 213182.

The efficacy pertaining to MACE including post-hoc analyses will be discussed in the efficacy section, and additional details can be found in the biometrics review by Dr Robert Abugov. The safety for SUSTAIN 6 was already discussed in the clinical review for the original Ozempic NDA, and it is already included in the prescribing information. Therefore, no safety information will be discussed in this review. Review of Relevant Individual Trials Used to Support Efficacy

#### 5.3. PIONEER 6

##### 5.3.1. Study Design

##### Overview and Objective

Study Title: PIONEER 6 – Cardiovascular outcomes trial - A trial investigating the cardiovascular safety of oral semaglutide in subjects with type 2 diabetes

##### Primary objective

To confirm that treatment with oral semaglutide does not result in an unacceptable increase in cardiovascular risk compared to placebo (rule out 80% excess risk) in subjects with type 2 diabetes at high risk of cardiovascular events.

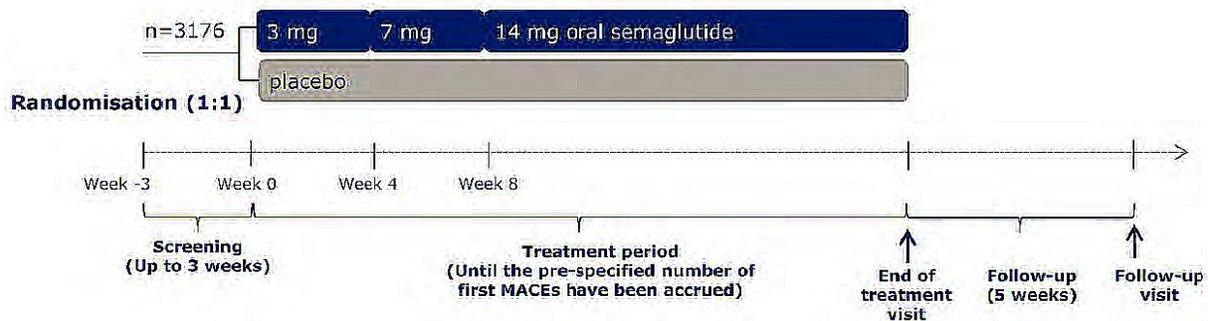
##### Secondary objectives

To compare the efficacy and safety of oral semaglutide versus placebo in subjects with type 2 diabetes at high risk of cardiovascular events.

## Trial Design

This trial was a randomized, double-blind, placebo-controlled, multinational, multi-center, designed to assess the cardiovascular safety of oral semaglutide versus placebo when added to standard-of-care in subjects with type 2 diabetes at high risk of cardiovascular events. The trial design is outlined in Figure 1 below.

**Figure 1 Trial Design PIONEER 6**



Source: Figure 9-1 Study Report

The duration of the treatment period was event driven aiming for at least 122 first EAC-confirmed MACE comprising cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

A total of 3176 adults with T2DM were planned to be randomized 1:1 to semaglutide or placebo.

The trial applied a targeted approach to collection of safety data focusing on SAEs, AEs leading to premature discontinuation of trial product and AEs for selected safety areas.

### Key Inclusion/Exclusion criteria:

Inclusion criteria include

- Adult patients with T2DM with HbA1C  $\geq 7\%$  at screening
- Age  $\geq 50$  at screening and clinical evidence of CV disease defined as at least one of the below criteria
  - a) prior MI.
  - b) prior stroke or TIA.
  - c) prior coronary, carotid or peripheral arterial revascularisation.
  - d)  $>50\%$  stenosis on angiography or imaging of coronary, carotid or lower extremity arteries.
  - e) history of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging or unstable angina with ECG changes.a

- f) asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or stress echo or any cardiac imaging.a
- g) chronic heart failure NYHA class II-III.
- h) chronic renal impairment, documented by eGFR 30-59 mL/min/1.73m<sup>2</sup> per MDRD.

OR

- Age  $\geq$ 60 at screening and meeting at least one of the below risk factors:
  - i) microalbuminuria or proteinuria.
  - j) hypertension and left ventricular hypertrophy by ECG or imaging.
  - k) left ventricular systolic or diastolic dysfunction by imaging.
  - l) ankle/brachial index <0.9.

Exclusion criteria include

- Use of GLP-1 RA, DPP-4 inhibitor, or pramlintide within 90 days prior to screening
- Any of the following: myocardial infarction, stroke or hospitalization for unstable angina or transient ischemic attack within the past 60 days prior to screening.
- History of pancreatitis
- Severe renal impairment
- Proliferative retinopathy or maculopathy requiring treatment
- History of diabetic ketoacidosis
- Heart failure NYHA class IV
- Personal or family history of MEN2 or familial medullary thyroid carcinoma

*Reviewer comment: For complete inclusion/exclusion criteria please see study report. The enrollment criteria are generally reasonable. Notably, the population proposed for enrollment is similar to the population enrolled in SUSTAIN 6, the CVOT for subcutaneous semaglutide.*

Dose selection/study treatments:

Only the 14 mg dose of oral semaglutide was studied in PIONEER 6.

All patients on semaglutide started with the 3 mg daily dose, followed by 7 mg daily after 4 weeks, and 14 mg daily after another 4 weeks. Patients were to remain on the 14 mg dose level throughout the maintenance period. However, if treatment with the trial product was associated with unacceptable AEs (as judged by the investigator), dose reductions and extensions of dose escalation periods were allowed.

Absorption of oral semaglutide is significantly affected by food and fluid in the stomach; therefore, trial products were to be administered once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. The trial product could be taken with up to half a glass of water (approximately 120 mL/4 fluid oz) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could be taken 30 minutes after administration of trial product.

**Procedures and Schedule:**

The study flowchart is outlined in the table below.

**Table 1 Study Flowchart PIONEER 6**

Trial Periods	Screening	Randomisation	Treatment														End of treatment	Follow-up
Visit (V) Phone (P)	V1	V2	P3	V4	V5	V6	P7 <sup>2</sup>	V8	P9 <sup>2</sup>	V10	P11 <sup>2</sup>	V12	P13 <sup>2</sup>	V14	P15 <sup>2</sup>	V16	V17 <sup>1</sup>	P18 <sup>1</sup>
Timing of visit (weeks after V2)	Up to -3	0	2	4	8	14	20	26	32	38	44	50	56	62	69	76	83	88
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3
Informed consent	X																	
In/exclusion criteria	X																	
Demography, tobacco use	X																	
Physical examination	X																	X
Eye examination	X <sup>3</sup>											X <sup>4</sup>						X <sup>4</sup>
Pregnancy test, urine dipsticks <sup>5</sup>	X																	X
Conc. illness, medical history	X																	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X																
Body weight		X		X	X	X		X		X		X		X		X	X	
Vital signs		X		X	X	X		X		X		X		X		X	X	
Electrocardiogram		X						X				X						X
Blood sampling		X		X	X	X		X		X		X		X		X	X	
- HbA <sub>1c</sub>		X			X	X		X		X		X		X		X	X	
- Fasting plasma glucose		X		X	X			X				X						X
- Lipids		X						X				X						X
- Biochemistry		X		X	X	X		X		X		X		X		X	X	
- Haematology		X		X	X	X		X		X		X		X		X	X	
- Hormones		X				X		X		X		X		X		X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaints			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IWRS call	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Randomisation		X																
Dispensing of trial product		X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Drug accountability				X	X	X	X	X	X	X	X	X	X	X	X	X		
REMINDERS																		
Handout ID card	X																	
Handout and instruct in BG meter use		X																
Attend visit fasting		X		X	X			X				X						X
End of trial																		X

<sup>1</sup> V17 (End of treatment) and P18 (Follow-up) are applicable for all randomised subjects. P18 can be conducted over the telephone. For a subject who prematurely discontinued trial product (i.e. more than 5 weeks prior to the anticipated V17), V17 can be postponed to the point when P18 is otherwise due.  
<sup>2</sup> Dispensing visit (i.e. a combination of dispensing trial product and collecting relevant information over the telephone. If the subject provides the required information to site staff when collecting trial product, the telephone contact can be omitted).  
<sup>3</sup> Fundus photography or dilated funduscopy were to be performed within 90 days prior to screening or within the period between screening and randomisation.  
<sup>4</sup> Fundus photography or dilated funduscopy should be performed at Visit 12 and 17 or within 5 weeks prior to those visits.  
<sup>5</sup> For women of childbearing potential only. In addition to the planned assessment at screening and end-of-treatment, urine dipstick pregnancy test should be performed at

Source: Table 9-3 Study Report

The patient was to remain in the trial regardless of lack of compliance with trial treatment, lack of adherence to the visit schedule, missed assessments, discontinuation of trial product for any reason or development of comorbidities or clinical outcomes.

The components of the primary endpoint (CV death, non-fatal MI and non-fatal stroke) underwent adjudication by the Events Adjudication Committee (EAC). Deaths and CV events were evaluated based on pre-defined diagnostic criteria in accordance with the American College of Cardiology/American Heart Association Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials, 2015.

## Study Endpoints

Primary endpoint:

- Time from randomization to first occurrence of a MACE, defined as CV death, non-fatal MI, or non-fatal stroke.

Secondary endpoints:

- Time from randomisation to first occurrence of an expanded composite MACE endpoint consisting of: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina requiring hospitalisation or heart failure requiring hospitalisation.
- Time from randomisation to first occurrence of each of the individual components in the expanded composite MACE endpoint
- Time from randomisation to first occurrence of a composite endpoint consisting of: all-cause death, non-fatal myocardial infarction or non-fatal stroke
- Time from randomisation to first occurrence of fatal or non-fatal myocardial infarction
- Time from randomisation to first occurrence of fatal or non-fatal stroke
- Time from randomisation to all-cause death
- Time to first AE leading to permanent trial product discontinuation
- Number of serious adverse events (SAEs)
- Change from baseline to last assessment of:
  - Eye examination category
  - Pulse rate
  - Systolic and diastolic blood pressure
  - Glycosylated haemoglobin (HbA1c)
  - Body weight
  - Lipids

Only the endpoints relevant for the proposed MACE reduction indication will be discussed in this review.

## Statistical Analysis Plan

Sample size calculations were made to ensure at least 90% power for testing the confirmatory hypothesis for the primary endpoint with respect to non-inferiority. The sample size calculation was based on the expected number of first EAC-confirmed MACEs in the FAS.

Calculations based on a log-rank test showed that a total of 122 first EAC-confirmed MACE would provide 90% power to rule out the upper bound of the 95% confidence interval of the HR (oral semaglutide vs placebo) exceeding 1.8, assuming a true HR of 1.0.

The expected event rates were calculated based on data generated for liraglutide (LEADER trial) and subcutaneous semaglutide (SUSTAIN 6 trial).

Analyses of the primary endpoint were performed for the treatment policy estimand.

The non-inferiority and superiority testing of the primary endpoint was performed in a pre-defined hierarchical order to control the overall type I error. In this sequence, non-inferiority had to be demonstrated before proceeding to test for superiority.

Secondary endpoints were not controlled for multiplicity.

The trial was powered with an assumption of a 1% lost to follow-up rate per year.

### Protocol Amendments

There were 3 substantial and no non-substantial amendments to the protocol. The details are outlined in the table below.

**Table 2 Protocol Amendments PIONEER 6**

Amendment number	Issue date	Timing of change (before/after FSFV)	Countries affected	Key changes
1	18-Feb-2016	Before FSFV	Germany (local)	Amendment created in order to comply with the local requirements for protocol wording about contraception.
2	21-July-2016	Before FSFV	Global (substantial)	Amendment created to incorporate an additional screening procedure and exclusion criterion related to diabetic retinopathy.
3	03-Nov-2016	Before FSFV	Global (substantial)	Additional eye examinations and additional data collection for events of diabetic retinopathy or related complications. Addition of bicarbonate as a part of the biochemistry laboratory assessments. Clarification in relation to physical examination. Minor corrections or clarifications.

**Abbreviations:** FSFV: first-subject-first-visit.

Source: Table 9-9 study report

None of these amendments are likely to have impacted the results of the study.

### Data Quality and Integrity: Sponsor's Assurance

The applicant states that the trial was monitored using a risk-based approach and both an external data monitoring committee (DMC) and internal safety committee performed safety surveillance.

## **Study Results**

### **Compliance with Good Clinical Practices**

The applicant states that the trial was conducted in accordance with ICH GCP.

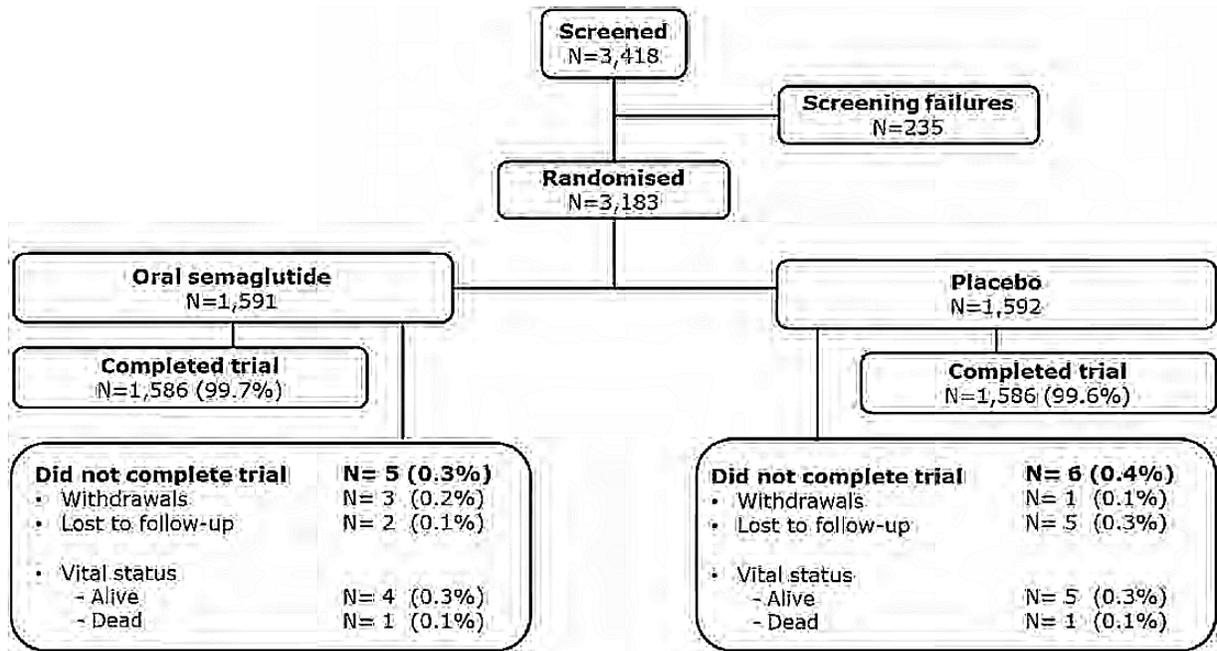
### **Financial Disclosure**

Of the total of 1025 investigators, none were NN employees, 16 had financial disclosure information, and one had financial disclosable information with certification of due diligence. None of these are likely to have impacted the outcome of the trial.

### **Patient Disposition**

A total of 3,418 patients were screened for this trial, of which 235 (6.9% of all screened) were screening failures. Eligible patients were randomized (1:1) to treatment with oral semaglutide (1,591 patients) or placebo (1,592 patients). An overview of patient disposition by treatment is provided in Figure 2. More than 99.6% of patients completed the trial (follow-up visit completed or died during trial). Eleven patients did not complete the trial due to either withdrawal of consent or being lost to follow-up. The number of non-completers was balanced between treatment groups and vital status was obtained for all non-completers at the end of the trial.

**Figure 2 Patient Flow**



Source: Figure 10-1 Study report

Patient withdrawals were few with no major differences between treatment groups. Permanent discontinuation of trial product was more frequent with oral semaglutide than with placebo, mainly due to GI AEs.

**Table 3 Patient Disposition PIONEER 6**

	Oral semaglutide N (%)	Placebo N (%)
Randomised	1591	1592
Exposed	1591 ( 100)	1591 (99.9)
Not exposed	0	1 ( 0.1)
Full analysis set	1591 ( 100)	1592 ( 100)
Treatment completers [1]	1347 (84.7)	1435 (90.1)
Permanent TP discontinuation - primary reason	244 (15.3)	156 ( 9.8)
Adverse event(s)	185 (11.6)	104 ( 6.5)
Lack of effect	4 ( 0.3)	5 ( 0.3)
Participation in another clinical trial [2]	0	0
Pregnancy	0	0
Intention of becoming pregnant	0	0
Calcitonin value >= 100 ng/L	0	0
Withdrawal of consent	0	0
Lost to follow-up	2 ( 0.1)	2 ( 0.1)
Other	53 ( 3.3)	45 ( 2.8)
Trial completers [3]	1586 (99.7)	1586 (99.6)
Attended follow-up visit (P18)	1563 (98.2)	1541 (96.8)
Died during trial	23 ( 1.4)	45 ( 2.8)
Non-completers - primary reason	5 ( 0.3)	6 ( 0.4)
Withdrawal by subject	3 ( 0.2)	1 ( 0.1)
Alive	3 ( 0.2)	1 ( 0.1)
Deceased	0	0
Lost to follow-up	2 ( 0.1)	5 ( 0.3)
Alive	1 ( 0.1)	4 ( 0.3)
Deceased	1 ( 0.1)	1 ( 0.1)

'[1]': subjects who were exposed and who did not discontinue trial product permanently  
 '[2]': simultaneous participation in any other clinical trial receiving an investigational medicinal product  
 '[3]': subjects who attended the follow-up visit (P18) or who died while considered active in trial;  
 'primary reason': according to the Dose Change form.  
 N: number of subjects; %: proportion of randomised subjects; TP: trial product.

Source: Table 10-1 Study report

A total of the 235 patients were screening failures. The reason for screening failure was for ~60% of subjects related to various eligibility criteria with exclusion criterion 17 (proliferative retinopathy or maculopathy requiring acute treatment) being the most frequent reason (29.4% of patients). For the remaining ~40% of patients, the reason for screening failure was listed as other.

### Protocol Violations/Deviations

#### Protocol deviations

Protocol deviations (PDs) were categorized as important/non-important. Important PDs were considered those that could significantly impact the completeness, accuracy and/or reliability of the trial data or that could significantly affect the patient's rights, safety or well-being.

In total, 492 important PDs were closed before database lock (DBL): 51 site level PDs and 441 patient level PDs. There were no important trial-level or country-level PDs. Overall, the important PDs were considered not to have an impact on trial conduct, patient safety or data interpretation. The summary of PD categories for the 492 PDs is presented in Table 4 below.

**Table 4 Summary of Important Site-Level and Subject-Level Protocol Deviations**

Category	Site-level PDs (n)	Subject-level PDs (n)			
		Screening failures	Oral semaglutide	Placebo	Total no of subject-level PDs
Informed consent	6 <sup>a</sup>	8	42	32	82
Inclusion/exclusion/randomisation criteria	1	-	58	55	113
Discontinuation criteria	-	-	-	-	-
Trial product handling	9	-	18	12	30
Treatment compliance	-	-	7	20 <sup>b</sup>	27
Assessment deviations	6	-	47	43	90
Other	29	2	50	47	99
<b>Total</b>	<b>51</b>	<b>10</b>	<b>222</b>	<b>209</b>	<b>441</b>

n: number of PDs; PD: protocol deviation; '-': indicate no PDs reported under this category

<sup>a</sup> One of the 6 site-level PDs (at Site 837) was re-classified to a subject-level PD (Subject ID (b) (6)) after the DBL cut-off date of 02 November 2018.

<sup>b</sup> One subject was never treated (Subject ID (b) (6))

Source: table 10-19 Study report

*Reviewer comment: I reviewed the details submitted for the PDs discussed above and I agree with the sponsor statement.*

### Table of Demographic Characteristics

Overall, demographics and baseline characteristics were well matched between patients randomized to semaglutide and placebo.

The mean age at baseline was 66 years. Less than 15% of patients were ≥75 years. A higher proportion of males (68.4%) than females were randomized, with a similar distribution between semaglutide and placebo groups.

By region, the highest proportion of patients was from North America (34.7%) , followed by Europe (30.1%). Most patients were White (72.3%), and of non-Hispanic or Latino ethnicity (84.9%).

The trial population was generally obese with a baseline mean BMI of 32.3 kg/m<sup>2</sup>.

The patient population had a mean HbA1c of 8.2% at baseline, and a relatively long mean duration of diabetes (14.9 years). Mean BP, pulse rate, lipids and smoking status were also well matched between the treatment groups.

**Table 5 Demographics and Baseline Characteristics PIONEER 6**

	Oral semaglutide		Placebo		Total	
	N	(%)	N	(%)	N	(%)
Number of subjects	1591		1592		3183	
Sex						
Male	1084	(68.1)	1092	(68.6)	2176	(68.4)
Age (years)						
Mean (SD)	66	(7)	66	(7)	66	(7)
Median	66		66		66	
Min; Max	50 ; 86		50 ; 88		50 ; 88	
Age group (years)						
50 <= to < 65	700	(44.0)	634	(39.8)	1334	(41.9)
65 <= to < 75	691	(43.4)	747	(46.9)	1438	(45.2)
75 <= to < 85	196	(12.3)	201	(12.6)	397	(12.5)
85 <=	4	(0.3)	10	(0.6)	14	(0.4)
Region						
Europe	475	(29.9)	484	(30.4)	959	(30.1)
North America	556	(34.9)	550	(34.5)	1106	(34.7)
South America	196	(12.3)	205	(12.9)	401	(12.6)
Africa	102	(6.4)	93	(5.8)	195	(6.1)
Asia	262	(16.5)	260	(16.3)	522	(16.4)
Race						
White	1148	(72.2)	1152	(72.4)	2300	(72.3)
Black or African American	89	(5.6)	103	(6.5)	192	(6.0)
Asian	324	(20.4)	306	(19.2)	630	(19.8)
American Indian or Alaska Native	14	(0.9)	15	(0.9)	29	(0.9)
Native Hawaiian or other Pacific Islander	5	(0.3)	1	(<0.1)	6	(0.2)
Other	11	(0.7)	15	(0.9)	26	(0.8)
Ethnicity						
Hispanic or Latino	253	(15.9)	261	(16.4)	514	(16.1)

'Baseline': defined as the latest assessment at or prior to the randomisation visit;  
 N: number of subjects; %: proportion of subjects; SD: standard deviation.

Source: Table 10-2 Study report

**Table 6 Diabetes and Weight Baseline Characteristics – PIONEER 6**

	Oral semaglutide	Placebo	Total
Number of subjects	1591	1592	3183
Duration of diabetes (years)			
Mean (SD)	14.7 (8.5)	15.1 (8.5)	14.9 (8.5)
Median	13.7	14.3	14.2
Min; Max	0.0 ; 56.1	0.0 ; 55.4	0.0 ; 56.1
HbA1c (%)			
Mean (SD)	8.2 (1.6)	8.2 (1.6)	8.2 (1.6)
Median	7.9	7.9	7.9
Min; Max	4.4 ; 15.2	4.2 ; 16.7	4.2 ; 16.7
Fasting plasma glucose (mg/dL)			
Mean (SD)	155.0 (58.1)	157.3 (60.8)	156.1 (59.5)
Median	143.1	145.5	144.2
Min; Max	27.8 ; 555.0	44.0 ; 594.5	27.8 ; 594.5
Body weight (kg)			
Mean (SD)	91.0 (21.4)	90.8 (21.0)	90.9 (21.2)
Median	88.1	88.5	88.3
Min; Max	40.0 ; 193.2	35.0 ; 176.1	35.0 ; 193.2
Body mass index (kg/m <sup>2</sup> )			
Mean (SD)	32.3 (6.6)	32.3 (6.4)	32.3 (6.5)
Median	31.3	31.4	31.4
Min; Max	18.6 ; 71.4	15.9 ; 68.4	15.9 ; 71.4

'Baseline': defined as the latest assessment at or prior to the randomisation visit;  
 N: number of subjects; SD: standard deviation.

Source: Excerpted from Tables 10-3 and 10-4 Study report

Mean eGFR at baseline was 74 mL/min/1.73 m<sup>2</sup>, and did not differ between treatment groups. Almost 30% of patients in both treatment groups had normal renal function. Less than 30% of patients had a history of renal impairment (reported as moderate renal impairment) at baseline. (b) (4)

### Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

#### Medical history and concomitant illnesses

As expected, the most common concomitant illnesses reported for the trial population at baseline were hypertension (76.0%), hyperlipidaemia (34.2%), dyslipidaemia (32.4%) and obesity (22.5%).

History of gallbladder disease (e.g., cholelithiasis, cholecystitis, biliary colic/pain), was reported in 17.2% of subjects, with no difference between oral semaglutide and placebo treatment groups. At baseline, 13.4% of subjects had had a cholecystectomy.

Overall, no noteworthy differences in medical history and concomitant illnesses at baseline between the oral semaglutide and placebo treatment groups were observed.

History of cardiovascular disease

The majority (84.7%) of patients were enrolled on the trial based on established CVD/CKD at baseline. A total of 488 patients (15.3%) were enrolled based on CV risk factors only. In total, 1,797 (56.5%) had established CV disease without CKD, 354 (11.1%) had CKD only, and 544 (17.1%) had both CVD and CKD.

Proportions of patients fulfilling each inclusion criterion were well-balanced across the oral semaglutide and placebo treatment groups. Among the patients enrolled in the trial, the most predominant CV disease at baseline were: prior arterial revascularization (47.2%), prior MI (36.1%), and moderate renal impairment (28.2%). The most frequent CV risk factor was microalbuminuria or proteinuria (33.0%).

**Table 7 Total Number of Patients Fulfilling the Inclusion Criteria by Evidence of CV Disease – FAS – PIONEER 6**

	Oral semaglutide N (%)	Placebo N (%)	Total N (%)
Number of subjects	1591	1592	3183
<b>Cardiovascular disease</b>			
a. prior myocardial infarction	561 (35.3)	589 (37.0)	1150 (36.1)
b. prior stroke or transient ischaemic attack	242 (15.2)	263 (16.5)	505 (15.9)
c. prior coronary, carotid or peripheral arterial revascularisation	733 (46.1)	768 (48.2)	1501 (47.2)
d. >50% stenosis on angiography/imaging of coronary, carotid/lower extremity arteries	427 (26.8)	453 (28.5)	880 (27.6)
e. history of symptomatic coronary heart disease	356 (22.4)	375 (23.6)	731 (23.0)
f. asymptomatic cardiac ischaemia	97 ( 6.1)	92 ( 5.8)	189 ( 5.9)
g. chronic heart failure NYHA class II-III	188 (11.8)	200 (12.6)	388 (12.2)
h. moderate renal impairment	463 (29.1)	435 (27.3)	898 (28.2)
<b>Cardiovascular risk factors</b>			
i. microalbuminuria or proteinuria	518 (32.6)	533 (33.5)	1051 (33.0)
j. hypertension and left ventricular hypertrophy by ECG or imaging	381 (23.9)	400 (25.1)	781 (24.5)
k. left ventricular systolic or diastolic dysfunction by imaging	337 (21.2)	335 (21.0)	672 (21.1)
l. ankle/brachial index < 0.9	81 ( 5.1)	94 ( 5.9)	175 ( 5.5)
<b>Stratum</b>			
Age ≥ 50 years and presence of CV disease (a-h)	1350 (84.9)	1345 (84.5)	2695 (84.7)
Age ≥ 60 years and presence of CV risk factors only (i.-l.)	241 (15.1)	247 (15.5)	488 (15.3)

N: number of subjects; %: proportion of subjects; NYHA: New York Heart Association; CV: cardiovascular.

Source: Table 10-8 study report

Baseline blood pressure and pulse were similar between the treatment groups, as were baseline lipid levels.

History of diabetes complications

An average of 36.3% of patients had peripheral neuropathy at baseline, and 34.1% of patients had a pre-existing or a history of diabetic nephropathy at baseline. A total of 28.2% of patients had a pre-existing or a history of diabetic retinopathy at baseline, most often non-proliferative diabetic retinopathy.

### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

There were 27 important subject-level PDs related to treatment compliance. The majority of the 27 subject-level PDs were related to subjects' intake of concomitant medications not allowed according to the protocol (24 PDs). One PD concerned a subject who did not take the trial product after being randomised as there was a delay in reduction of subject's ongoing treatment with gliclazide (160 mg/day). This subject was later admitted to hospital due to orthostatic hypotension and severe ataxia after which the subject was not willing to start treatment with trial product. Two PDs were reported in category 'other'. One was related to wrong background medication (DPP-4 inhibitor) prescribed to the subject while on trial product. The second PD concerned a wrong dose assigned to a subject in IWRS (semaglutide 14 mg instead of 7 mg) due to which 10 incorrect doses were taken.

#### Concomitant medications at baseline

##### Antidiabetic medications

At baseline the majority of patients were treated with anti-diabetic medication (<1.6% of patients did not use any diabetes medication at baseline). Baseline use of antidiabetic medication was well-balanced across treatment groups. The most commonly used anti-diabetic medication at baseline was metformin (77.4% of patients) followed by insulin (60.6% of patients) and sulfonylureas (SUs) (32.3%). A total of 9.6% of patients were using a SGLT-2 inhibitor at baseline. Although this was an exclusion criterion, 3 patients were using GLP-1 RAs or DPP-4 inhibitors at baseline.

#### **Table 8 Antidiabetic Medications at Baseline**

	Oral semaglutide N (%)	Placebo N (%)	Total N (%)
Number of subjects	1591	1592	3183
Insulin treatment			
INSULINS	968 ( 60.8)	962 ( 60.4)	1930 ( 60.6)
Non-insulin glucose-lowering medication			
BIGUANIDES	1221 ( 76.7)	1242 ( 78.0)	2463 ( 77.4)
SULFONYLUREAS	517 ( 32.5)	510 ( 32.0)	1027 ( 32.3)
SGLT2 INHIBITORS	165 ( 10.4)	140 ( 8.8)	305 ( 9.6)
THIAZOLIDINEDIONES	65 ( 4.1)	53 ( 3.3)	118 ( 3.7)
ALPHA GLUCOSIDASE INHIBITORS	36 ( 2.3)	43 ( 2.7)	79 ( 2.5)
OTHER	26 ( 1.6)	26 ( 1.6)	52 ( 1.6)
DPP-4 INHIBITORS	2 ( 0.1)	0	2 ( 0.1)
GLP-1 ANALOGUES	1 ( 0.1)	0	1 ( 0.0)

The start and stop dates of the anti-diabetic medication were before and after the date of the randomisation, respectively.

N: number of subjects; %: proportion of subjects.

Source: Table 10-6 Study report

The anti-diabetic medications most frequently initiated after baseline were insulins (47.2% of patients), metformin (15.0% of patients) and SUs (14.3% of patients). Initiation of SGLT-2 inhibitors was lower with oral semaglutide (4.5%) than with placebo (8.4%). Antidiabetic medications initiated after baseline are outlined in the table below.

**Table 9 Antidiabetics Initiated After Baseline**

	Oral semaglutide N (%)	Placebo N (%)	Total N (%)
Number of subjects	1591	1592	3183
Insulin treatment			
INSULINS	730 ( 45.9)	773 ( 48.6)	1503 ( 47.2)
Non-insulin glucose-lowering medication			
BIGUANIDES	230 ( 14.5)	246 ( 15.5)	476 ( 15.0)
SULFONYLUREAS	225 ( 14.1)	231 ( 14.5)	456 ( 14.3)
SGLT-2 INHIBITORS	71 ( 4.5)	133 ( 8.4)	204 ( 6.4)
ALPHA GLUCOSIDASE INHIBITORS	17 ( 1.1)	30 ( 1.9)	47 ( 1.5)
THIAZOLIDINEDIONES	15 ( 0.9)	31 ( 1.9)	46 ( 1.4)
OTHER	16 ( 1.0)	10 ( 0.6)	26 ( 0.8)
DPP-4 INHIBITORS	9 ( 0.6)	15 ( 0.9)	24 ( 0.8)
GLP-1 ANALOGUES	3 ( 0.2)	8 ( 0.5)	11 ( 0.3)

N: number of subjects; %: proportion of subjects.

Source: Table 10-7 Study report

### Cardiovascular medications

Almost 94% of patients received antihypertensive therapy at baseline and approximately 85% of patients were treated with lipid lowering medication, primarily statins.

Approximately 80% of patients were treated with anti-thrombotic medication, mainly acetylsalicylic acid and adenosine diphosphate (ADP) receptor inhibitors, such as clopidogrel. Diuretics, mainly loop diuretics and thiazides, were used by approximately 40% of the patients.

**Table 10 CV Medications at Baseline**

	Oral sema N (%)	Placebo N (%)	Total N (%)
Number of subjects	1591	1592	3183
Anti-hypertensiva	1495 ( 94.0)	1493 ( 93.8)	2988 ( 93.9)
Beta blockers	934 ( 58.7)	959 ( 60.2)	1893 ( 59.5)
ACE inhibitors	682 ( 42.9)	660 ( 41.5)	1342 ( 42.2)
Angiotensin receptor blockers	635 ( 39.9)	624 ( 39.2)	1259 ( 39.6)
Calcium channel blockers	500 ( 31.4)	528 ( 33.2)	1028 ( 32.3)
Others	109 ( 6.9)	125 ( 7.9)	234 ( 7.4)
Lipid lowering drugs	1336 ( 84.0)	1376 ( 86.4)	2712 ( 85.2)
Statins	1287 ( 80.9)	1312 ( 82.4)	2599 ( 81.7)
Fibrates	149 ( 9.4)	145 ( 9.1)	294 ( 9.2)
Ezetimibe	84 ( 5.3)	81 ( 5.1)	165 ( 5.2)
Other lipid lowering drugs	23 ( 1.4)	19 ( 1.2)	42 ( 1.3)
Statins in combinations with other products	13 ( 0.8)	14 ( 0.9)	27 ( 0.8)
Bile acid sequestrants	5 ( 0.3)	7 ( 0.4)	12 ( 0.4)
Anti-thrombotic medication	1248 ( 78.4)	1279 ( 80.3)	2527 ( 79.4)
Acetylsalicylic acid (ASA)	1024 ( 64.4)	1060 ( 66.6)	2084 ( 65.5)
ADP receptor inhibitors (excluding ASA)	342 ( 21.5)	361 ( 22.7)	703 ( 22.1)
Vitamin K antagonists	83 ( 5.2)	66 ( 4.1)	149 ( 4.7)
Direct factor Xa inhibitors	38 ( 2.4)	37 ( 2.3)	75 ( 2.4)
Direct thrombin inhibitors	14 ( 0.9)	10 ( 0.6)	24 ( 0.8)
Diuretics	621 ( 39.0)	640 ( 40.2)	1261 ( 39.6)
Thiazides	274 ( 17.2)	296 ( 18.6)	570 ( 17.9)
Loop diuretics	266 ( 16.7)	254 ( 16.0)	520 ( 16.3)
Aldosterone antagonists	102 ( 6.4)	98 ( 6.2)	200 ( 6.3)
Thiazide-like diuretics	80 ( 5.0)	79 ( 5.0)	159 ( 5.0)

'ongoing at randomisation': the start and stop dates of the cardiovascular related medication were before and after the date of the randomisation, respectively; N: number of subjects; %: proportion of subjects

Source: Table 10-13 Study report

The number of patients initiating cardiovascular medication after baseline was slightly lower with oral semaglutide than with placebo. The cardiovascular medications most frequently initiated after baseline were statins (13.2% of patients), beta-blockers (11.9% of patients), angiotensin receptor blockers (9.6%) and calcium channel blockers (9.3% of patients).

**Table 11 CV Medications Added After Baseline**

	Oral sema N (%)	Placebo N (%)	Total N (%)
Number of subjects	1591	1592	3183
Anti-hypertensiva	440 ( 27.7)	476 ( 29.9)	916 ( 28.8)
Beta blockers	188 ( 11.8)	190 ( 11.9)	378 ( 11.9)
Angiotensin receptor blockers	144 ( 9.1)	162 ( 10.2)	306 ( 9.6)
Calcium channel blockers	131 ( 8.2)	165 ( 10.4)	296 ( 9.3)
ACE inhibitors	127 ( 8.0)	127 ( 8.0)	254 ( 8.0)
Others	43 ( 2.7)	58 ( 3.6)	101 ( 3.2)
Lipid lowering drugs	255 ( 16.0)	256 ( 16.1)	511 ( 16.1)
Statins	211 ( 13.3)	208 ( 13.1)	419 ( 13.2)
Fibrates	33 ( 2.1)	31 ( 1.9)	64 ( 2.0)
Ezetimibe	23 ( 1.4)	33 ( 2.1)	56 ( 1.8)
Other lipid lowering drugs	9 ( 0.6)	6 ( 0.4)	15 ( 0.5)
Bile acid sequestrants	7 ( 0.4)	5 ( 0.3)	12 ( 0.4)
Statins in combinations with other products	5 ( 0.3)	3 ( 0.2)	8 ( 0.3)
Anti-thrombotic medication	199 ( 12.5)	180 ( 11.3)	379 ( 11.9)
Acetylsalicylic acid (ASA)	100 ( 6.3)	85 ( 5.3)	185 ( 5.8)
ADP receptor inhibitors (excluding ASA)	81 ( 5.1)	87 ( 5.5)	168 ( 5.3)
Direct factor Xa inhibitors	39 ( 2.5)	38 ( 2.4)	77 ( 2.4)
Vitamin K antagonists	25 ( 1.6)	12 ( 0.8)	37 ( 1.2)
Direct thrombin inhibitors	4 ( 0.3)	7 ( 0.4)	11 ( 0.3)
Diuretics	170 ( 10.7)	209 ( 13.1)	379 ( 11.9)
Loop diuretics	107 ( 6.7)	130 ( 8.2)	237 ( 7.4)
Thiazides	47 ( 3.0)	52 ( 3.3)	99 ( 3.1)
Aldosterone antagonists	39 ( 2.5)	37 ( 2.3)	76 ( 2.4)
Thiazide-like diuretics	18 ( 1.1)	22 ( 1.4)	40 ( 1.3)

N: number of subjects; %: proportion of subjects.

Source: Table 10-14 Study report

## Exposure

The trial duration was event-driven and consequently, the planned observation- and treatment time varied between subjects depending on when they were recruited into the trial. The in-trial observation period relates to the observation time for each subject. The median time in-trial was 485 days (~16 months) ranging from 13 days to 608 days.

**Table 12 Exposure and Observation Time FAS**

	Oral semaglutide	Placebo	Total
Number of subjects	1591	1592	3183
In-trial (days)			
Mean (SD)	482 (71)	477 (79)	480 (75)
Median (Q1, Q3)	490 (428, 535)	483 (428, 528)	485 (428, 532)
Min; Max	24 ; 607	13 ; 608	13 ; 608
Total (years)	767546 (2101)	759997 (2081)	1527543 (4182)
In-trial (months)			
Mean (SD)	15.8 (2.3)	15.7 (2.6)	15.8 (2.5)
Median (Q1, Q3)	16.1 (14.1, 17.6)	15.9 (14.1, 17.3)	15.9 (14.1, 17.5)
Min; Max	0.8 ; 19.9	0.4 ; 20.0	0.4 ; 20.0
Total (years)	25217.1 (2101.4)	24969.1 (2080.8)	50186.2 (4182.2)
On-treatment (plus 38 days) (months)			
Mean (SD)	14.6 (4.1)	15.0 (3.6)	14.8 (3.9)
Median (Q1, Q3)	15.4 (12.9, 17.1)	15.5 (13.6, 17.1)	15.5 (13.2, 17.1)
Min; Max	0.8 ; 19.9	0.0 ; 19.1	0.0 ; 19.9
Total (years)	23181.6 (1931.8)	23844.1 (1987.0)	47025.7 (3918.8)

N: number of subjects; SD: standard deviation; Q1: 1st quartile, Q3: 3rd quartile.

Source: Table 10-16 Study report

The treatment time (i.e. duration of exposure including any treatment pauses) for the individual patients was up to 82 weeks with the majority (74.5%) of patients being treated for 53 to 79 weeks.

### Efficacy Results - Primary Endpoint

A total of 137 first MACE with onset during the in-trial observation period were confirmed by the EAC. The proportion of patients with first MACE was lower with oral semaglutide than with placebo; a total of 61 patients (3.8%) experienced EAC-confirmed MACE with oral semaglutide versus 76 patients (4.8%) with placebo. The difference between treatments in overall number of patients with MACE was primarily attributable to a smaller number of first stroke and CV death with oral semaglutide than with placebo. Non-fatal MI occurred more frequently with semaglutide vs placebo.

**Table 13 First EAC-Confirmed MACE – FAS In-Trial**

	Oral semaglutide				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	1591				1592			
Observation time (years), first event	2070				2046			
First EAC-confirmed MACE	61	( 3.8)	61	2.9	76	( 4.8)	76	3.7
Myocardial infarction, non-fatal	37	( 2.3)	37	1.8	31	( 1.9)	31	1.5
Stroke, non-fatal	11	( 0.7)	11	0.5	16	( 1.0)	16	0.8
Cardiovascular and undetermined cause of death	13	( 0.8)	13	0.6	29	( 1.8)	29	1.4

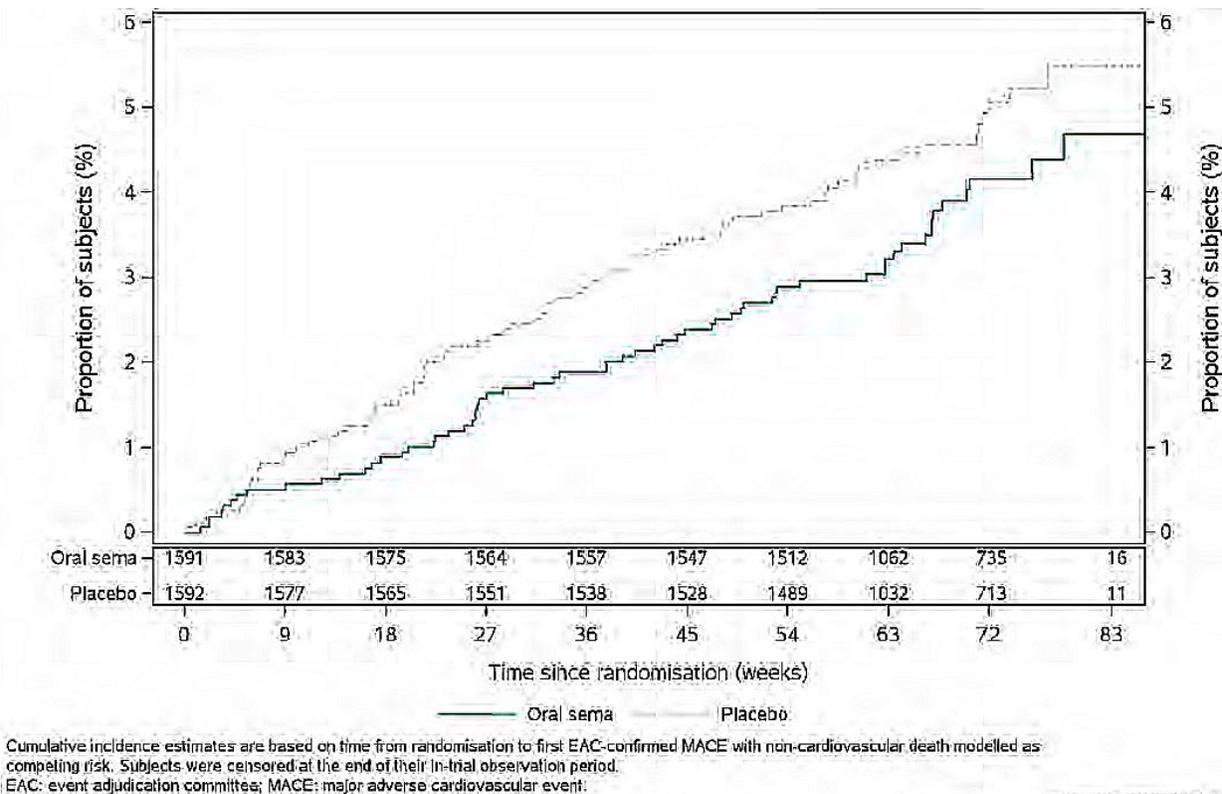
N: number of subjects with at least one event; %: proportion of subjects with at least one event; E: number of events; R: events per 100 years of observation; EAC: event adjudication committee; MACE: major adverse cardiovascular event.

Source: Table 11-2 Study report

The primary analysis of time to first EAC-confirmed MACE resulted in an estimated HR of 0.79 [0.57; 1.11] 95% CI for oral semaglutide relative to placebo. The upper bound of the 95% CI was below 1.8, confirming non-inferiority of oral semaglutide relative to placebo with respect to cardiovascular safety ( $p < 0.0001$ ). Because the upper bound of the 95% CI was above 1.0, superiority of oral semaglutide vs placebo was not confirmed ( $p = 0.1749$ ).

MACE had onset throughout the entire in-trial observation period, with no clustering of events over time.

**Figure 3 Time to First-EAC-Confirmed MACE – Cumulative Incidence Plot – FAS In-Trial**



Source: Figure 11-2 Study report

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**Data Quality and Integrity - Reviewers' Assessment**

The applicant submitted datasets and multiple documents addressing the study results. I did not find any issues with the data quality.

**Efficacy Results - Secondary and other relevant endpoints**

Selected secondary endpoints relevant for the CV reduction indication are discussed below.

All MI

A total of 37 events were recorded with semaglutide (2.3%) and 35 events with placebo (1.9%) with HR 1.04, 95% CI 0.66, 1.66.

#### All stroke

A total of 13 events were recorded with semaglutide (0.8%) vs 17 events (1.1%) with placebo, with a HR of 0.76 and 95% CI 0.37, 1.56.

#### CV death (including undetermined death)

A total of 15 patients died of CV causes in the semaglutide arm (0.9%) vs 30 patients on placebo (1.9%), HR 0.49 (0.27, 0.92).

#### All cause death

In total, 23 patients died in the semaglutide arm (1.4%) vs 45 patients in the placebo arm (2.8%), with HR 0.51 (0.31, 0.84). Although this finding was nominally significant, the significance is not clear in such a short-term study, and the endpoint was not controlled for type 1 error.

#### **Dose/Dose Response**

Not applicable as only one dose of semaglutide was studied.

#### **Durability of Response**

Not applicable.

#### **Persistence of Effect**

The understanding of the persistence of effect is limited by the fact that the study was of limited duration, and it is not known whether the potential benefit on CV outcomes would persist after the discontinuation of the study drug.

#### **Additional Analyses Conducted on the Individual Trial**

##### Shrinkage analysis combining results of PIONEER 6 and SUSTAIN 6 (subcutaneous semaglutide)

As advised by the FDA, the applicant provided a Bayesian shrinkage analysis combining results from this study with those from a study of semaglutide for subcutaneous injection, SUSTAIN-6,

The results of the shrinkage analysis are presented in the table below:

#### **Table 14 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)

Trial 4221 – PIONEER 6, Trial 3744 – SUSTAIN 6  
Source: Table 6 Biometrics review by Dr Robert Abugov

*Reviewer comment: Even using the results from SUSTAIN 6 for the purpose of supporting PIONEER 6 via a bayesian shrinkage analysis, the results of PIONEER 6 did not demonstrate superiority for MACE.*

See Biometrics review by Dr Robert Abugov for additional analyses pertaining to PIONEER 6.

### 5.3.2. Subpopulations

Subgroup analyses were performed by the applicant based on the treatment policy estimand for the efficacy trials to evaluate whether the overall treatment effect of oral semaglutide on glycemic control is consistent across subgroups and can be applied broadly to the T2DM population.

Generally, the efficacy response to semaglutide was consistent across sub-populations of major demographic factors (age, sex, race and ethnicity), relevant disease factors at baseline (duration of diabetes, body weight, BMI, and renal function), background diabetes treatment (metformin monotherapy, metformin + SU, other) and region (Africa, Asia+Australia, Europe, North America [US+Canada] and South America); hence, the estimated mean change from baseline and estimated treatment differences (ETD) between semaglutide and comparator were comparable across and within the different subgroups.

Refer to Biometrics review by Dr Robert Abugov for the FDA’s analysis of subgroups.

### 5.3.3. Dose and Dose-Response

Not applicable as only one dose of semaglutide was studied.

### 5.3.4. Onset, Duration, and Durability of Efficacy Effects

The understanding of the persistence of effect is limited by the fact that the study was of limited duration, and it is not known whether the potential benefit on CV outcomes would persist after the discontinuation of the study drug.

## 5.4. Additional Efficacy Considerations

### 5.4.1. Considerations on Benefit in the Postmarket Setting

The PIONEER 6 trial evaluated cardiovascular outcomes using oral semaglutide 14 mg in patients with T2DM with established CV disease or multiple risk factors. The majority population was white, therefore generalizability of the data to less represented subgroups is unclear. Additionally, this study enrolled patients with history of CV disease, and therefore the findings can not necessarily be applied to patients with T2DM without such risk factors.

#### 5.4.2. Other Relevant Benefits

Not applicable as no new indication will be included in the prescribing information for Rybelsus.

### 5.5. Integrated Assessment of Effectiveness

(b) (4)

The applicant's evidence of effectiveness derives from one pre-market CVOT, PIONEER 6, comparing the addition of 14 mg oral semaglutide to standard of care in adult patients with T2DM and CV disease where semaglutide was shown to be numerically but not statistically superior to placebo regarding time to first MACE. The applicant also performed a Bayesian shrinkage analysis using the results of the subcutaneous semaglutide pre-market CVOT, SUSTAIN 6, however, this analysis also failed to reach statistical significance.

In PIONEER 6, 3183 patients were randomized (1:1) to receive semaglutide 14 mg or placebo. Over 99% of patients in either treatment group completed the trial, and more than 85% completed the treatment. Median follow up time was 16.1 months.

A total of 137 first MACE with onset during the in-trial observation period were confirmed by the EAC. The proportion of patients with first MACE was lower with oral semaglutide than with placebo; a total of 61 patients (3.8%) experienced EAC-confirmed MACE with oral semaglutide versus 76 patients (4.8%) with placebo. This difference did not achieve statistical significance for superiority, the HR was 0.79 [0.57; 1.11] 95% CI for oral semaglutide relative to placebo.

Events had onset throughout the entire observation period, with no clustering of events over time as assessed from time of randomization.

Non-inferiority of semaglutide versus placebo was confirmed, but superiority was not demonstrated even after Bayesian shrinkage analysis using results with subcutaneous semaglutide.

## 6. Review of Safety

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### 6.1. Safety Review Approach

The safety of semaglutide in PIONEER 6 was already reviewed at the time of the original Rybelsus NDA review. No safety information will be reviewed in this section.

## **6.2. Review of the Safety Database**

### **6.2.1. Overall Exposure**

Not applicable.

### **6.2.2. Relevant characteristics of the safety population:**

Not applicable.

### **6.2.3. Adequacy of the safety database**

Not applicable.

## **6.3. Adequacy of Applicant's Clinical Safety Assessments**

### **6.3.1. Issues Regarding Data Integrity and Submission Quality**

Not applicable.

### **6.3.2. Categorization of Adverse Events**

Not applicable.

### **6.3.3. Routine Clinical Tests**

Not applicable.

## **6.4. Safety Results**

### **6.4.1. Deaths**

See Efficacy section.

### **6.4.2. Serious Adverse Events**

Not applicable.

### **6.4.3. Dropouts and/or Discontinuations Due to Adverse Effects**

Not applicable.

**6.4.4. Significant Adverse Events**

Not applicable.

**6.4.5. Treatment Emergent Adverse Events and Adverse Reactions**

Not applicable.

**6.4.6. Laboratory Findings**

Not applicable.

**6.4.7. Vital Signs**

Not applicable.

**6.4.8. Electrocardiograms (ECGs)**

Not applicable.

**6.4.9. QT**

Not applicable.

**6.4.10. Immunogenicity**

Not applicable.

**6.5. Analysis of Submission-Specific Safety Issues**

Not applicable.

**6.6.4 Month Safety Update**

Not applicable.

**6.7. Safety Analyses by Demographic Subgroups**

Not applicable.

**6.8. Specific Safety Studies/Clinical Trials**

Not applicable.

**6.9. Additional Safety Explorations**

Not applicable.

**6.9.1. Human Carcinogenicity or Tumor Development**

Not applicable.

**6.9.2. Human Reproduction and Pregnancy**

Not applicable.

**6.9.3. Pediatrics and Assessment of Effects on Growth**

Not applicable.

**6.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Not applicable.

**6.9.5. Safety Concerns Identified Through Postmarket Experience**

Not applicable.

Not applicable.

**6.9.6. Expectations on Safety in the Postmarket Settings**

Not applicable.

**6.9.7. Additional Safety Issues From Other Disciplines**

Not applicable.

**6.10. Integrated Assessment of Safety**

Not applicable.

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**7. Advisory Committee Meeting and Other External Consultations**

Not applicable.

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**8. Labeling Recommendations**

## 8.1. Prescription Drug Labeling

The applicant proposed the following changes to the prescribing information:

(b) (4)



## 8.2. Nonprescription Drug Labeling

Not applicable.

## **9. Risk Evaluation and Mitigation Strategies (REMS)**

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Not applicable.

## **10. Postmarketing Requirements and Commitments**

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Not applicable.

## **11. Appendices**

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Not applicable.

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